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Clinical and Neuroimaging Outcomes of Direct Thrombectomy vs Bridging Therapy in Large Vessel Occlusion: Analysis of the SELECT Cohort Study

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Abstract

Objective:

To evaluate the comparative safety and efficacy of direct endovascular thrombectomy(dEVT) compared to bridging therapy(BT:IV-tPA+EVT) and assess if BT potential benefit relates to stroke severity, size and initial presentation to EVT vs. non-EVT center.

Methods:

In a prospective multicenter cohort-study of imaging selection for endovascular thrombectomy[SELECT], anterior-circulation large vessel occlusion (LVO) patients presenting to EVT-capable centers within 4.5hours from last-known-well were stratified into BT vs. dEVT. The primary outcome was 90-day functional independence[modified Rankin Scale(mRS)=0-2]. Secondary outcomes included a shift across 90-day mRS grades, mortality, symptomatic intracranial hemorrhage. We also performed subgroup-analyses according to initial presentation to EVT-capable center (direct versus transfer), stroke severity and baseline infarct core volume.

Results: We identified 226 LVOs (54%:men, mean age:65.6±14.6years, median NIHSS-score: 17, 28% received dEVT). Median time from arrival to groin-puncture did not differ in BT-patients when presenting directly[dEVT:1.43 (IQR=1.13-1.90) hours vs. BT:1.58(IQR=1.27-2.02)hours,p=0.40] or transferred to EVT-capable centers[dEVT:1.17 (IQR: 0.90-1.48) hours vs. BT:1.27 (IQR: 0.97-1.87) hours,p=0.24]. BT was associated with higher odds of 90-day functional independence (57% vs. 44%,aOR=2.02,95%CI:1.01-4.03,p=0.046) and functional improvement (adjusted cOR=2.06,95%CI:1.18-3.60,p=0.011), and lower likelihood of 90-day mortality (11% vs. 23%,aOR: 0.20,95%CI:0.07-0.58,p=0.003). No differences in any other outcomes were detected. In subgroup-analyses, BT patients with baseline NIHSS-scores<15 had

higher functional independence likelihood compared to dEVT (aOR=4.87,95%CI:1.56-15.18,p=0.006); this association was not evident for patients with NIHSS-scores≥15 (aOR=1.05,95%CI:0.40-2.74,p=0.92). Similarly, functional outcomes improvements with BT were detected in patients with core volume strata (Ischemic core <50cc: aOR: 2.10, 95% CI:1.02-4.33, p=0.044 vs ischemic core ≥50cc: aOR: 0.41,95% CI:0.01-16.02,p=0.64) and transfer status (transferred: aOR: 2.21,95% CI:0.93-9.65,p=0.29 vs direct to EVT center: aOR:1.84,95%CI:0.80-4.23,p=0.15).

Conclusions: Bridging therapy appears to be associated with better clinical outcomes, especially with milder NIHSS-scores, smaller presentation core volumes and those who were "dripped and shipped". We did not observe any potential benefit of bridging therapy in patients with more severe strokes.

Classification of Evidence: This study provides Class III evidence that for patients with ischemic stroke from anterior-circulation LVO within 4.5 hours from last-known-well, bridging therapy compared to direct endovascular thrombectomy leads to better 90-day functional outcomes.

Introduction

Endovascular thrombectomy (EVT) is the current standard of care treatment for acute ischemic stroke (AIS) patients with a proximal large vessel occlusion (LVO) in the anterior circulation,[1] as it has been robustly associated with both significant functional improvement and survival increase.[2] Despite the fact that more than 80% of the participants in pivotal EVT trials received intravenous alteplase (tPA) prior to EVT,[3] and that current international recommendations advocate intravenous thrombolysis (IVT) prior to the initiation of EVT for all eligible LVO patients (Class of Recommendation I, Level of evidence),[1,4] concerns have been raised regarding the utility of tPA pretreatment for LVO patients that have been selected for EVT.[5–7]

The arguments in favor of direct EVT (dEVT) include the potential delay in EVT initiation with tPA pretreatment, the low over all recanalization rates with IV tPA prior to thrombectomy[8,9], increased thrombus fragility and migration with increased risk of distal emboli[10], increased risk for systemic and hemorrhagic complications with bridging therapy (BT: IVT plus EVT), and the increased costs of tPA administration[5,11,12].The utility of IVT pretreatment has been further questioned after the publication of observational registry data suggesting better outcomes for LVO patients presenting directly to an EVT capable stroke center bypassing the interhospital transfers from primary stroke centers that can only initiate tPA administration.[10,11]

On the other hand, there are arguments in favor of IV thrombolysis prior to EVT such as the potential for early reperfusion that was observed in 7-8% of early window EVT trials' patients [8,9], thrombus softening and facilitation of successful reperfusion[13], potential role of IV

tPA in patients who do not achieve successful reperfusion with EVT, and the effect on distal residual occlusions following EVT.

Additionally, the potential adjunctive benefit from IVT may not occur across all patients receiving EVT and rather would be spcific to selected subgroups as related to stroke severity at the time of presentation and whether IVT is delivered at non-EVT center "drip and ship" or presenting directly to an EVT-capable center.

We aimed to investigate the comparative safety and efficacy of dEVT compared to BT for AIS patients with anterior circulation LVO presenting within 4.5 hours from last known well in the SELECT (Optimizing Patient Selection for Endovascular Treatment in Acute Ischemic Stroke - NCT02446587) study. We also sought to assess if the potential effect of bridging therapy was mediated by stroke severity, stroke size measured by ischemic core volume and presentation status to the EVT-capable center (direct versus secondary transfer).

Methods

SELECT Trial Methods

The methods and results of SELECT cohort study have been published previously.[14,15] Briefly, consecutive acute ischemic stroke patients with anterior circulation large vessel occlusion (ICA, M1 or M2 segments of MCA), no or minimal pre-stroke deficit (mRS 0-1) and National Institutes of Health Stroke Scale (NIHSS) score of ≥6, presenting to 9 US large volume EVT centers from January 2016 to February 2018 were enrolled in the study. The initial enrollment window was up to 8 hours from last known well (LKW) to groin puncture for EVT patients and LKW to Emergency Room arrival for medical management only. This window was extended to up to 24 hours after results of DAWN study were presented in May 2017. All patients received a

unified pre-specified imaging protocol with NCCT, CTA, and CTP with core infarct and mismatch determination using RAPID software (iSchemaView, Menlo Park, CA). The pre-specified favorable profiles on CT (ASPECTS ≥ 6) and CTP (i. core-volume measured on CBF (rCBF <30%) of <70cc and ii. ratio between the critically hypoperfused tissue (Tmax>6 seconds) and ischemic core (rCBF <30%) volume ≥1.2 with an absolute difference of ≥10 cc) were provided to the site investigators, but the decision to proceed with thrombectomy vs medical management alone was left at the discretion of the treating physician. Final infarct volume was measured on MR DWI sequences obtained after the procedure (up to 24-72 hours from stroke onset) using manual segmentation of the region of interest (ROI). If post-procedure MRI was not available, non-contrast CT was used to evaluate the final infarct size. An independent neuroimaging core lab blinded to clinical outcomes and enrollment site evaluated all imaging. Assessors blinded to treatment allocation and core lab imaging evaluations obtained modified Rankin Scale (mRS) score assessment at 90-day follow-up. Written informed consent was obtained from all patients or their legally authorized representatives prior to enrollment. The study aimed to evaluate different selection methodologies for endovascular therapy, to assess the correlation between the profiles on CT and CTP with the treatment decision and clinical outcomes after thrombectomy, to compare them against each other and identify which method provides the highest predictive ability in the selection of patients for EVT.

Study Population

We performed a prespecified subanalysis of SELECT including patients with LVO who arrived at the EVT-capable center within 4.5 hours from LKW. All patients who received EVT were

included in this subanalysis. The study cohort was stratified based on IV tPA administration status into bridging therapy if they received IV tPA prior to thrombectomy (BT: IVT + EVT) and direct EVT (dEVT) if they did not receive IV tPA. SELECT trial inclusion criteria mandated that patients only receive IV tPA if they met the AHA guidelines for IV tPA administration[15]. SELECT was an intention to treat (ITT) study, thus patients who were taken to for thrombectomy but demonstrated reperfusion on first angiogram run were included in the EVT arm and in the BT group for this analysis.

Standard Protocol Approvals, Registrations, and Patient Consents

The study protocol for SELECT was approved at local institutional review boards for all sites and the study was prospectively registered at clinicaltrials.gov (NCT02446587). All participants and/or their legally authorized representatives provided written informed consent prior to enrollment in the study.

Interventions

All endovascular procedures were performed with the use of stent retrievers or other devices approved by the US Food and Drug Administration. Standard endovascular procedures, according to the practice of each site, were followed. Administration of tPA was decided based on patient eligibility criteria if they met the AHA guidelines and recommendations.[1] The decision to proceed with direct EVT instead of BT was at the discretion of the local investigators in a non-randomized fashion, and after taking into account the absolute and relative contra-indications for tPA administration.[1]

Outcomes

The primary efficacy outcome was the rate of functional independence, defined as modified Rankin Scale (mRS) scores of 0-2 at 90 days after AIS onset. We also evaluated the following efficacy outcomes: 1) the rate of patients with excellent functional outcomes at 90 days (defined as mRS scores of 0-1), 2) functional improvement at 90 days defined as a 1-point decrease across all mRS grades (shift analysis).

Safety outcomes included 1) the rates of symptomatic intracerebral hemorrhage (ICH) per ECASS II and SITS-MOST criteria, defined as worsening of the National Institutes of Health Stroke Scale (NIHSS) score of 4 or more accompanied with evidence of any ICH on follow-up imaging (ECASS II) or parenchymal hemorrhage type I or II (SITS MOST),[16,17] 2) the rates of asymptomatic ICH on follow-up neuroimaging, 3) the rates of neurological worsening within 24 hours from symptom onset, defined as an increase in the NIHSS score of 4 or more points within 24 hours from hospital admission, 3) the rates of all-cause 90-day mortality. Procedural and Imaging outcomes included 1) the rates of successful reperfusion (mTICI ≥ 2b) and rates of successful reperfusion after first pass 2) the final infarct volume measured on follow-up MRI diffusion weighted images or CT scans, when follow-up MRI was not available and 3) the absolute infarct growth after comparing baseline ischemic core on CT Perfusion and follow-up MRIs.

Statistical Analysis

Continuous variables were presented as means with corresponding standard deviations, or medians with corresponding interquartile ranges. Dichotomous variables were presented with their absolute numbers and percentages. In case of continuous variables, baseline characteristics and outcomes between the two groups were compared with the use of t-test if the variables had a normal distribution or Mann-Whitney U test if the variables had a non-normal distribution, and with the Pearson's $\chi 2$ test if the all expected cell values were above 5 or Fisher's exact test if any expected cell values were below 5 for categorical variables. Shapiro Wilk test was used to assess the normality of distribution. Time metrics including time from arrival to EVT capable center to groin puncture were compared between the two groups. The likelihood of functional independence (mRS 0-2) at 90 days according IVT pretreatment history was also assessed in univariable and multivariable binary logistic regression models, adjusting for the potential predefined confounders of age, National Institutes of Health Stroke Scale (NIHSS) score at presentation, baseline ischemic core volume, serum glucose at presentation, location of the intracranial occlusion, transfer status and time from symptom onset to arrival to EVT capable center. The distribution of mRS scores (0-6 points) at 90 days between patients receiving dEVT or BT was assessed using Cochran Mantel Haenszel test as well as unadjusted and adjusted (for the same baseline variables used in the binary logistic regression models) ordinal logistic regression analyses (shift analyses). The unadjusted and adjusted odds ratios (OR) and common odds ratios (cORs) with the corresponding 95% confidence intervals (95% CIs) were reported for all univariable and multivariable logistic regression analyses.

We further explored the effect of tPA pretreatment on the primary outcome of functional independence (mRS 0-2) at 90 days in pre-defined subgroup analyses according to 1) stroke severity using an admission NIHSS-score of 15 as a cut-off, and 2) ischemic core volume (relative cerebral blood flow<30%) on admission using a cut-off of 50cc on CTP. A sensitivity analysis using the cutoff of 17 for presentation NIHSS score was also performed. We also evaluated the effect of bridging therapy by the occlusion location at the time of presentation.

Finally, we performed further analyses on all patient baseline characteristics, outcomes of interest and subgroup comparisons for patients that were admitted within 4.5 hours directly to EVT-capable comprehensive stroke care centers as well as those who presented initially to non-EVT center then were transferred to an EVT-capable center "drip and ship" cases. In all analyses we reported P values as 2-sided, and P values less than 0.05 were considered as statistically significant for reported associations. Statistical significance for reported interactions was set at $p<0.1$.

Data Availability

The individual patient data will not be made available. Analysis codes and outputs will be made available upon reasonable requests after review by the study steering and publication committees.

Results

Baseline Characteristics

Overall, of 285 patients who received EVT, we identified a total of 226 LVO patients (54% men, Figure 1) fulfilling our prespecified inclusion criteria. Mean age was 65.6±14.6 years

and median NIHSS score at presentation was 17 (IQR: 12-21). 66% (n=150) patients presented directly to EVT center while 34% (76) were transfers. Median time from last known well to groin puncture was 3.3 (IQR: 1.9 – 4.4) hours. Patients with BT (n=162, 72%) were younger (p=0.001) and had significantly lower prevalence of congestive heart failure (p<0.001), coronary artery disease (p<0.001), atrial fibrillation (p=0.002) and diabetes mellitus (p=0.033) compared to patients receiving dEVT (Table 1). Median time from last known well to IV tPA bolus was 1.6 (IQR: 1.2 – 2.3) hours. On baseline neuroimaging, patients receiving BT had lower median ASPECTS score on admission CT (8 vs. 9, p=0.007) and larger ischemic core volumes median (IQR) (11.4 (1.5 – 37) ml vs. 3.9 (0-32.15 p=0.042) ml compared to patients receiving dEVT (Table 1). The reasons for IV tPA ineligibility are listed in table e-1 (Data available from Dryad https://doi.org/10.5061/dryad.sxksn0323). Treatment with anticoagulation or a coagulopathy disorder and recent major surgery were the two main reasons for not receiving IV tPA. 3 patients in the BT group demonstrated successful reperfusion on first angiogram run and did not receive further intervention. Primary occlusion was observed in ICA in 41(18%), in MCA-M1 in 136 (60%) and in MCA-M2 in 49 (22%) patients. Further results based on occlusion location are provided in the supplemental results.

Time Metrics for Direct EVT vs Bridging Therapy

No statistically significant difference (p=0.99) was observed in median time from last known well to arrival to EVT-capable center for patients who received BT [1.5 (IQR: 0.9-2.9) hours] and dEVT [1.6 (IQR: 0.8-2.9) hours]. The median times from arrival to EVT-capable center to groin puncture did not differ between the two groups [BT: 1.6 (IQR: 1.1-2.0) hours vs dEVT: 1.3 (IQR: 1.1-1.8) hours, p=0.21]. The overall times from last known well to groin

puncture (including transfer times) also were similar between patients who received IV tPA (median (IQR): 3.35 (2.47-4.38) hours) and patients who did not receive IV tPA (median (IQR): 3.28 (2.12-4.45) hours), p=0.45.

An analysis of patients who presented directly (n=150) to EVT-capable centers within 4.5 hours of LKW demonstrated that dEVT patients (n=43) presented at 1.0 (IQR: 0.6-2.2) hours, whereas patients who received bridging therapy (n=107) presented at 1.1 (IQR: 0.7-1.6) hours from LKW. Median time from arrival at EVT capable center to groin puncture did not differ between the two groups [dEVT: 1.4 (IQR: 1.1-1.9) hours vs. BT: 1.6 (IQR: 1.3-2.0) hours, p=0.40]. 53 (50%) patients received thrombectomy procedure within less 1 hour of IV tPA bolus. Table 2 describes the various time metrics for patients who directly presented to EVT capable centers within 4.5 hours of stroke onset and received EVT.

Similarly, evaluating patients who were transferred (n=76) to EVT capable centers within 4.5 hours of LKW demonstrated that dEVT (n=21) presented at 2.8 (IQR: 2.4-3.2) hours, whereas BT (n=55) presented at 3.0 (IQR: 2.5-3.8) hours. Median time from arrival at EVT capable center to groin puncture did not differ between the two groups [dEVT: 1.2 (IQR: 0.9-1.5) hours vs BT: 1.3 (IQR: 1.0-1.9) hours, p=0.24], Table 2. Four (7%) of the fifty five transferred patients in the BT group received IV tPA after arriving at the EVT capable center, while 51 (93%) were thrombolyzed at the non-EVT center prior to transfer.

Outcomes of Direct EVT vs Bridging Therapy

Table 3 and Figure 2 show the comparisons of clinical and imaging outcomes between the two groups. No statistically significant difference in 90-day functional independence between BT group and dEVT group (BT: 56.8% vs. dEVT: 43.8%, OR:1.69, 95% CI: 0.94-3.03,

p=0.077). In addition, the distribution of mRS-scores at 90 days was lower with a shift towards better functional outcomes (p=0.046 by Cochran Mantel Haenszel test) in the BT group (Figure 3) that corresponded to a cOR of 1.66 (95%CI: 0.99-2.76, p=0.053) for 90-day functional improvement on unadjusted ordinal logistic regression analyses. When these associations were adjusted for potential confounders, IV-tPA administration prior to EVT was independently associated with higher likelihood of both functional independence (adjusted OR=2.02, 95%CI: 1.01-4.03, p=0.046) and a shift towards better functional outcomes (adjusted cOR=2.06, 95% CI: 1.18-3.60, p=0.011).

We also observed lower mortality rates at 90 days in patients treated with BT compared to dEVT (10.5% vs. 21.9%, OR:0.42; 95% CI: 0.19-0.91; p=0.025) with reduced 3-month mortality odds with IV tPA administration (aOR: 0.20, 95% CI: 0.07-0.58, p=0.003) in a multivariable analysis. No other difference between the two groups were detected with regards to the remaining safety outcomes including symptomatic (ECASS II - 6.2% in BT vs. 6.3% in dEVT, OR: 0.98, 95% CI: 0.30-3.27; p>0.99, SITS-MOST – 1.2% in BT vs 0% in dEVT) and asymptomatic ICH (37.7% in BT vs. 29.7% in dEVT; OR: 1.43; 95% CI: 0.77-2.67; p=0.26).

Procedural outcomes for EVT did not differ between patients who received and did not receive bridging therapy, with rates of successful reperfusion mTICI≥2b (BT: 133 (83.1%) vs dEVT: 53 (82.8%), OR: 1.02; 95% CI: 0.47-2.20; p=0.96) and successful reperfusion achieved with first pass of stent retriever (BT: 72 (47.2%) vs dEVT: 28(44.4%), OR: 1.11, 95% CI: 0.58-2.10; p=0.82) similar in both groups. The rates of TICI 2b (BT: 13.1% vs dEVT: 14.1%), TICI 2c (BT: 13.1% vs dEVT: 12.5%) and TICI 3 (BT: 56.9% vs dEVT: 56.2%) were also similar between the two groups.

Final infarct volume (BT: 28.20 (5.47, 77.74) ml vs dEVT: 14.45 (2.55, 70.32) ml, p=0.23) and infarct growth (BT: 12.56 (0.12, 51.6) ml vs dEVT: 6.01 (0.48, 46.67) ml, p=0.47) also were not statistically significantly different between the two groups.

Outcomes Based on Presentation Stroke Severity

In the pre-defined subgroup analyses (Figure 3), patients presenting with baseline NIHSS scores less than 15 points treated with BT had significantly higher rates and likelihood of 90-day functional independence (BT: 83% vs. dEVT: 50%, adjusted OR=4.87, 95%CI: 1.56-15.18, p=0.006) (Table e-2); this association was not evident in patients presenting with baseline NIHSS-scores≥ 15 points (BT: 41.2% vs. dEVT: 38.2%, adjusted OR=1.05, 95%CI: 0.40-2.74, p=0.92; Table e-3). An interaction on the treatment effect according to baseline stroke severity was also uncovered (p for interaction: 0.04). Figure 4A illustrates the higher likelihood of achieving functional independence in BT patients with NIHSS<15 as compared to patients receiving dEVT, which decreases as NIHSS increases.

Similarly, patients treated with BT also demonstrated lower rates of mortality (BT: 0% vs dEVT: 13%, p=0.011) in those with baseline NIHSS score <15. The rates of mortality were numerically lower in patients with NIHSS ≥15 (BT: 17% vs dEVT: 29%; OR: 0.47, 95% CI: 0.19-1.18, p=0.11), but the difference did not reach statistical significance. The rates of sICH and neurological worsening were similar across treatment arms in both NIHSS strata.

A sensitivity analysis using the cutoff of 17 also demonstrated similar results with better functional independence (BT: 78% vs dEVT: 54%, aOR: 2.64, 95% CI=1.04-6.37, p=0.042) and reduced mortality (BT: 1.1% vs dEVT: 13.5%, p=0.009) with NIHSS≤17; and no statistically significant difference in functional independence (BT: 33% vs dEVT: 30%, aOR: 1.07, 95%

CI=0.34-3.37, p=0.91) and mortality (BT: 21.1% vs dEVT: 33.3%, p=0.21) with NIHSS >17. An interaction term between NIHSS strata (≤17 vs >17) and IV thrombolysis on functional independence demonstrated a p-value of 0.008.

Outcomes Based on Presentation Ischemic Core Size

Patients presenting with baseline ischemic core volume of less than 50cc treated with BT had significantly higher rates and likelihood of 90-day functional independence (BT: 61.9% vs. dEVT: 46.4%, adjusted OR=2.10, 95%CI: 1.02-4.33, p=0.044) compared to patients receiving dEVT (Table e-4); this association was not evident in patients presenting with ischemic core volume of ≥ 50cc (BT: 26% vs. dEVT: 25%, adjusted OR=0.41, 95% CI: 0.01-16.02, p=0.64) (Table e-5). However, the interaction term on the treatment effect according to the baseline ischemic core volume was not significant (p for interaction: 0.23). An almost inverse linear association between the baseline ischemic core volume and the likelihood of good functional outcome at 90 days was uncovered for both patients treated with dEVT and BT. Figure 4B illustrates the higher likelihood of achieving functional independence at 90 days in BT patients with small core infarcts as compared to dEVT with average marginal probabilities decreasing in both groups as core infarcts increase. Significantly lower deaths were observed in patients with ischemic core volume of <50cc treated with BT (BT: 5% vs dEVT: 18%, OR:0.24, 95% CI: 0.09-0.68; p=0.004), while mortality rates were similar in patients with ischemic core volume of ≥50cc (BT: 43% vs dEVT: 50%, OR: 0.77, 95% CI: 0.15-3.86; p>0.99). No difference in the rates of symptomatic ICH (BT: 4% vs dEVT: 5%, OR: 0.80, 95% CI: 0.19-3.30, p=0.72) and neurological worsening (BT: 7% vs dEVT: 9%, OR: 0.78, 95% CI: 0.25-2.39; p=0.66) were observed in patients with ischemic core < 50cc. Similarly, in patients with ischemic core ≥50cc,

the rates of neurological worsening (BT: 36% vs dEVT:13%, OR: 4.0, 95% CI: 0.41-38.65, p=0.37) and symptomatic hemorrhage (BT: 17% vs dEVT: 13%, OR: 1.47, 95% CI: 0.14-15.55, p>0.99) did not differ significantly.

Outcomes Based on Presentation Status - Direct versus Transfer

In patients presented directly within 4.5 hours to EVT capable centers (n=150, 29% treated with dEVT), rates of excellent outcomes (BT: 49 (46%) vs dEVT: 19 (44%), OR: 1.06, 95% CI: 0.52-2.17, p=0.86) did not differ between BT and dEVT. Furthermore, there were no significant differences in functional independence (BT: 66 (62%) vs dEVT: 22 (51%), OR=1.54, 95% CI: 0.75-3.14, p=0.24) and lower mortality (BT: 10 (9%) vs dEVT: 8 (19%), OR: 0.45, 95% CI: 0.16-1.23, p=0.11) in patients receiving BT (Table e-6, Figure e-1a). In adjusted multivariable logistic regression analyses, there was no association between BT and 90-day functional independence (adjusted OR=1.84, 95%CI: 0.80-4.23, p=0.15) and 90-day functional improvement (cOR=1.41, 95%CI: 0.76-2.65, p=0.28 and adjusted cOR=1.80, 95%CI:0.91-3.55, p=0.089). We did not observe a significant interaction of BT in patients presenting directly to the EVT-capable center after stratification for baseline stroke severity (p for interaction=0.39) or infarct core volume (p for interaction=0.41).(Figure e-2)

When analyzing patients who were transferred to an EVT capable center within 4.5 hours of last known well (n=76), the rates of excellent outcomes were significantly higher in patients receiving BT (20 (36%) vs dEVT: 2 (10%), OR: 5.43, 95% CI: 1.14-25.76, p=0.024), but with no difference in functional independence (BT: 26 (47%) vs dEVT: 6 (29%), OR: 2.24, 95% CI: 0.76-6.63, p=0.14) and mortality rates (BT: 7 (13%) vs dEVT: 6 (29%), OR: 0.36, 95% CI: 0.11-1.25, p=0.10). However, there was an overall shift towards better functional outcomes with

BT (adj cOR: 4.51 (95% CI: 1.44-14.15), p=0.010) (Table e-7, Figure e-1b). Logistic regression models, however, did not show significant improvement in functional independence with BT in adjusted (aOR: 2.21 (95% CI: 0.50-9.65), p=0.29) analyses. Subgroup analyses demonstrated a significant interaction of BT prior to transfer of patients to the EVT center after stratification for baseline stroke severity (p=0.014).

Discussion

This prespecified subanalysis of the SELECT cohort study[14,15] showed that IV tPA administration prior to EVT in AIS patients with anterior circulation LVOs may be associated with increased likelihood of functional independence and functional improvement at 90 days for, while it is also related to a decrease in the odds of 90-day mortality. We observed no difference in other efficacy or safety outcomes, including the risk of symptomatic or asymptomatic ICH and neurological worsening. Additionally, IVT was not associated with delays in EVT as the median time from hospital arrival to groin puncture were similar in the two groups. Furthermore, we detected an interaction that may modify the beneficial effect of BT compared to dEVT in LVO patients. More specifically, BT appears to be more effective in LVO patients with mild or moderate baseline stroke severity (NIHSS-scores<15 points), who were transfers to EVT centers and thoe with smaller infarct core volume.

Prior observational studies attempted to assess the adjunctive benefit of bridging therapy on endovascular thrombectomy outcomes with mixed results. Some demonstrated better outcomes with IV TPA[18–23], whereas others showed no improvement in functional independence or mortality rates[3,13,24]. However, many of these studies represented single center data[13,18–20,23,24], small sample sizes (<100)[13,18,21,23,24] and/or retrospective study designs[18–23].

Our results are in accordance with a recent systematic review and meta-analysis suggesting that bridging therapy is independently related to a higher likelihood of 3-month good functional outcome without any evidence for safety concerns, including the risk of symptomatic ICH.[25] However, this was not a patient-level meta-analysis with adjustments only limited to the studies level. Since the rate of successful reperfusion with first or multiple passes were similar between the two groups, the beneficial effect of IVT pretreatment on clinical outcomes may be related to improvement in collateral circulation because of dissolution of distal microthrombi, and reduction of the likelihood of infarction in new (previously unaffected territory) complicating EVT.[5,7] Our findings do not support previous results suggesting that pretreatment with IVT is associated with increased risk of sICH and time delays in the onset of EVT.[5]

Our results suggested a modulation of potential IVT effect by stroke severity. These findings may be related to increased baseline NIHSS-scores being indicative of high clot burden, which is in turn associated with reduced drug permeability and low probability of successful recanalization following IVT.[26–28] Recent reports underscored that the length of LVO is inversely associated with the likelihood of tPA-induced recanalization and good functional outcomes in patients receiving IV tPA only.[29,30] However, the relationship of IV thrombolysis effect with stroke severity and clot length is not well established in patients undergoing EVT. This finding has potential implications for in-field triage suggesting that patients with milder stroke might be the best candidates to transport to the nearest IV tPA centers, while those with more severe strokes should be taken directly to EVT capable centers. This is supported by our finding that transferred patients with less severe strokes were more likely to benefit from bridging therapy as compared to those with more severe strokes. The in-field severity-based paramedic triage scales (RACE, LAMS, ACT-FAST etc) have been demonstrated to have reduced sensitivity to identify

patients with LVO, but milder strokes. While not definitive, the data demonstrating benefit for IV tPA in milder strokes and LVO may help balance the need for timely EVT intervention vs bridging with IV tPA administration as well as preventing overtriage to EVT centers using these triage scores.

Our study identified patients with mild to moderate stroke severity (NIHSS <15) at presentation derive significant benefit from bridging therapy, with limited if any benefit was observed in patients with more severe strokes. While our study population excluded minor stroke patients, these were evaluated in a recent study by Seners et al.[31] in a multicenter retrospective cohort study. They identified an adjunctive benefit of thrombectomy in these group of patients over IV thrombolysis. These results suggest a significant role of IV thrombolysis in patients with minor strokes and a large vessel occlusion that may benefit from adjunctive reperfusion therapies. Further randomized data is required to definitively identify the optimal treatment strategies in these patients with minor strokes due to large vessel occlusions.

While functional independence was significantly improved by bridging therapy in patients with smaller baseline ischemic core, the rates were similar in patients who did and did not receive tPA if the baseline ischemic core was larger than 50 cm^3. Our findings are consistent with prior reports assessing the relationship between IV tPA with stroke size and suggesting lower recanalization rates and worse outcomes in patients with lower ASPECTS[32]. A recent post-hoc analysis from the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials (HERMES) collaboration uncovered no effect modification of EVT by baseline ischemic core volume, as quantified by the ASPECTS score[33]. Similarly, another study describing the analysis based on the ischemic core volume measured by perfusion or diffusion weighted imaging found EVT to be effective in patients with upto 125-150 cc of infarct core volume.[34]

While these studies examined the effect of EVT as compared to no EVT, our study examined the potential effect of bridging therapy in patients who received EVT and found it to be effective only in patients with smaller ischemic core.

We used the cutoffs of Ischemic core size of 50 cc and NIHSS of 15 or more for the subgroup analysis. Ischemic core size of 50 cc or more has been one of the standardized definitions, used in SWIFT PRIME[9] and SELECT large core analysis[14]. It has also been the definition for enrollment for ongoing SELECT 2[35] randomized clinical trial assessing the efficacy and safety of EVT in patients with large core strokes. Additionally, since stroke severity remains a vital clinical variable that clinicians rely heavily on while making treatment decisions for acute ischemic strokes, we aimed to identify a cutoff that clinically determines moderately severe versus severe strokes. Within large vessel occlusions, a severity of 15, is a reasonable clinical cutoff for that strata. We further conducted a sensitivity analysis with an NIHSS cutoff of 17, since this cutoff was the median in prior thrombectomy RCTs[36] and was assessed in recent trials assessing bridging therapy[37], with similar findings to the NIHSS cutoff of 15 that we utilized in the SELECT cohort.

The modulation of IV thrombolysis effect on EVT outcomes by stroke severity and initial infarct size may be clinically relevant as several RCTs are assessing bridging therapy versus direct thrombectomy. Since thrombolysis potential treatment effect appear to be driven by patients with milder strokes and smaller to moderate infarcts, our results suggest that such studies should be powered to detect a differential treatment effect based on baseline stroke severity.

Prior data suggested shorter times from stroke onset to thrombectomy in patients receiving direct thrombectomy[24]. Our data did not show IV tPA administration to be associated

with delays in time metrics since both patients presenting directly to EVT-capable center and those who were transferred has similar times from last known well and EVT arrival to the initiation of thrombectomy. Our results are consistent with recent large registry results suggesting no delay with IV tPA in both transfer and direct patients[38].

Finally, we identified no improvement with bridging therapy in the outcomes of patients who presented directly to an EVT capable stroke center. On the other hand, we observed higher likelihood of better outcomes with BT in transferred patients. It should be noted that in half of the patients directly presenting to EVT capable centers, the IV tPA infusion was not complete at the time of the beginning of EVT procedure (Time from tPA bolus to groin puncture <60 min), which may have affected the overall efficacy of IV tPA in those patients. It is plausible that more time afforded for the IV tPA to work in transfer patients may have resulted in better outcomes as compared to transfer patients who did not receive IV tPA. This finding also highlights the importance of swift tPA delivery, irrespective of the setting, as earlier onset to treatment times are associated with faster and more frequent tPA-induced recanalization, with earlier onset-to-recanalization time finally being the key determinant for improved functional recovery.[39] This finding is also important since direct access to EVT in the US is limited to only 1/5th of the population[40]. Thus, until more effective in-field triage algorithms are available, most EVT patients will continue to be seen and treated with tPA at the nearest non-EVT stroke centers first. Randomized trials are ongoing to evaluate the role of direct EVT vs bridging therapy in IV tPA eligible patients[41,42]

Recently, 3 Randomized trials evaluating the role of direct EVT vs bridging therapy in EVT eligible patients who presented directly to EVT capable centers were published. DIRECT-MT[43] and DEVT[44] found non-inferiority of direct EVT as compared to bridging therapy with IV tPA,

whereas SKIP[37] failed to achieve non-inferiority of dEVT approach. All three trials set up generous non-inferiority margins: of 20% effect size in DIRECT-MT[43]; 26% effect size in SKIP[37] and 10% absolute clinical effect (43% vs 33% functional independence) in DEVT trial[44]. In DIRECT-MT, 27% of the eligible study population declined to participate and 10% of the study population did not receive thrombectomy. Furthermore, in line with our findings, the trial reported 87% of the enrolled patients not completing their IV tPA infusion before the start of EVT. SKIP and DEVT did not report the proportions, but specified beginning of EVT as soon as possible, prior to completion of IV thrombolysis. In the SKIP trial, the times from randomization to the initiation of thrombectomy was 20 and 22 minutes in the EVT alone and bridging groups respectively, while randomization to IV tPA time was at a mean of 14 minutes, leaving a mean of 8 minutes from the initiation of IV tPA to groin puncture. These represent very short times which are inadeqaute for IV thrombolysis completion which plausibly reduce the potential benefit with bridging therapy. The SKIP trial also utilized a lower dose thrombolysis regimen (0.6 mg/kg instead of the standard 0.9 mg/kg dose of IV alteplase). These considerations have been described in detail in a recent commentary on DIRECT-MT & SKIP trials.[45]

The most common scenario in practice is for patients to present initially to the closest center with capability to deliver thrombolysis, and then transfer to an EVT center, allowing the Alteplase time to work. All aforementioned trials included only patients who presented directly to EVT centers, thus excluding patients who are most likely to benefit from the bridging therapy. In contrast, 34% of our study cohort includes patients transferred to EVT capable centers and our finding that “drip and ship” patients were more likely to benefit from bridging therapy may be due to the fact they had time for thrombolysis to deliver its potential effect. These trials also

lacked evaluation using advanced perfusion imaging. Additionally, in SELECT cohort we evaluated perfusion imaging parameters, which was not available in the aforementioned trials, and found that in patients with large ischemic core (≥50 ml), bridging therapy was not associated with improved functional outcomes.Our results provide an insight on the potential subgroups of patients who may benefit from IV thrombolysis prior to EVT. Specifically, we found that those with mild to moderate strokes and those small to moderate infarct size are more likely to have adjunctive benefit from bridging therapy. These findings highlight that trials assessing bridging therapy potential benefit may only show significance if they were enriched with selected subpopulations. Furthermore, our results supported that the adjunctive benefit of IV tPA are more likely in transferred patients as compared to those presenting directly to a thrombectomy capable center. This finding is particularly relevant since the decision to bridge or not bridge with tPA is often made in the non-EVT center before it is even certain that the patient will be receiving EVT. To accurately assess the true advantage of bridging therapy versus direct thrombectomy will require a randomized intention to treat analysis of BT vs no BT in LVO patients who meet both tPA and EVT treatment criteria presenting to both non-EVT and EVT hospitals.

Our analysis based on clot location did not show significant improvement in functional independence with bridging therapy, nor we found a significant interaction of bridging therapy with clot location. However, our analysis may have been underpowered because of the small number of patients with M2 occlusions (n=49) in our dataset. This does not preclude more distal locations to be potential targets for IV thrombolysis as we report the highest unadjusted improvement in functional independence of 24% with bridging therapy in patients with M2 occlusion.

Our study has several limitations. Patients were not randomized to BT vs dEVT, and there is a risk for potential unmeasured confounders that cannot be incorporated in multivariable models including a risk for selection bias as all treatment decisions were made by the treating physicians at the participating institutions. Only one patient who did not receive IV tPA was actually eligible for IV tPA, which may create potential selection bias as compared to RCTs evaluating IV tPA adjunctive benefit where only tPA eligible patients are randomized. The two groups, however, had largely similar baseline characteristics. Another limitation is the relatively small sample size of some of our subgroups resulting in low statistical power to uncover significant differences. Especially for subgroups analyses complex associations can confound analysis of clinical outcomes. Finally, while SELECT adopted an intention-to-treat paradigm for enrolled patients, there is a possibility that patients achieving successful recanalization after IV-tPA administration and before the initiation of EVT were excluded from enrollment in SELECT. As it has been previously estimated that approximately 1 out of 10 AIS patients with LVO achieve successful reperfusion after tPA infusion that obviates the need for further endovascular reperfusion therapies,[34] this additional advantage of tPA pretreatment becomes very relevant, particularly for patients transferred from non-EVT to an EVT-capable center in order to receive thrombectomy. With EXTEND-IA TNK demonstrating improved recanalization rates while using IV tenecteplase, the effect observed can even be larger, especially in countries which have deferred to the Tenecteplase based management strategies for acute strokes.[46] In addition, a recent meta-analysis of available RCTs reported that patients with confirmed LVO receiving Tenecteplase had higher odds of mRS-scores 0 to 2 (OR=2.06 [95% CI: 1.15-3.69]), successful recanalization (OR=3.05 [95% CI: 1.73-5.40]), and functional improvement defined as 1-point

decrease across all mRS grades (common OR=1.84 [95% CI: 1.18-2.87]) at 3 months compared with patients with confirmed LVO receiving alteplase[47].

In conclusion, we found that bridging therapy may be associated with more favorable 90-day functional outcomes, without safety concerns in AIS patients with anterior circulation LVO specially in patients with milder strokes, smaller initial infarcts and those who were "dripped and shipped". Ongoing randomized-controlled clinical trials comparing dEVT to BT in tPA-eligible AIS patients with LVO will provide more definitive data. Our findings shed light on how those studies might be optimally designed and interpreted. For now, it is appropriate to follow current guidelines that recommend IVT pretreatment for all eligible patients.

Appendix 1: Authors

Name	Location	Contribution
Amrou Sarraj, MD	Houston, TX, USA	Concept and Design, Acquisition, analysis, or interpretation of data, Drafting of the manuscript, Administrative, technical, or material support, Supervision
James Grotta, MD	Houston, TX, USA	Critical revision of the manuscript
Gregory W. Albers, MD	Stanford, CA, USA	Acquisition, analysis, or interpretation of data, Critical revision of the manuscript
Ameer E. Hassan, DO	Harlingen, TX, USA	Acquisition, analysis, or interpretation of data, Critical revision of the manuscript
Spiros Blackburn, MD	Houston, TX, USA	Acquisition, analysis, or interpretation of data, Critical revision of the manuscript
Arthur L. Day, MD	Houston, TX, USA	Critical revision of the manuscript
Clark Sitton, MD	Houston, TX, USA	Acquisition, analysis, or interpretation of data, Critical revision of the manuscript
Michael Abraham, MD	Kansas City, KS, USA	Acquisition, analysis, or interpretation of data, Critical revision of the manuscript
Chunyan Cai, PhD	Houston, TX, USA	Statistical Analysis, Critical revision of the manuscript
Mark Dannenbaum, MD	Houston, TX, USA	Acquisition, analysis, or interpretation of data, Critical revision of the manuscript
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Sheryl Martin-Schild, MD	New Orleans, LA, USA	Critical revision of the manuscript
Sean Savitz, MD	Houston, TX, USA	Critical revision of the manuscript
Georgios Tsivgoulis, MD	Athens, Greece	Drafting and critical revision of the manuscript

Appendix 2: Coinvestigators

Name	Location	Role	Contribution
Peng R. Chen	The University of Texas Health Science Center at Houston, Hosuton TX, USA	Site Co-investigator	enrollment at local site
Diogo Haussen	Emroy University, Atlanta GA, USA	Site Principal-investigator	Overseeing execution of the study at local site, enrollment at local site
Raul G Nogueira	Emroy University, Atlanta GA, USA	Site Principal-investigator	Overseeing execution of the study at local site, enrollment at local site
Michael Frankel	Emroy University, Atlanta GA, USA	Site sub-investigator	enrollment at local site
Indrani Acosta	Florida University, Gainesville FL, USA	Site Principal-investigator	Overseeing execution of the study at local site, enrollment at local site
Evan Allen	Florida University, Gainesville FL, USA	Site sub-investigator	enrollment at local site
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Randall Edgell	Saint Louis University, St Louis MO, USA	Site Principal-investigator	Overseeing execution of the study at local site, enrollment at local site
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Appendix 2 Coinvestigators-http://links.lww.com/WNL/B383

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Figure Legends

Figure 1. Flow diagram of SELECT participants included in the analysis

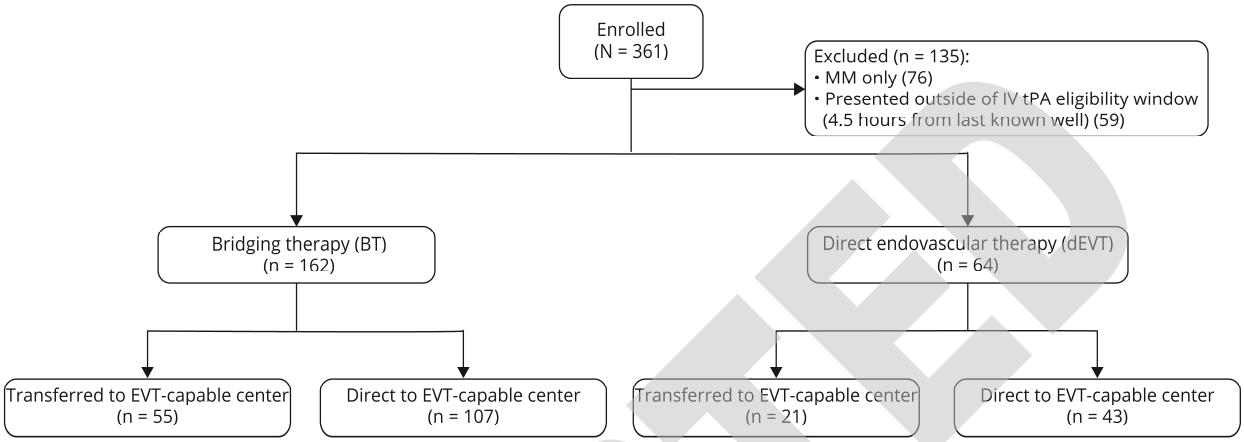


Figure 2. Distribution of the modified Rankin Scale scores at 90 days according to the history of intravenous tissue plasminogen activator pretreatment in patients presenting within 4.5 hours from stroke onset. The distribution of mRS-scores between the two groups was compared using Cochran Mantel Haenszel test, with patients treated with bridging therapy demonstrating significantly better functional outcomes at 90-day follow-up. (p=0.046).

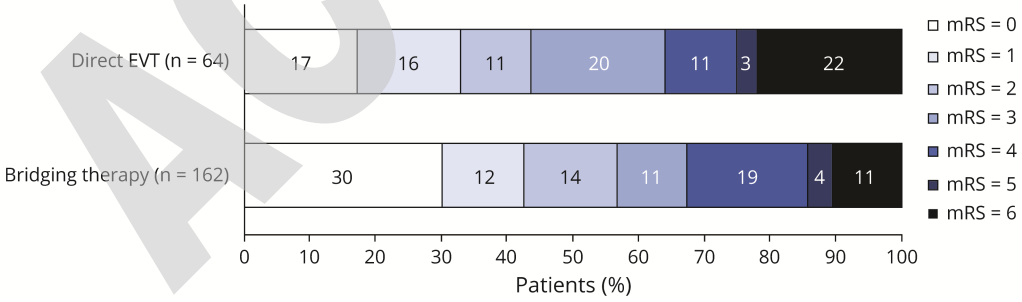


Figure 3 Subgroup analyses on the probability of functional independence (mRS 0-2) at 90 days according to the history of intravenous tissue plasminogen activator pretreatment. Bridging therapy was associated with a significantly higher odds of functional independence in patients with NIHSS <15 and ischemic core <50cc, whereas no significant difference in functional independence was observed in patients with NIHSS ≥15 and ischemic core≥50cc. The effect of tPA was more pronounced in patients who were transferred to the EVT capable center as compared to patients who presented directly.

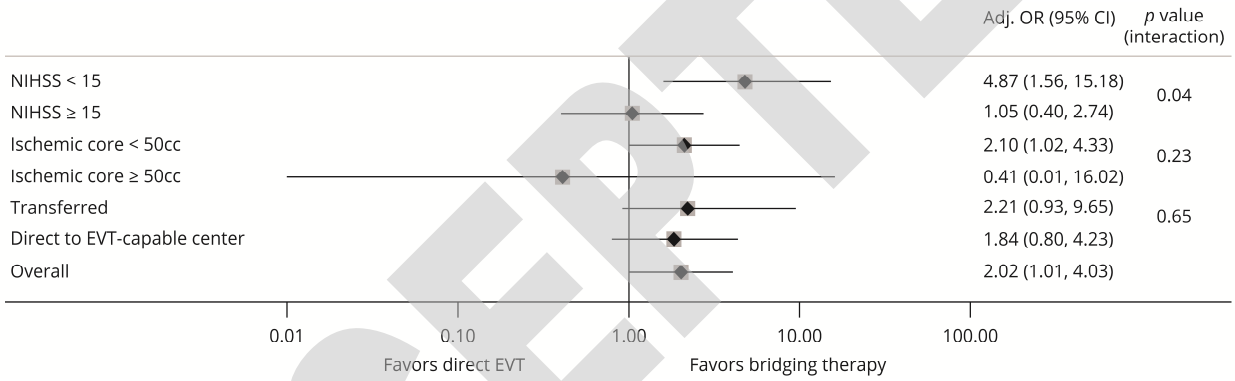
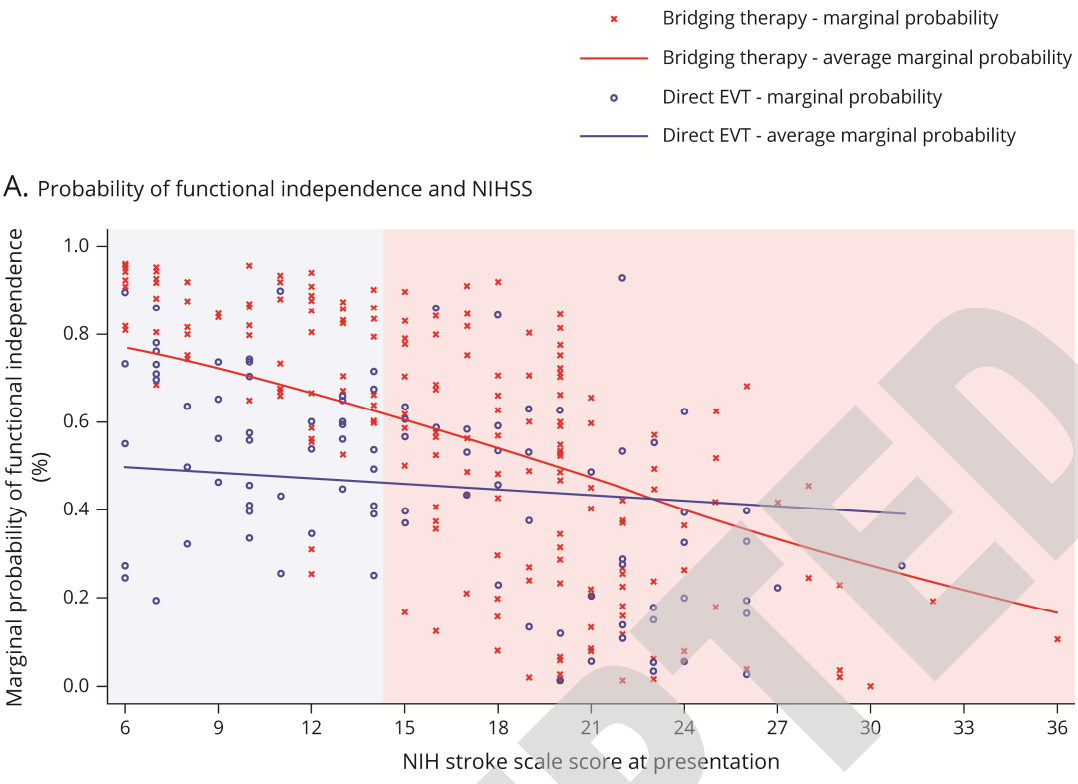
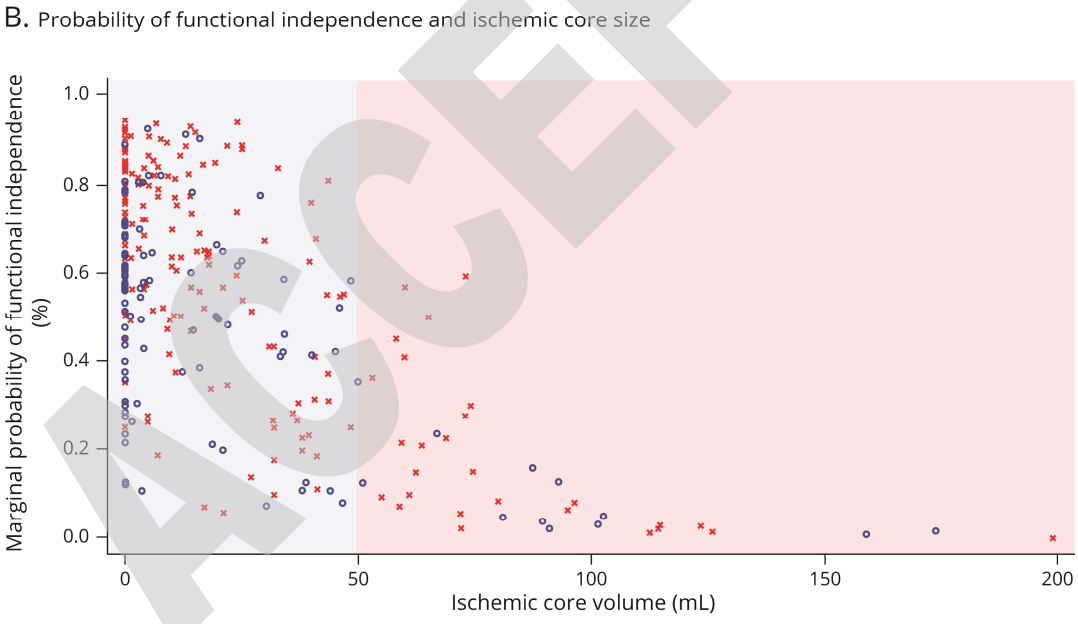


Figure 4. A) Graphical representation on the association of the marginal probability for functional independence (mRS 0-2) according to NIH Stroke Scale score at presentation, stratified by the history of intravenous alteplase administration prior to endovascular thrombectomy. ***In patients with NIHSS<15 (indicated by the blue area), the average marginal probabilities are significantly higher in patients receiving bridging therapy; whereas in patients with NIHSS≥15 (indicated by the red area), the difference between average marginal probabilities decreases and then inverts so that the average marginal probabilities for direct EVT is higher than for bridging therapy.***

B) Graphical representation on the association of the marginal probability for functional independence (mRS 0-2) according to baseline ischemic core volume, stratified by the history of

intravenous alteplase administration prior to endovascular thrombectomy. ***In patients with ischemic core <50 ml (indicated by the blue area), the average marginal probabilities are significantly higher in patients receiving bridging therapy; whereas in patients with ischemic core ≥50 ml (indicated by the red area), the difference between average marginal probabilities decreases and marginal probabilities in both groups become almost similar as the ischemic core size increases.***





TABLES

Table 1. Baseline characteristics of included patients presenting within 4.5 hours

	No IV-tPA (n=64)	**Received IV-tPA (n=162)**	**p-value**
Age, median (IQR)	73.5 (64, 80.5)	65 (54, 75)	0.001[a]
Males, n (%)	34 (53.1%)	87 (53.7%)	0.94[b]
Serum Glucose (mg/dL), median (IQR)	125.5 (105.5, 161.5)	122 (106, 148)	0.45[a]
Hypertension, n (%)	53 (82.8%)	117 (72.7%)	0.11[b]
Congestive Heart Failure, n (%)	17 (27.0%)	11 (6.8%)	<0.001[b]
Coronary Artery Disease, n (%)	24 (38.1%)	24 (15.1%)	<0.001[b]
Atrial Fibrillation, n (%)	32 (50.8%)	47 (29.0%)	0.002[b]
Diabetes Mellitus, n (%)	24 (37.5%)	38 (23.5%)	0.033[b]
Prior Transient Ischemic Attack (%)	5 (8.1%)	7 (4.3%)	0.27[b]
Prior Stroke, n (%)	11 (17.5%)	17 (10.6%)	0.16[b]
Current Smoking, n (%)	6 (9.8%)	25 (16.2%)	0.23[b]
Past Smoking, n (%)	13 (20.6%)	32 (21.1%)	0.95[b]
Clot location, n (%)	ICA: 9 (14.1%)	32 (19.8%)	0.27[b]
	MCA-M1: 37 (57.8%)	99 (61.1%)	
	MCA-M2: 18 (28.1%)	31 (19.1%)	
Transfer to study site, n (%)	21 (32.8%)	55 (34.0%)	0.87[b]
Time from Last known well to arrival to EVT capable center (Hours), median (IQR)	1.63 (0.75, 2.88)	1.50 (0.85, 2.85)	0.99[a]
Time from Last Known well to IV tPA Bolus (Hours), median (IQR)		1.60 (1.24 – 2.33)	
NIH Stroke Scale score, median (IQR)	15 (10, 22)	17 (12, 21)	0.53[a]
Time from arrival to EVT capable center to CT acquisition (minutes), median (IQR)	10 (4.5, 21)	10 (4, 17)	0.52[a]
Time from arrival to EVT capable center to CTP acquisition (minutes), median (IQR)	19 (11.5, 36)	18.5 (10, 28)	0.31[a]
ASPECTS on Baseline CT, median (IQR)	9 (7.5, 10)	8 (6, 9)	0.007[a]

	No IV-tPA (n=64)	**Received IV-tPA (n=162)**	**p-value**
Ischemic Core Volume, median (IQR)	3.9 (0, 32.15)	11.4 (1.5, 37)	0.042[a]
Time from Last Known Well to Procedure (Hours), median (IQR)	3.28 (2.12, 4.45)	3.35 (2.47, 4.38)	0.45[a]
General Anesthesia	24 (37.5%)	77 (47.8%)	0.16[b]

IV-tPA: intravenous tissue plasminogen activator, IQR: interquartile range, ICA: internal carotid artery, MCA: middle cerebral artery, NIH: National Institutes of Health, CT: computed tomography, CTP: CT perfusion, ASPECTS: Alberta Stroke Program Early CT Score.

[a] Assessed using Mann-Whitney U Test

[b] Assessed using Pearson's $\chi 2$ Test

[c] Assessed using Fisher's Exact Test

Table 2. Time metrics in patients transferred to EVT capable center and patients presenting directly to EVT capable center within 4.5 hours of last known well

Time metrics for patients transferred to EVT capable center	**Received IV-tPA**	**No IV-tPA**
Time from Last Known Well to Arrival to EVT Capable Center (minutes), median (IQR)	182 (151, 225)	169 (145, 189)
Time from Last Known Well to IV tPA Bolus (minutes), median (IQR)	86 (67, 133)	N/A
Time from IV tPA Bolus to Arrival to EVT Capable Center (minutes), median (IQR)	75 (56, 108)	N/A
Time from Arrival to CTP Acquisition (minutes), median (IQR)	14 (7, 23)	18 (14, 30)
Time from CTP Acquisition to Procedure (minutes), median (IQR)	62.5 (47, 93)	46 (36, 69)
Time from Groin Puncture to Successful Reperfusion/End of Procedure, median (IQR)	40 (30, 59)	32 (15, 60)
Time metrics for patients presenting directly to EVT capable center	**Received IV-tPA**	**No IV-tPA**
Time from Last Known Well to Arrival to EVT Capable Center (minutes), median (IQR)	63 (40, 98)	58 (38, 129)
Time from Arrival to CTP Acquisition (minutes), median (IQR)	20 (13, 33)	19 (9, 40)
Time from CTP Acquisition to IV tPA Bolus (minutes), median (IQR)	14 (4, 28)	N/A
Time from IV tPA Bolus to Procedure (minutes), median (IQR)	57 (39, 81)	N/A
Time from CTP Acquisition to Procedure (minutes), median (IQR)	70 (51, 94)	65 (50, 77)
Time from Groin Puncture to Successful Reperfusion/End of Procedure, median (IQR)	35 (23, 59)	35 (25, 62)

Table 3. Outcomes of included patients presenting within 4.5 hours

	No IV-tPA (n=64)	**Received IV-tPA (n=162)**	**p-value**
90-day Functional Independence (mRS 0-2), n (%)	28 (43.8%)	92 (56.8%)	0.077[b]
90-day Excellent Functional Outcome (mRS 0-1), n (%)	21 (32.8%)	69 (42.6%)	0.18[b]
90-day Mortality, n (%)	14 (21.9%)	17 (10.5%)	0.025[b]
Symptomatic ICH, n (%) – ECASS II	4 (6.3%)	10 (6.2%)	>0.99[c]
Hemorrhagic Transformation type I	1 (1.6%)	5 (3.1%)	
Hemorrhagic Transformation type II	1 (1.6%)	3 (1.9%)	
Parenchymal Hemorrhage type I	2 (3.1%)	0 (0%)	
Parenchymal Hemorrhage type II	0 (0%)	2 (1.2%)	
Symptomatic ICH, n (%) – SITS MOST	0 (0%)	2 (1.2%)	>0.99[c]
Asymptomatic ICH, n (%)	19 (29.7%)	61 (37.7%)	0.26[b]
Neurological Worsening, n (%)	6 (9.7%)	18 (11.4%)	0.71[b]
Successful Reperfusion (mTICI ≥ 2b), n (%)	53 (82.8%)	133 (83.1%)	0.96[b]
Successful Reperfusion with single pass, n (%)	28 (44.4%)	72 (46.2%)	0.82[b]
Reperfusion status			0.27[c]
0	1 (1.5%)	5 (3.1%)	
1	4 (6.3%)	0 (0%)	
2a	6 (9.4%)	22 (13.8%)	
2b	9 (14.1%)	21 (13.1%)	
2c	8 (12.5%)	21 (13.1%)	
3	36 (56.3%)	91 (56.9%)	
Final Infarct Volume (cc), median (IQR)	14.45 (2.55, 70.32)	28.20 (5.47, 77.74)	0.23[a]
Infarct Growth (cc), median (IQR)	6.01 (0.48, 46.67)	12.56 (0.12, 51.6)	0.47[a]

mTICI: modified Thrombolysis in Cerebral Ischemia, IV: intravenous, tPA: tissue plasminogen activator, mRS: modified Rankin Scale, ICH: intracranial hemorrhage, DWI: diffusion weighted imaging, IQR: interquartile range

[a] Assessed using Mann-Whitney U Test

[b] Assessed using Pearson's $\chi 2$ Test

[c] Assessed using Fisher's Exact Test