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Title:

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Date:

2019-03-01

Citation:

Maingard, J., Shvarts, Y., Motyer, R., Thijs, V., Brennan, P., O'Hare, A., Looby, S., Thornton, J., Hirsch, J. A., Barras, C. D., Chandra, R. V., Brooks, M., Asadi, H. & Kok, H. K. (2019). Outcomes of endovascular thrombectomy with and without bridging thrombolysis for acute large vessel occlusion ischaemic stroke. *Internal Medicine Journal*, 49 (3), pp.345-351. <https://doi.org/10.1111/imj.14069>.

Persistent Link:

<https://hdl.handle.net/11343/285533>

**OUTCOMES OF ENDOVASCULAR THROMBECTOMY WITH AND
WITHOUT BRIDGING THROMBOLYSIS FOR ACUTE LARGE VESSEL
OCCLUSION ISCHAEMIC STROKE**

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This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: [10.1111/imj.14069](https://doi.org/10.1111/imj.14069)

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Short Title:

Thrombectomy outcomes with and without thrombolysis in acute stroke

Keywords:

Interventional neuroradiology, endovascular, stroke, large vessel occlusion, thrombectomy, thrombolysis, reperfusion, IV tPA

Manuscript Word Count: 1987 (excluding abstract, tables, legends and references)

Abstract word count: 243

Introduction

Endovascular thrombectomy (EVT) is now considered the standard of care in the management of acute ischaemic stroke (AIS) secondary to large vessel occlusion (LVO) in the anterior circulation. Evidence stems from large randomised controlled trials, including large pooled analyses demonstrating improved functional

independence using combined EVT and bridging thrombolysis with intravenous (IV) tissue plasminogen activator (tPA) over thrombolysis alone¹⁻⁸. While the benefit of thrombolysis within 4.5 hours of AIS has been firmly established⁹⁻¹³, studies suggest limitations in its ability to achieve acceptable reperfusion rates in LVO cases.¹⁴⁻¹⁸ Given these potential limitations, uncertainties remain as to the degree of benefit obtained with bridging thrombolysis when used in conjunction with EVT for LVO AIS or whether this practice confers additional risk.

The administration of thrombolysis not only presents a significant cost to health care systems^{19, 20}, but may impact on delays in time from imaging to groin puncture in comprehensive stroke centres, or time from imaging to patient transfer to these centres.^{19, 21-23} These potential delays are of concern given the time dependent effect on EVT outcomes.²⁴ Thrombolysis is also associated with small but theoretical risks including anaphylaxis, early recurrent ischaemic stroke and coagulopathy, the latter potentially resulting in systemic or intracranial haemorrhage.^{19, 22, 25}

Multiple single-centre studies have analysed AIS patient outcomes for EVT without thrombolysis, reporting comparable functional and safety outcomes when compared to EVT in addition to thrombolysis.^{20, 22, 23, 26-28} However, a recent meta-analysis of the original randomised controlled trials showed conflicting evidence from these single-centre studies and reported lower rates of 90-day severe functional impairment or death as indicated by a modified Rankin Scale (mRS) of 5-6 and a trend towards

improved 90-day functional outcome in patients receiving thrombolysis alongside EVT.²⁹ The aim of this study was to investigate the clinical outcomes in AIS patients undergoing EVT with or without bridging thrombolysis with IV alteplase.

Methods

We performed a retrospective review of a prospectively collected database over a 6-year period between June 2010–July 2016 from 24 hospitals in a large catchment area in the Republic of Ireland. A ‘drip and ship’ model of care was utilised with hospital distances to the primary stroke centre (with 24/7 endovascular capability) ranging from 5.4 to 233 kilometres. Baseline patient demographics, clinical characteristics, imaging findings and clinical outcomes were analysed. Patients were eligible for inclusion provided all such details were available for analysis. Clinical outcome was assessed based on the mRS, with a favourable 90-day functional outcome defined as a score of 0-2 indicating functional independence. Successful reperfusion was defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of e2b. Symptomatic intracranial haemorrhage (sICH) was defined as intracranial haemorrhage associated with deterioration from baseline National Institutes of Health Stroke Scale (NIHSS) by e4 points. Patients were divided into two groups based on either having received thrombolysis or proceeding to EVT directly (no thrombolysis). Some patients included in this retrospective review were also included in the interventional arm of the ESCAPE trial (n=17).³

Patients with AIS were selected for EVT using the same selection criteria as those utilised by the ESCAPE trial.³ Thus, all patients were evaluated with an initial unenhanced CT brain, allowing for assessment of the Alberta Stroke Program Early CT Score (ASPECTS).³⁰ Next, multiphase CT angiography was performed and provides assessment of intracranial arterial occlusion(s) and grading of the leptomeningeal collateral circulation. All patients eligible for thrombolysis received IV alteplase, however failure to receive thrombolysis did not preclude patients from EVT. All patients received standard of care for a LVO AIS at their respective centres, and intervention with EVT was instigated based on eligibility criteria previously described³. Patients with a contraindication for thrombolysis who were eligible for EVT received EVT alone.

Statistical analyses were performed with SPSS 23 (IBM, Armonk, NY). Continuous data were expressed as mean±standard deviation (SD) for parametric means or median and interquartile range (IQR) otherwise. Odds ratios were expressed with a 95% confidence interval. Continuous variables were analysed with one-way analysis of variance (ANOVA) or Mann-Whitney U tests for parametric and nonparametric data, respectively. Categorical data was analysed with Pearson Chi-Square or Fisher's exact tests. Univariate and multivariate logistic regression analyses were used to identify predictors of clinical outcome that were significantly influenced by the administration of bridging thrombolysis and both raw and adjusted odds ratios were calculated. These variables included age, sex, hypertension, hyperlipidaemia,

ischemic heart disease, diabetes, atrial fibrillation, previous stroke, NIHSS, ASPECTS, collateral grade, general anaesthesia during EVT, number of passes, successful reperfusion mTICI e2b, sICH, interval from symptom onset to groin puncture and time to reperfusion. Changes in functional outcome were analysed in XLSTAT (Addinsoft, NY) using the Cochran–Mantel–Haenszel test (CMHT). Statistical significance was defined as $p < 0.05$.

Results

Baseline characteristics

A total of 355 patients who underwent EVT for AIS were included in the study. As this was a prospectively collected database no patients were excluded from analysis. The mean age was 67 ± 14 years and 55% of the cohort were male. Bridging thrombolysis was administered in 210 patients (59%) prior to EVT and the remaining 145 patients (41%), ineligible for thrombolysis either due to delayed presentation or other clinical contraindications, underwent EVT directly. A ‘drip and ship’ model of care was utilised in 164 patients (46%). Both groups were comparable in terms of stroke severity with a mean NIHSS score of 17 at presentation as well as similar ASPECTS on unenhanced CT at presentation (Table 1). The vast majority of EVT procedures were performed using local anaesthesia or light sedoanalgesia only (97%).

Outcomes

Successful reperfusion (mTICI e2b) was achieved in 80% (n=284) of patients with a trend towards greater success in the thrombolysis group (Table 2). The reperfusion rate was higher in the group receiving IV tPA (unadjusted OR 2.2, 95% CI: 1.29-3.73, $p=0.004$) although this effect was attenuated when all variables were considered (adjusted OR [AOR] 1.22, 95% CI: 0.60-2.5, $p=0.580$). Patients who received thrombolysis also had significantly faster times from symptom onset-to-groin puncture (257 versus 342 minutes, $p<0.001$) and onset-to-first reperfusion (297 versus 385 minutes, $p<0.001$). However, the time from groin puncture to first reperfusion did not differ significantly between groups. Fewer thrombectomy passes (2 versus 3, $p=0.012$) were required to achieve successful reperfusion in the thrombolysis group.

Tables 1 and 2 summarise the clinical outcomes for patients who received bridging thrombolysis. There was significantly better functional independence at 90-days (adjusted OR [AOR] 2.17, 95% CI:1.06-4.44, $p=0.033$) in the thrombolysis group. There was a lower 90-day mortality in the thrombolysis group after adjusting for confounding factors (AOR 0.79, 95% CI: 0.36-1.74, $p=0.551$). There were no significant differences in terms of collateral grade, major complication or sICH between groups. Overall, the distribution in 90-day mRS scores showed better functional independence in the thrombolysis group ($p=0.571$, Cochran–Mantel–Haenszel test, Figure 1).

Multivariate regression analysis, adjusting for all baseline clinical and technical parameters including NIHSS and ASPECTS, demonstrated that successful reperfusion was the strongest predictor of favourable 90-day clinical outcome (AOR 10.4, 95% CI:3.6-29.7, $p<0.001$). Other factors associated with a good functional outcome were younger age (AOR 0.93, 95% CI:0.90-0.96, $p<0.001$), lesser stroke severity (AOR 0.89, 95% CI:0.84-0.96, $p=0.001$) and fewer thrombectomy passes (AOR 0.85, 95% CI:0.75-0.97, $p=0.013$). The 90-day mortality was increased in older patients (AOR 1.04, 95% CI:1.00-1.07, $p=0.048$) and those who developed sICH (AOR 3.94, 95% CI:1.16-13.5, $p=0.028$). Baseline stroke severity, ASPECTS and collateral circulation grades were not predictive of 90-day outcomes.

Discussion

This study has shown that patients with AIS who received bridging thrombolysis prior to EVT had significantly reduced mortality and improved 90-day functional independence without additional major complications or sICH.

Multiple single-centre studies have compared outcomes in patients undergoing EVT in addition to IV thrombolysis versus EVT alone, reporting comparable reperfusion rates, functional outcomes, safety parameters and mortality rates between both groups.^{20, 22, 23, 26-28} Broeg-Morvay et al. also performed multivariate matching analysis in their study, demonstrating lower rates of sICH and lower mortality in patients treated with EVT alone.²² Interestingly, results from these single-centre

studies differ from a meta-analysis evaluating outcomes for EVT with bridging thrombolysis versus EVT alone.²⁹ In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines, seven of the major EVT randomised controlled trials were deemed eligible for inclusion in this meta-analysis: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE and PISTE.^{2-6, 8, 31} While the meta-analysis results displayed substantial heterogeneity, patients who received IV thrombolysis in addition to EVT had a significantly lower rate of severe disability or death (mRS 5-6) and a non-significant trend towards better 90-day functional independence (mRS 0-2), similar to this study. These findings suggest that EVT should be used in parallel with IV thrombolysis, where possible.

However, this meta-analysis acknowledged several limitations, including the low sample size in the EVT monotherapy group and that the trials were not designed to assess the effect of IV thrombolysis in conjunction with EVT. Failure to randomly assign patients to IV thrombolysis versus placebo introduces variance in baseline patient characteristics and in times to groin puncture, confounding results with selection bias. This failure to randomise the thrombolysis arm may also be considered a limitation in several single-centre studies including ours and those by Leker et al., Rai et al., Weber et al. and Wee et al., in which IV thrombolysis was administered to all presenting patients unless contraindicated.^{20, 26-28}

A similar 2017 meta-analysis evaluated for variation in outcomes between groups

receiving endovascular clot retrieval with IV thrombolysis and endovascular treatment alone. Following PRISMA guidelines 13 studies were included including data from 7 randomised controlled trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND IA, SWIFT and STAR). Analysis revealed results in accordance with other meta-analyses; IV thrombolysis combined with EVT had significantly improved 90-day functional independence (mRS 0-2; OR 1.27, 95% CI 1.05-1.55, $p=0.02$) and significantly lower rates of mortality compared to EVT alone. These findings further support that IV thrombolysis, where not contraindicated, should be used together with EVT.³²

Other analyses have reached different conclusions. Subgroup analysis by the HERMES collaboration suggests benefit of EVT for patients presenting with LVO AIS, who were not treated with IV thrombolysis.⁷ In their pooled analysis of the SWIFT and STAR studies, Coutinho et al, did not find significant benefit in functional outcomes with bridging IV thrombolysis. However, interestingly, even after adjusting for confounders such as international normalised ratio (INR) and antiplatelet use, they found lower rates of sICH (adjusted OR 0.03, 95% CI 0.00-1.28) in those receiving bridging IV tPA,³³ IV thrombolysis can have significant implications on time to intervention, health care expenditure and patient safety. However, thrombolysed patients may benefit from treatment of distal emboli, a degree of reperfusion in cases of failed EVT and partial lysis of the thrombus

reducing the number of stent-retriever passes and procedure times.¹⁹

Our results showed benefit of bridging thrombolysis prior to EVT for patients with AIS, with significantly reduced mortality and improved 90-day functional independence without additional major complications or sICH. There was a borderline trend towards better reperfusion rates in the thrombolysis group. These results can be partially explained through the effects of tPA on clot lysis in aiding cerebral reperfusion. It has been shown that tissue plasminogen factors play a role in the clotting cascade as fibrinolytics via the conversion of plasminogen into plasmin. Thus, it would seem that the use of IV thrombolysis before EVT acts to lyse the offending clot to some extent, if not completely.³⁴ IV thrombolysis may result in clot lysis prior to EVT, or partially lyse the clot to permit some reperfusion before EVT is conducted, resulting in reduced time of cerebral hypoxia and mitigating irreversible neuronal damage. Additionally, partial clot lysis may allow for more successful reperfusion with EVT as suggested by the need for fewer thrombectomy passes to achieve reperfusion in our cohort.

Our findings contrast with several published studies which suggest that IV thrombolysis can be problematic in stroke treatment, potentially resulting in higher rates of sICH and lower rates of successful reperfusion compared with cohorts treated with EVT alone.^{28,35} This may be attributed to the fact that many of these were smaller studies and were therefore underpowered to accurately evaluate these

parameters. A larger study with higher power demonstrated an increase in sICH at 24-36 hours with the use of thrombolysis and EVT, but showed no differences in functional independence or mortality at 90-days.³⁶

The overall onset-to-groin puncture as well as onset-to-reperfusion times were longer in the EVT only (no thrombolysis) group of our cohort. This may be due to initial presentation outside the 4.5-hour time-window rendering patients in this group ineligible for thrombolysis. Nevertheless, there was no difference in groin puncture to first reperfusion time between groups. Successful reperfusion remained the strongest predictor of functional independence in our series.

There are several limitations to our study. Several satellite centres were involved in a ‘drip and ship’ model of care, making it difficult to account for variance in regional clinical practice and decisions on eligibility for IV thrombolysis. Being a retrospective study, the two treatment arms were not randomly allocated. Data was maintained on a central database at the time of presentation and was analysed retrospectively. Furthermore, unmeasured patient confounders such as anticoagulation, that contraindicate IV thrombolysis and indicate a population predisposed to poorer outcomes have the potential to impact results.

Conclusion

Our study demonstrates better 90-day functional independence in patients who

received bridging IV thrombolysis prior to EVT versus direct EVT for the treatment of LVO AIS without additional risk of complications or sICH. These findings are similar to those reported previously in a meta-analysis and support the need for a prospective, randomised controlled trial to definitively address the role of IV thrombolysis in the era of EVT.

Sources of Funding: None

Disclosures: Dr. John Thornton is on the scientific advisory board for Neuravi, Ireland. Personal fees. Prof. Vincent Thijs has received consulting fees for Medtronic. Personal fees.

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Abstract

Introduction

Endovascular thrombectomy (EVT) for management of large vessel occlusion (LVO) acute ischaemic stroke (AIS) is now current best practice. The aim of this study was to determine if bridging intravenous alteplase therapy confers any clinical benefit.

Methods

A retrospective study of patients treated with EVT for LVO was performed. Outcomes were compared between patients receiving thrombolysis and EVT with EVT alone. Primary endpoints were reperfusion rate, 90-day functional outcome and mortality using the modified Rankin scale (mRS) and symptomatic intracranial haemorrhage (sICH).

Results

A total of 355 patients who underwent EVT were included: 210 with thrombolysis (59%) and 145 without (41%). The reperfusion rate was higher in the group receiving IV tPA (unadjusted OR 2.2, 95% CI: 1.29-3.73, $p=0.004$) although this effect was attenuated when all variables were considered (adjusted OR [AOR] 1.22, 95% CI: 0.60-2.5, $p=0.580$). The percentage achieving functional independence (mRS 0-2) at 90-days was higher in patients who received bridging IV tPA (AOR 2.17, 95% CI: 1.06-4.44, $p=0.033$). There was no significant difference in major complications including sICH (AOR 1.4, 95% CI: 0.51-3.83, $p=0.512$). There was lower 90-day mortality in the bridging IV tPA group (AOR 0.79, 95% CI: 0.36-1.74, $p=0.551$).

Fewer thrombectomy passes (2 versus 3, $p=0.012$) were required to achieve successful reperfusion in the IV tPA group. Successful reperfusion (mTICI e2b) was the strongest predictor for 90-day functional independence (AOR 10.4, 95% CI:3.6-29.7, $p<0.001$).

Conclusions

Our study supports the current practice of administering intravenous alteplase before endovascular therapy.

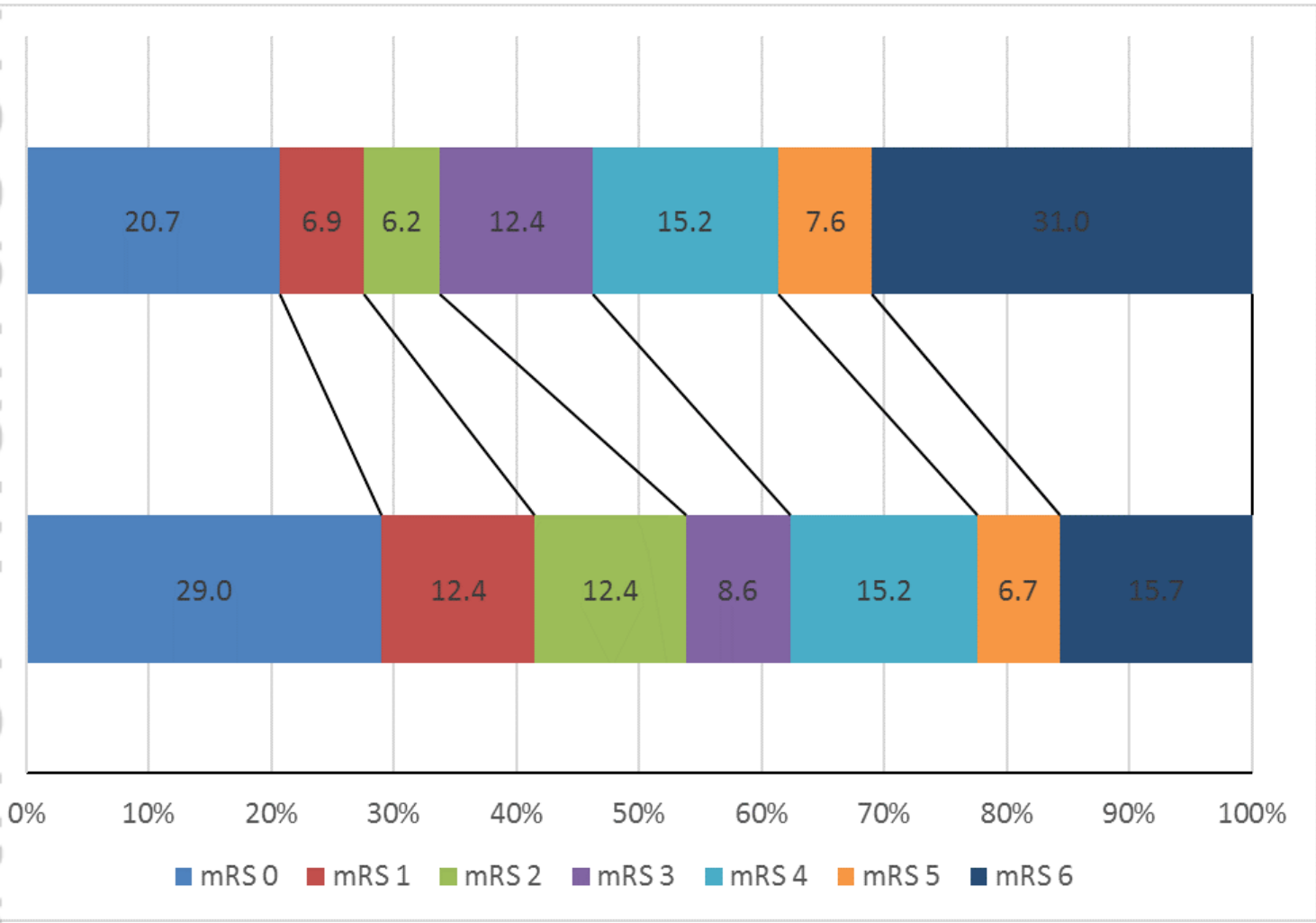


Figure1.png

Table 1. Baseline clinical, imaging and outcome characteristics of both study groups.

| Outcome variable | Thrombolysis (n=210) | No thrombolysis (n=145) | p-value |
|------------------------------------------------------------------|---------------------------------|------------------------------------|----------------|
| Mean age, years (SD) | 66 (14) | 68 (14) | 0.271 |
| Male sex, n (%) | 116 (55) | 81 (56) | 0.914 |
| Median ASPECTS (IQR) | 9 (2) | 9 (3) | 0.029* |
| Mean NIHSS score (SD) | 17 (5) | 17 (6) | 0.812 |
| Grade 2 or 3 collateral circulation, n (%) | 93 (55) | 79 (66) | 0.065 |
| Mean onset time to groin puncture, mins (SD) | 257 (104) | 342 (223) | <0.001* |
| Mean onset time to first reperfusion, mins (SD) | 297 (110) | 385 (225) | <0.001* |
| Median time from groin puncture to first reperfusion, mins (IQR) | 32 (30) | 33 (38) | 0.330 |
| Successful reperfusion†, n (%) | 179 (85) | 105 (72) | 0.003* |
| Median number of EVT passes, n (IQR) | 2 (3) | 3 (5) | 0.012* |
| Major complication, n (%) | 24 (11) | 21 (15) | 0.395 |
| Symptomatic ICH, n (%) | 15 (7) | 14 (10) | 0.396 |
| Functional independence (mRS 0-2) at 3 months, n (%) | 113 (54) | 49 (34) | <0.001* |
| Mortality at 3 months, n (%) | 33 (16) | 45 (31) | 0.001* |

n=Number, IQR=Interquartile range, SD=Standard deviation, ICH=Intracranial haemorrhage, mRS=modified Rankin score, †=TICI 2b or greater. *indicates statistical significance.

Table 2. Univariate and multivariate logistic regression outcomes for patients who received bridging intravenous thrombolysis prior to thrombectomy.

| Outcome variable | Unadjusted OR (95% CI) | p-value | Adjusted OR (95% CI) | p-value |
|-----------------------------------------------|-----------------------------------|----------------|---------------------------------|----------------|
| Functional independence (mRS 0-2) at 3 months | 2.28 (1.47-3.54) | <0.001* | 2.17 (1.06-4.44) | 0.033* |
| Mortality at 3 months | 0.41 (0.25-0.69) | 0.001* | 0.79 (0.36-1.74) | 0.551 |
| Successful reperfusion† | 2.20 (1.29-3.73) | 0.004* | 1.22 (0.60-2.50) | 0.580 |
| Good collateral grade (2-3) | 0.64 (0.39-1.03) | 0.069 | 0.72 (0.42-1.23) | 0.225 |
| Major complication | 0.76 (0.41-1.43) | 0.420 | 1.15 (0.52-2.57) | 0.730 |
| Symptomatic ICH | 0.72 (0.34-1.54) | 0.434 | 1.40 (0.51-3.83) | 0.512 |

n=Number, OR=Odds Ratio, CI=Confidence Interval, ICH=Intracranial haemorrhage (ICH), mRS=modified Rankin score, †=TICI 2b or greater. *indicates statistical significance.

**OUTCOMES OF ENDOVASCULAR THROMBECTOMY WITH AND WITHOUT
BRIDGING THROMBOLYSIS FOR ACUTE LARGE VESSEL OCCLUSION
ISCHAEMIC STROKE**

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Short Title:

Thrombectomy outcomes with and without thrombolysis in acute stroke

Keywords:

Interventional neuroradiology, endovascular, stroke, large vessel occlusion, thrombectomy, thrombolysis, reperfusion, IV tPA

Manuscript Word Count: 1987 (excluding abstract, tables, legends and references)

Abstract word count: 243