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Association of Reperfusion Success and Emboli in New Territories with Long-Term Mortality After Mechanical Thrombectomy

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Abstract

BACKGROUND: The degree of reperfusion is the most important modifiable predictor of 3-month functional outcome and mortality in ischemic stroke patients treated with mechanical thrombectomy. Whether the beneficial effect of reperfusion also leads to an improvement in long-term mortality is unknown.

METHODS: Patients undergoing mechanical thrombectomy between 01/2010 and 12/2018 were included. Post-thrombectomy degree of reperfusion and emboli in new territory were core-lab adjudicated. Reperfusion was evaluated according to the expanded thrombolysis in cerebral infarction scale (eTICI). Vital status was obtained from the Swiss population register. Adjusted hazard ratio (aHR) using time-split Cox regression models were calculated. Subgroup analyses were performed in patients with borderline indications.

RESULTS: Our study included 1264 patients (median follow-up per patient: 2.5 years). Patients with successful reperfusion had longer survival times, attributable to lower hazards of death within 0–90 days and >90 days – 2 years (aHR 0.34, 95% CI 0.26–0.46 and aHR 0.37, 95% CI 0.22–0.62). This association was homogeneous across all predefined subgroups (*P* for interaction >0.05). Among patients with successful reperfusion, a significant difference in hazards of death was observed between eTICI2b50 and eTICI3 (aHR 0.51, 95% CI 0.33–0.79). Emboli in new territory were present in 5% of patients, and were associated with increased mortality (aHR 2.3, 95% CI 1.11–4.86).

CONCLUSION: Achievement of successful, and ideally complete, reperfusion without emboli in new territory is associated with a reduction of long-term mortality in patients

treated with mechanical thrombectomy, and this was evident across several subgroups.

Non-standard Abbreviations and Acronyms

ENHT	emboli in initially non-hypoperfused territory
ENT	emboli in new territory
LVO	large vessel occlusion
MeVO	medium vessel occlusion
MT	mechanical thrombectomy
SAMS	Swiss Academy of Medical Sciences
STAR	Solitaire FR Thrombectomy for Acute Revascularisation

Introduction

Randomized controlled trials have consistently shown that mechanical thrombectomy (MT) in acute ischemic stroke patients with large vessel occlusion in the anterior circulation reduces 3-month mortality.[1] The REVASCAT and MR CLEAN follow-up studies demonstrated a sustained functional outcome benefit of added MT in the 1- and 2-year follow-up after the index stroke, respectively. However, there was no significant difference in mortality between the best medical treatment and MT groups, although the point estimates favored MT.[2,3] Successful reperfusion is a potentially modifiable and important predictor of 3-month functional outcome after MT.[4] However, long-term mortality after MT has only been investigated in a small real-world observational study (N=89).[5] The aim of this study was to investigate the association of long-term mortality with reperfusion success applying the most recent modification of the expanded Thrombolysis in Cerebral Infarction (eTICI) scale[6] in consecutive stroke patients treated with MT.

Method

Study Cohort

This retrospective observational study included all consecutive patients treated with second-generation MT at a comprehensive stroke center between January 1, 2010 and December 31, 2018 extracted from a single-center prospective stroke registry. Patients with missing long-term follow-up data or anterior-posterior and lateral post-procedure angiographic imaging, as well as those with severe motion artifacts were excluded. The local ethics committee approved this study in accordance with Swiss law (reference ID: 2019-00547, Kantonale Ethikkomission Bern). The requirement for consent for the assessment of long-term mortality was waived by the local ethics committee for patients who had not withdrawn their general consent.

Endpoints

The primary endpoint of this study was the survival rate during long-term follow-up and its association with post-thrombectomy reperfusion status. A TICI-score ≥ 2b50 after MT was defined as successful reperfusion. The secondary endpoints were the relation between long-term mortality and emboli in new territory (ENT) or emboli in initially non-hypoperfused territory (ENHT).[7,8]

Data Collection

Baseline data and 90-day follow-up data from all consecutive patients who underwent MT between 01/2010 and 12/2018 were extracted from the local stroke registry. Their vital status was extracted between 09/2019 and 05/2020 from the Swiss Population Registry, which documents the vital status of all inhabitants of Switzerland every month. The follow-up time was defined as the interval between the index stroke treated with MT and the date of the last update of the Swiss Registry. For deceased patients, the follow-up time was defined as the interval between MT and the date of death. Reperfusion success was core-lab adjudicated by 3 neuroradiologists (J.K., C.K., E.P.) using the most recent modification of the eTICI scale proposed by Liebeskind et al.[6] In brief, eTICI2a, eTICI2b50, and eTICI2b67 reflect capillary reperfusion in less than half (1–49%), 50–66%, and 67–89% of the target territory, respectively. Reperfusion of 90–99% is graded as eTICI2c, while eTICI3 indicates complete reperfusion.[6] The reliability of the core lab was validated using a random sample of 142 patients and by calculating interrater reliability (Krippendorf's alpha: 0.87, 95% CI 0.83–0.91). First pass TICI2c/3 was defined as achieving eTICI2c/3 after one MT maneuver.[9,10] ENT was defined as a new occlusion in a territory unaffected at baseline (i.e. in a territory not distal to the initial occlusion site) .[11] An ENHT was defined as an emboli in a territory distal to the occlusion site, but without hypoperfusion on initial imaging (e.g. A2 emboli after a Carotid-T occlusion were the ACA territory was initially perfused via the AcomA, see eFigure I for illustration).[7]

Statistical Analysis

Baseline characteristics of included and excluded patients, as well as patients with successful versus unsuccessful reperfusion were compared using Fisher's exact test and the Mann-Whitney U-test, depending on the variable type. The main outcome of the survival analysis was the survival rate with strata of successful versus unsuccessful reperfusion of different eTICI scores. Right-censored data over a time frame of 2556.75 days (=7 years) were considered for statistical analysis. We censored data at 7 years because the population at risk was below 10 patients per group in the main analysis. Kaplan-Meier curves were plotted to display survival rates with strata of angiographic reperfusion success, and Kaplan-Meier estimates were used to describe survival rates at 90 days, 2 years, and 5 years. Semi-parametric multivariable Cox regression with a robust variance estimate was used to calculate aHRs and corresponding 95% confidence intervals (95% CI). All models included the following clinically selected covariates influencing outcome in stroke patients: age, sex, year of treatment, pre-stroke disability, arterial hypertension, dyslipidemia, history of smoking, coronary artery disease, previous stroke, National Institutes of Health Stroke Scale (NIHSS) on admission, occlusion site, time from symptom-onset/last-seen-well to groin puncture, and intravenous alteplase. Because the Cox proportional hazards assumption was violated for the main variables of interest (see Supplementary Methods 1 for further details), we used the following time splits to allow for varying hazard ratios over time: 0–90 days, >90 days – 2 years (>90 – 730.5 days), and 2–7 years (>730.5–2556.75 days). The rationale for these time splits was that the survival rate dropped soon after the index event and stabilized thereafter. Additionally, visual inspection of landmark Kaplan-Meier curves showed evidence of different hazards of death between 90 days and 2 years for patients with successful and unsuccessful reperfusion, but not thereafter. Subgroup analyses regarding the association of successful versus unsuccessful reperfusion with survival rates were performed for the period 0–2 years. The following subgroups were used: ASPECTS (0–5, 6–8, and 9–10), MeVO (medium vessel occlusion) versus LVO (large vessel occlusion), and anterior versus posterior circulation occlusions. To evaluate the heterogeneity of aHRs across the subgroups, interaction terms of the abovementioned subgroups with successful versus unsuccessful reperfusion were incorporated into the multivariable Cox regression model for the period from day 0 – 2 years. The last step was a sensitivity analysis using between-group symmetry metrics based on the restricted mean survival time at 1, 2, and 5 years, respectively. These analyses were adjusted with an ANCOVA-type analysis. Analyses were performed using R (v 3.6.0, R Core Team). Further details of the R packages used can be found in the Supplementary Methods 2. Statistical significance level was defined as $\alpha = 0.05$ and all tests were 2-sided.

Results

Study Population

Altogether, 1313 patients who underwent MT between 01/2010 and 12/2018 were screened. Thirty-seven patients were lost to follow-up (28 not found in the Swiss

Population Registry, 9 with an unknown date of death) and 1276 had known vital status at the time of follow-up (eFigure II in the Data Supplement). A further 12 patients were excluded because of missing anterior-posterior and lateral post-procedure angiographic imaging or severe motion artifacts. After censoring of data with N<10 per stratum at risk (see Methods), median follow-up was 2.5 years, corresponding to a cumulative follow-up of 3498 patient–years.

Baseline Characteristics

There were some significant differences in baseline characteristics between included and excluded patients (eTable I in the Data Supplement). Patients who were included had lower ASPECTS scores (8 versus 7, *P*=0.03), higher NIHSS on admission, and distribution of occlusion sites was different. No differences in the rate of successful reperfusion were seen between included and excluded patients (86.9% versus 81.1%, *P*=0.32).

Of the patients who were included, those with successful reperfusion (n=1098) represented 86.9% and those with unsuccessful reperfusion (n=166) represented 13.1% of the study population.

Baseline characteristics of included patients with successful and unsuccessful reperfusion are summarized in Table 1. Patients in whom reperfusion was successful had shorter intervals from onset time to groin puncture (median: 232 min, IQR: 168–357 min, *P*<0.01) than patients in whom reperfusion was unsuccessful (median: 249.5 min, IQR: 185–445). ASPECTS was higher in patients with successful reperfusion (median: 8 versus 7, IQR: 6–9 versus 5.5–8, *P*<0.01) and more patients in this group received intravenous alteplase (41.7% versus 30.1%, *P*<0.01).

Association Between Reperfusion Success and Long-Term Mortality

Observed 90-day, 2-year, and 5-year survival rates were 53.6% versus 78.0%, 41.8% versus 69.0%, and 38.1% versus 59.8% for patients with unsuccessful and successful reperfusion, respectively (Figure 1A, log-rank test P<0.01). On multivariable Cox regression, after adjusting for prespecified covariates (see Methods), successful reperfusion was associated with lower hazards of death within the period from 0–90 days (aHR 0.34, 95% CI 0.26–0.45, Figure 2A and Figure 3) and >90 days–2 years (aHR 0.37, 95% CI 0.22–0.62, Figure 2B and Figure 3). During the period from 2–7 years there was no significant difference regarding the hazards of death between the groups (aHR 1.13, 95% CI 0.39–3.28, Figure 2B and Figure 3).

The reduced hazards of death between day 0 and 2 years in patients who had undergone successful reperfusion were noted in all prespecified subgroups and there was no evidence of significant heterogeneity (eFigure III). Specifically, the aHRs of achieving successful reperfusion were 0.49 (95% CI 0.27–0.88) for MeVO, 0.33 (95% CI 0.08–1.30) for posterior circulation strokes, and 0.36 (95% CI 0.22–0.58) for patients with ASPECTS 0–5. Moreover, the associations of reperfusion success and mortality was discernible in patients treated between 2010 and 2014 and those treated between 2015 and 2018 (eFigure IV).

Association between Grade of Successful Reperfusion and Long-term Mortality

The observed 90-day, 2-year, and 5-year survival rates of patients with different grades of successful reperfusion are shown in Supplementary Table 2. Significantly longer survival was observed in patients with eTICI3 as opposed to eTICI2b50 and eTICI2b50 + eTICI2b67 versus eTICI2c/3 (Figure 1B). Correspondingly, the better the reperfusion grade, the lower the hazard ratios on multivariable Cox regression (eFigure V in the Data Supplement). Achieving eTICI3 was associated with a reduced hazard of death when compared to eTICI2b50 (eTICI2b50 as reference, aHR 0.46, 95% CI 0.30–0.74). This difference was evident in the first 90 days after the index event, but no differences in the hazards of death between different grades of successful reperfusion were seen thereafter (eFigure V in the Data Supplement). Overall, a first-pass eTICI2c/3 was associated with reduced long-term mortality (eFigure VI).

Association between ENT and/or ENHT and Long-term Mortality

There were 52 ENT (in 3 cases ENT in multiples branches) and 12 ENHT, leading to new embolisations in 63 patients (one patient with both ENT and ENHT) out of 1264 patients (5.0%). 23% (n=23) were defined as proximal ENT/ENHT, with embolisation present in the M3-Segment of the Artery Cerebri Media, A2-Segment of the Artery Cerebri Anterior and P2-Segment of the Artery Cerebri Posterior or more proximally. Observed 90-day, 2-year, and 5-year survival rates were 75.2% versus 66.7%, 66.2% versus 52.2%, and 58.0% versus 40.9% for patients with and without ENT/ENHT, respectively (log-rank test $P<0.01$, eFigure VII in the Data Supplement). Occurrence of ENT/ENHT differed across eTICI scores, with more ENT/ENHT observed after higher TICI grades (eTable III in the Data Supplement). After adjusting for confounders (see methods) and eTICI, occurrence of ENT/ENHT was independently associated with increased hazards of death in the 91–730 day period (aHR 2.15, 95% CI 1.04–4.44, eFigure VIII in the Data Supplement). Mortality was particularly increased in those with proximal ENT/ENHT (log-rank $p<0.01$, eFigure IX).

Sensitivity Analyses using Restricted Mean Survival Time Estimates

Crude and adjusted differences in restricted mean survival times according to reperfusion quality corroborated most of the results noted above (see eTable IV in the Data Supplement for an overview). In the adjusted analyses, patients with successful reperfusion had higher mean survival across all potential follow-up intervals (e.g., net restricted mean survival difference at 5 years: 329 days [95% CI 204–455 days]). Restricted mean survival differences for TICI3 versus TICI2b50 were only significant when considering follow-up times of 1 year and 2 years (e.g., net mean survival difference at 2 years: 64 days [95% CI 7–121 days]). The association of ENT/ENHT with long-term mortality was only significant in the unadjusted analyses (eTable IV in the Supplement).

Discussion

The main findings of this study are: (1) Successful reperfusion defined as eTICI ≥ 2b50 is associated with lower mortality during long-term follow-up, which is attributable to lower hazards of death in the first 2 years. (2) This association was also evident in borderline indication groups, including patients presenting with low ASPECTS, posterior circulation strokes, or medium vessel occlusions. (3) Among patients with successful reperfusion, increasing reperfusion grade was associated with lower mortality and significant differences were observed between eTICI2b50 and eTICI3. (4) The occurrence of ENT/ENHT may lead to an additional increase in the risk of long-term mortality.

Survival Benefit in Patients Receiving Reperfusion Therapies

In the Third International Stroke Trial (IST-3), intravenous thrombolysis was not associated with any overall survival benefit after 3 years.[12] However, there was a significantly lower hazard of death between 8 days and 3 years if patients survived the early period during which an increased risk of death following intravenous thrombolysis was observed.[12] MT has been shown to further improve reperfusion rates. This has been suggested to be one of the main drivers of therapy success in the pivotal MT trials comparing best medical treatment (BMT) with MT.[13] Correspondingly, MT was associated with a reduction in 3-month mortality as compared to BMT alone.[1] The 1- and 2-year follow-up of the MR CLEAN and REVASCAT trial did not find a significant reduction of mortality in patients receiving MT[2,3]; however, these trials were not powered to detect such an effect. Moreover, a meta-analysis of these 2 studies and the 1-year follow-up of the IMS III trial[14] yielded point estimates favoring MT (OR 0.82; 95% CI 0.63–1.06; P=0.12).[15] In our study of consecutive patients undergoing MT, which had a cumulative follow-up of 3498 years, successful reperfusion was associated with a sustained survival benefit. Importantly, this was also observed in a subset of patients with borderline indications with no evidence of relevant heterogeneity. Although these observations may not be a sufficient basis for treatment recommendations even if all-cause mortality is considered as a relevant outcome, they may serve as an indicator of potential therapy effect. This is also supported by data suggesting that outcome for patients with unsuccessful reperfusion is not worse than that of patients treated with BMT.[16] Certainly, avoiding mortality is only one aspect of a potential treatment benefit and the definition and interaction between good functional outcome, patient-reported quality of life[17], and what constitutes futile reperfusion are still under discussion.[18] Although not necessarily specific to the disease, all-cause mortality remains an objective "hard" endpoint. Interestingly, the association of reduced hazards of death was relatively stable throughout the first 2 years, suggesting that the observed difference cannot solely be attributed to higher survival rate in successfully reperfused patients in the hyperacute and acute phase. Reassuringly, the observed survival differences, which were accumulated over the first 2 years, were not attenuated in the very long-term follow-up as evidenced by comparable hazards of death in survivors at 2 years following successful and unsuccessful reperfusion.

Beyond Successful Reperfusion and Emboli in New Territory

More complete reperfusion beyond TICI2b was associated with reduced disability and lower day-90 mortality. However, the magnitude of this association differed considerably across cohorts and grading systems.[19–21] Liebeskind et al. recently proposed the 7-point eTICI score, which adds prognostic value due to being finer grained in the > 50% reperfusion categories.[6] Substantial differences in clinical outcomes were observed when applying the newly proposed subdivisions of 50–66% (eTICI2b50), 67–89% (eTICI2b67), and 90–99% (eTICI2c) in the 90-day follow-up of the HERMES data.[6] Liebeskind et al. found that day-90 mortality in patients with TICI2b50 reperfusion (12.6%) was double that of patients with eTICI3 reperfusion (6.3%), whereas mortality rates of patients with TICI2b67 and TICI2c were in between.[6] Moreover, we found an association between ENT/ENHT and increased mortality. Although angiographically-graded ENT/ENHT underestimates the true rate of emboli,[7,22] previous studies have shown that angiographically evident ENT/ENHT are associated with increased disability.[7,22,23] It therefore seems likely that efforts aimed at further decreasing thrombus fragmentation would also reduce long-term mortality. Moreover, there is an ongoing debate on whether patients with successful but <TICI3 reperfusion should be further treated to achieve complete reperfusion.[24]

This is especially relevant as distal thrombectomy has been reported to be safe and technically feasible, as well as potentially beneficial, and dedicated devices have been introduced to the market.[25,26] Moreover, post-thrombectomy intra-arterial thrombolysis is still favored by some interventionalists.[27,28] Lastly, the observed beneficial effects of first-pass TICI2c/3 fit well into recent observations of a beneficial effect of first-pass complete reperfusion.[9,10,29]

Limitations

This retrospective and observational study has several limitations. First, 49 patients (3.7%) were lost to follow-up, which may have resulted in bias as patients with available follow-up data had different baseline characteristics to those without. Second, as all patients were treated at one center, the findings may not be generalizable. Third, although patients were treated with a second-generation devices, MT was not a well-established as acute stroke therapy at the beginning of the recruitment period, which could introduce bias regarding interventionalist experience and in-hospital work-flows. Fourth, a control group of patients without MT is lacking and a comparison of successful versus unsuccessful reperfusion as the means of estimating potential treatment effects is biased, because non-captured variables could have influenced the operators' decision to stop the intervention or use further bailout strategies. Hence, the surmised association between successful reperfusion and reduced mortality may be too favorable. Fifth, other potential confounders, such as secondary prophylaxis, medication adherence, and general care, which may influence mortality after the index stroke, could not be included in the multivariate analysis. Last, landmark analyses were carried out to allow for changing hazard ratios of the variables of interest as well as covariates over time, because the proportional hazards assumption was violated.

Conclusion

Achieving successful, and ideally complete reperfusion, is associated with long-term mortality reduction in patients undergoing MT for an acute ischemic stroke, even if they have borderline indication criteria. This study also suggests a potential association between ENT/ENHT and increased mortality. Technical advances geared toward improving angiographic reperfusion and reducing peri-interventional embolisation in new territory may improve long-term survival.

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Competing Interests Statement

Dr. Fischer reports grants during the conduct of the study from Medtronic, Stryker, and CSL Behring, unrelated to the submitted work. Dr. Gralla is a global principal investigator of STAR (Solitaire FR Thrombectomy for Acute Revascularisation), Clinical Event Committee member of the PROMISE study (Prospective, Multicenter, Observational, Single-Arm European Registry on the ACE Reperfusion Catheters and the Penumbra System in the Treatment of Acute Ischemic Stroke; Penumbra), and a principal investigator and consultant for the SWIFT DIRECT study (Solitaire With the Intention for Thrombectomy Plus Intravenous tPA Versus DIRECT Solitaire Stent-Retriever Thrombectomy in Acute Anterior Circulation Stroke; Medtronic) and receives Swiss National Science Foundation grants for magnetic resonance imaging in stroke. Dr. Kaesmacher reports grants from the Swiss Academy of Medical Sciences/Bangerter Foundation, Swiss Stroke Society, and Clinical Trials Unit Bern during the conduct of the study. Dr. Arnold reports personal fees from Bayer, Bristol-Myers Squibb, Medtronic, Amgen, Daiichi Sankyo, Nestlé Health Sciences, Boehringer Ingelheim, and Covidien during the conduct of the study. Dr. Meinel reports research support from the Bangerter Rhyner Foundation, Swiss National Foundation, and the Swiss Heart Foundation. Dr. Heldner reports research support from the Bangerter Foundation, scientific advisory board honoraria from Amgen, and personal fees from Bayer.

Contributorship Statement

Morin Beyeler contributed to conception and design, data acquisition, analysis and interpretation of data, and writing of the publication.

Loris Weber contributed to data acquisition, data interpretation and critical revision of the manuscript for important intellectual content.

Christoph Kurmann contributed to data acquisition, data interpretation and critical revision of the manuscript for important intellectual content.

Mattia Branca contributes to analysis and interpretation of data, critical revision of publication for important intellectual content.

Urs Fischer contributed to conception and design, critical revision of the publication for important intellectual content, and supervision.

Johannes Kaesmacher contributes to conception and design, analysis and interpretation of data, writing of the publication, critical revision of the publication for important intellectual content, and supervision.

All other authors contributed to interpretation of data and critical revision of the manuscript for important intellectual content.

Data Sharing

Data are available upon reasonable request

Supplementary Materials

Expanded Materials & Methods

eFigure I-IX

eTable I-IV

References

1. Lin Y, Schulze V, Brockmeyer M, et al. Endovascular Thrombectomy as a Means to Improve Survival in Acute Ischemic Stroke A Meta-analysis. 2020;76(7):850-854. doi:10.1001/jamaneurol.2019.0525

2. Dávalos A, Cobo E, Molina CA, et al. Safety and efficacy of thrombectomy in acute ischaemic stroke (REVASCAT): 1-year follow-up of a randomised open-label trial. *Lancet Neurol*. 2017;16(5):369-376. doi:10.1016/S1474-4422(17)30047-9

3. Van Den Berg LA, Dijkgraaf MGW, Berkhemer OA, et al. Two-year outcome after endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2017;376(14):1341-1349. doi:10.1056/NEJMoa1612136

4. Dekker L, Geraedts VJ, Hund H, et al. Importance of Reperfusion Status after Intra-Arterial Thrombectomy for Prediction of Outcome in Anterior Circulation Large Vessel Stroke. *Interv Neurol*. 2018;7(3-4):137-147. doi:10.1159/000486246

5. Zhao W, Shang S, Li C, et al. Long-term outcomes of acute ischemic stroke patients treated with endovascular thrombectomy: A real-world experience. *J Neurol Sci*. 2018;390(March):77-83. doi:10.1016/j.jns.2018.03.004

6. Liebeskind DS, Bracard S, Guillemin F, et al. ETICI reperfusion: Defining success in endovascular stroke therapy. *J Neurointerv Surg*. 2019;11(5):433-438. doi:10.1136/neurintsurg-2018-014127

7. Kaesmacher J, Kurmann C, Jungi N, et al. Infarct in new territory after endovascular stroke treatment: A diffusion-weighted imaging study. *Sci Rep*. 2020;10(1):1-10. doi:10.1038/s41598-020-64495-2

8. Goyal M, Menon BK, Demchuk A, et al. Proposed methodology and classification of Infarct in New Territory (INT) after endovascular stroke treatment. *J Neurointerv Surg*.

2017;9(5):449-450. doi:10.1136/neurintsurg-2015-011839

9. Zaidat OO, Castonguay AC, Linfante I, et al. First Pass Effect. 2018:660-666. doi:10.1161/STROKEAHA.117.020315

10. Kang D-H, Kim BM, Heo JH, et al. Effects of first pass recanalization on outcomes of contact aspiration thrombectomy. 2020;(5):466-470. doi:10.1136/neurintsurg-2019-015221

11. Goyal M, Menon BK, Demchuk A, et al. Proposed methodology and classi fi cation of Infarct in New Territory (INT) after endovascular stroke treatment. 2017:449-450. doi:10.1136/neurintsurg-2015-011839

12. 2016; Effects of alteplase on survival after ischaemic stroke 3 year follow-up of a randomised, controlled, open-label trial; Berge.pdf.

13. Manning NW, Chapot R, Meyers PM. Endovascular Stroke Management: Key Elements of Success. *Cerebrovasc Dis*. 2016;42(3-4):170-177. doi:10.1159/000445449

14. Palesch YY, Yeatts SD, Tomsick TA, et al. Twelve-Month Clinical and Quality-of-Life Outcomes in the Interventional Management of Stroke III Trial. 2015:1321-1327. doi:10.1161/STROKEAHA.115.009180

15. Mccarthy DJ, Diaz A, Sheinberg DL, et al. Long-Term Outcomes of Mechanical Thrombectomy for Stroke : A Meta-Analysis. 2019;2019.

16. Communication S. Incomplete or failed thrombectomy in acute stroke patients with Alberta Stroke Program Early Computed Tomography Score 0 – 5 – how harmful is trying ? 2020. doi:10.1111/ene.14358

17. Rethnam V, Bernhardt J, Johns H, et al. Look closer : The multidimensional patterns of post-stroke burden behind the modified Rankin Scale. 2020;0(0):1-9.

doi:10.1177/1747493020951941

18. Chen M. Why futile recanalization matters. 2015:925-926. doi:10.1136/neurintsurg-2020-016789

19. Lecouffe NE, Kappelhof M, Treurniet KM, et al. What Should Be the Angiographic Target for Endovascular Treatment in Ischemic Stroke ? 2020:1790-1796. doi:10.1161/STROKEAHA.119.028891

20. Rizvi A, Seyedsaadat SM, Murad MH, et al. Redefining success': A systematic review and meta-analysis comparing outcomes between incomplete and complete revascularization. *J Neurointerv Surg*. 2019;11(1):9-13. doi:10.1136/neurintsurg-2018-013950

21. Kaesmacher J, Dobrocky T, Heldner MR, et al. Systematic review and meta-analysis on outcome differences among patients with TICI2b versus TICI3 reperfusions : success revisited. 2018;(October 2017):910-917. doi:10.1136/jnnp-2017-317602

22. Times R, Rempel JL, Butcher K, et al. Infarct in a New Territory After Treatment Administration in the ESCAPE Randomized Controlled Trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to. 2016:2993-2998. doi:10.1161/STROKEAHA.116.014852

23. Chalumeau V, Blanc R, Redjem H, et al. Anterior cerebral artery embolism during thrombectomy increases disability and mortality. 2018:1057-1062. doi:10.1136/neurintsurg-2018-013793

24. Kaesmacher J, Ospel JM, Meinel TR, et al. Thrombolysis in Cerebral Infarction 2b. 2020;(November):1-11. doi:10.1161/STROKEAHA.120.030157

25. Goyal M, Ospel JM, Menon BK, Hill MD. MeVO : the next frontier ? 2020;12(6):545-547.

26. Lobotesis K, Meila D, Meyer L, Raphaeli G, Gupta R. Thrombectomy for Distal , Medium Vessel. 2020;(September):2872-2884. doi:10.1161/STROKEAHA.120.028956

27. Kaesmacher J, Bellwald S, Dobrocky T, et al. Safety and Efficacy of Intra-arterial Urokinase After Failed, Unsuccessful, or Incomplete Mechanical Thrombectomy in Anterior Circulation Large-Vessel Occlusion Stroke. *JAMA Neurol*. 2019:1-9. doi:10.1001/jamaneurol.2019.4192

28. Castonguay AC, Jumaa MA, Zaidat OO, et al. Insights Into Intra-arterial Thrombolysis in the Modern Era of Mechanical Thrombectomy. *Front Neurol*. 2019;10. doi:10.3389/fneur.2019.01195

29. Nikoubashman O, Dekeyzer S, Riabikin A, et al. First-Pass Complete Reperfusion Improves Clinical Outcome. 2019:2140-2146. doi:10.1161/STROKEAHA.119.025148

Figure legends

Figure 1 – Kaplan-Meier curves with strata of reperfusion success

A, Survival curve with 95% confidence intervals according to strata of successful reperfusion (defined as eTICI2b50–eTICI3). Patients with successful reperfusion had higher survival rates (log-rank test *P*<0.01). At 5 years, estimated survival of patients with successful reperfusion was 59.8%, whereas in those with unsuccessful reperfusion it was 38.1%. **B**, Kaplan-Meier curve confined to patients with successful reperfusion. Significant differences in survival were observed when comparing eTICI3 with eTICI2b50 (log-rank test *P*=0.02), as well as comparing eTICI2c/3 with eTICI2b50+TICI2b67 (log-rank *P*=0.04).

eTICI indicates expanded Thrombolysis in Cerebral Infarction.

Figure 2 – Landmark Kaplan-Meier curves with strata of successful reperfusion

A, Kaplan-Meier curve with landmark analysis set at 90 days and truncated at 730 days displaying the first 2 periods selected for the split analysis. Lower hazards of death in patients with successful reperfusion are seen during both time periods, corresponding to the adjusted hazard ratio of 0.34 and 0.37 observed for these periods on multivariable Cox regression analyses; **B**, In patients who survived the first 2 years, hazards of death did not differ between patients with successful and unsuccessful reperfusion, suggesting that the cumulative survival difference seen in the first 2 years appears to be sustained on long-term follow-up up to 7 years.

eTICI indicates expanded Thrombolysis in Cerebral Infarction.

Figure 3 – Crude and adjusted hazard ratios of successful reperfusion in different follow-up periods

Crude and adjusted hazard ratios were calculated by applying Cox regression models either with successful versus unsuccessful reperfusion only, or with additional adjustments for covariates as outlined in the Methods section. Cox regression models were run separately for each prespecified landmark period. There were comparable hazard ratios of achieving successful reperfusion within the first 90 days and from >90 days – 2 years suggesting continuing lower hazards of death within the first 2 years if reperfusion is successful. After 2 years, the cumulated survival difference remained stable, without significant differences in the hazards of death between patients with successful and unsuccessful reperfusion who had survived the first 2 years (period 2–7 years).

eTICI indicates expanded Thrombolysis in Cerebral Infarction; 95% CI, 95% confidence intervals.

	Included patients (N=1264)	**Successful reperfusion (eTICI2b50– eTICI3, N=1098)**	**Failed reperfusion (eTICI 0– eTICI2a, N=166)**	***P* value**
Baseline				
Age at admission (median, IQR, y)	74.25 (60.06–82.16)	74.41 (62.1–82.2)	73.76 (62–82.03)	0.98
Sex, female, No./total No. (%)	630/1264 (49.8)	544/1098 (49.5)	86/166 (51.8)	0.62
Independence before stroke No./total No. (%)	1111/1258 (88.3)	971/1094 (88.8)	140/164 (85.4)	0.24
Risk factors No./total No. (%)				
Diabetes	215/1260 (17.1)	185/1094 (16.9)	30/166 (17.5)	0.74
Hypertension	883/1261 (70)	771/1095 (70.4)	112/166 (67.5)	0.47
Dyslipidemia	697/1254 (55.6)	611/1090 (56.1)	86/164 (52.4)	0.40
Smoking	304/1255 (24.2)	266/1092 (24.4)	38/163 (23.3)	0.84
Previous stroke	156/1262 (12.4)	141/1096 (12.9)	15/166 (9.6)	0.20
Coronary artery disease	243/1254 (19.4)	212/1090 (19.4)	31/164 (18.9)	0.92
Stroke characteristics				
Time to admission (median, IQR)	150 (79–272)	149 (77.5–261.5)	165 (88.5–320)	0.1
Transfer patients No./total No. (%)	430/1263 (34)	373/1097 (34)	57/166 (34.3)	0.93
Admission MRI No. / total No. (%)	644/1621 (51.1)	555/1096 (50.6)	76/165 (53.9)	0.45
Time to groin puncture (median, IQR)	237 (170–364)	232 (168–357)	249.5 (185–445)	0.004*
ASPECTS (median, IQR)	8 (6–9)	8 (6–9)	7 (5.5–8)	0.002*
NIHSS on admission (median, IQR)	15 (9–20)	15 (9–20)	15 (9–20)	0.44
Dichotomized NIHSS (≥ 5) No./total No. (%)	1154/1258 (91.7)	1002/1093 (91.7)	152/165 (92.1)	1

Anterior circulation No./total No. (%)	1159/1264 (91.7)	1002/1098 (91.3)	157/166 (94.6)	0.17
Site of occlusion No./total No. (%)				
Internal carotid artery	310/1263 (24.5)	271/1907 (24.7)	39/166 (23.5)	0.001*
M1	638/1263 (50.5)	567/1097 (51.7)	71/166 (42.8)	
M2	198/1263 (15.7)	154/1097(14)	44/177 (26.5)	
Posterior circulation	104/1263 (8.2)	95/1097(8.7)	9/166 (5.4)	
Other occlusion	13/1263 (1)	10/1097(0.9)	3/166 (1.8)	
TOAST No./total No. (%)				
Large-artery atherosclerosis	146/1260 (11.6)	124/1094 (11.3)	22/166 (15.1)	0.04*
Cardioembolism	541/1260 (42.9)	486/1094 (44.4)	55/166 (33.1)	
Stroke of other determined etiology	84/1260 (6.7)	69/1094 (6.3)	15/166 (9.0)	
Stroke of undetermined etiology	489/1260 (38.8)	415/1094 (37.9)	74/166 (44.6)	
Stroke treatment				
IVT No./total No. (%)	508/1264 (40.2)	458/1098 (41.7)	50/166 (30.1)	0.005*
ENT/ENHT No./total No. (%)	63/1264 (5)	58/1098 (5.3)	5/166 (3)	0.25

eTICI indicates expanded Thrombolysis in Cerebral Infarction; IQR, interquartile range; ASPECTS, Alberta Stroke Program Early CT Score; NIHSS, National Institutes of Health Stroke Scale; TOAST, Trial of ORG 10172 in Acute Stroke Treatment; ICA, internal carotid artery; M1, first segment of the middle cerebral artery; M2, second segment of the middle cerebral artery; IVT, intravenous thrombolysis; ENT, embolus in new territory; ENHT, embolus in initially non-hypoperfused territory; *, $P<0.01$.

Table 1. Comparison of Baseline Characteristics Between Patients with Successful and Unsuccessful Reperfusion