Original research

Benefit and risk of intravenous alteplase in patients with acute large vessel occlusion stroke and low ASPECTS

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ABSTRACT

Background The benefit of best medical treatment including intravenous alteplase (IVT) before mechanical thrombectomy (MT) in patients with acute ischemic stroke and extensive early ischemic changes on baseline CT remains uncertain. The purpose of this study was to evaluate the benefit of IVT for patients with low ASPECTS (Alberta Stroke Programme Early CT Score) compared with patients with or without MT.

Methods This multicenter study pooled consecutive patients with anterior circulation acute stroke and ASPECTS≤5 to analyze the impact of IVT on functional outcome, and to compare bridging IVT with direct MT. Functional endpoints were the rates of good (modified Rankin Scale (mRS) score ≤2) and very poor (mRS ≥5) outcome at day 90. Safety endpoint was the occurrence of symptomatic intracranial hemorrhage (sICH).

Results 429 patients were included. 290 (68%) received IVT and 168 (39%) underwent MT. The rate of good functional outcome was 14.4% (95% CI 7.1% to 21.8%) for patients who received bridging IVT and 24.4% (95% CI 16.5% to 32.2%) for those who underwent direct MT. The rate of sICH was significantly higher in patients with bridging IVT compared with direct MT (17.8% vs 6.4%, p=0.004). In multivariable logistic regression analysis, IVT was significantly associated with very poor outcome (OR 2.22, 95% CI 1.05 to 4.73, p=0.04) and sICH (OR 3.44, 95% CI 1.18 to 10.07, p=0.02). Successful recanalization, age, and ASPECTS were associated with good functional outcome.

Conclusions Bridging IVT in patients with low ASPECTS was associated with very poor functional outcome and an increased risk of sICH. The benefit of this treatment should therefore be carefully weighed in such scenarios. Further randomized controlled trials are required to validate our findings.

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INTRODUCTION

The application of intravenous alteplase is a standard of care for patients with acute ischemic stroke (AIS) presenting within 4.5 hours of symptom onset, as well as for patients with only subtle signs of lesion progression on baseline imaging.[1–4] The clinical benefit of intravenous thrombolysis with alteplase (IVT) has been demonstrated in previous landmark trials.[5 6] However, the effect of IVT on outcome in patients with large baseline ischemic cores who also undergo thrombectomy has not yet been thoroughly investigated. Current guidelines from the American Heart Association (AHA) specifically state that the application of alteplase is recommended in the setting of mild to moderately extensive early ischemic changes on CT, but should not be administered to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation.[7] This recommendation is partly due to insufficient evidence for patients with extensive regions of clear hypoattenuation, making it difficult to define a specific threshold of acute hypoattenuation on non-enhanced CT (NECT) imaging for safe IVT administration, especially in the endovascular era.[3] A potential harm or benefit of IVT may be of particular importance in bridging strategies considering the increasing number of patients with large ischemic cores (ie, low Alberta Stroke Programme Early CT Score—ASPECTS) that are currently enrolled in randomized trials (eg, TENSION,[8] TESLA,[9] IN EXTREMIS-LASTE,[10 11] SELECT II,[12] RESCUE-LIMIT (NCT03702413)). Therefore, the difficulty in differentiating between moderate and obvious hypoattenuation without the help of a validated threshold, together with the poor interrater reliability of ASPECTS rating,[13] could result in varying policies for IVT administration in patients with low ASPECTS in the clinical routine, with a subsequent unknown impact on safety and functional outcomes.

The aim of this multicenter study was to investigate the impact of IVT in patients with an ASPECTS of 0–5 in clinical practice, that is, outside of randomized trials, and to compare the outcomes of patients receiving bridging IVT with those directly undergoing mechanical thrombectomy (MT). We hypothesized that bridging IVT before MT is associated with an improved functional outcome at the 90-day follow-up evaluation, with no associated significant increase in symptomatic intracranial hemorrhage (sICH).

METHODS

Study cohort

Patients enrolled in the German Stroke Registry—Endovascular Treatment trial (GSR-ET; ClinicalTrials.gov identifier: NCT03356392) treated between July 2015 and April 2018 were screened. The GSR-ET is an ongoing, open-label, prospective, multicenter registry of consecutively recruited patients who have undergone MT at 25 sites in Germany. A detailed description[14] and the major outcome findings of the GSR-ET study design have been previously published.[15] Additionally, three further tertiary stroke centers contributed patients receiving IVT and/or MT fulfilling the study inclusion criteria because the GSR-ET only includes patients with MT. A flow chart of patient inclusion can be found in the online supplemental material.

The a priori defined inclusion criteria for this study were (1) AIS due to anterior circulation large vessel occlusion, (2) CT-based diagnosis and treatment decision-making, (3) baseline ASPECTS of 0–5 assessed on NECT scan by a board certified neuroradiologist, (4) complete clinical baseline and outcome parameters, including the National Institute of Health Stroke Scale (NIHSS) and modified Rankin Scale (mRS) score at day 90, (5) absence of intracranial hemorrhage and preexisting territorial thromboembolic infarctions on admission NECT. Baseline patient characteristics were retrieved from the medical records.

The study was conducted in accordance with the ethical guidelines of the local ethics committee and the Declaration of Helsinki. The leading ethic committee approved the GSR-ET. Additionally, approval from local ethics committees of the participating hospitals was obtained. Only anonymized data were analyzed. The requirement of informed consent was waived by ethics committees.

All patients who received IVT were compared with those who underwent direct MT without previous IVT with regard to functional outcomes and complications at the 90-day follow-up. A further outcome analysis was performed after stratification by the degree of recanalization following MT. Patients who received IVT before MT according to established guidelines were assembled into the bridging IVT group, while direct MT required the absence of IVT. The modified Thrombolysis in Cerebral Infarction (mTICI) scale was used to assess the degree of revascularization, with mTICI 2b–3 defined as successful recanalization. Good and very poor functional outcomes were defined as mRS 0–2 and mRS 5–6, respectively.[16–20] The mRS was evaluated at the 90-day follow-up by a physician or a trained and certified mRS nurse. sICH was defined according to the second European-Australasian Acute Stroke Study (ECASS II) as presence of intracerebral hemorrhage and a four-point neurological deterioration on the NIHSS.[21]

Statistical analyses

Standard descriptive statistics were used for all presented data. For group comparison, Student t-tests (normal distribution) including CIs or SD and Mann-Whitney U tests (non-normal distribution) with interquartile range (IQR) were performed (table 1). The occurrence of sICH was analyzed and compared using χ^2 tests.

To determine the treatment effect of IVT on functional outcome and the occurrence of sICH, we used inverse probability weighted regression adjustments using logit outcome and treatment models adjusted for baseline and treatment variables (age, sex, NIHSS, ASPECTS, atrial fibrillation, time from onset to imaging, mTICI in a stepwise approach, and number of passes). Multivariable logistic regression models were generated using the same aforementioned independent variables. Subsequently, inverse probability weighted regression adjustments (IPWAs) and multivariable logistic regression were repeated excluding MT related variables: number of retrievals, and mTICI (replaced by MT) acknowledging that the implementation of mTICI and number of retrievals results in an exclusion of patients without MT (online supplemental material, online supplemental tables 3 and 4).

Table 1 Patients' baseline, procedural and outcome characteristics

Baseline, procedural and outcome characteristics	Intravenous treatment with alteplase, n=290	No intravenous treatment, n=139	P values
Median age, years (IQR)	72 (60–79)	75 (66–81)	0.02*
Female sex, n (%)	161 (56)	81 (58)	0.31
Median admission NIHSS (IQR)	19 (16–22)	18 (15–21)	0.36
Median ASPECTS (IQR)	4 (3–5)	4 (3–5)	0.64
Median time from onset to imaging, minutes (IQR)	119 (78–156)	139 (98–165)	0.32
MT, n (%)	90 (31)	78 (56)	<0.001
mTICI 2b–3, n (%)	68 (76)	53 (68)	0.36
sICH, n (%)	37 (13)	5 (4)	0.004*
Median mRS at 90 days, (IQR)	5 (4–6)	5 (4–6)	0.06
mRS 0–2, n (%)	43 (15)	21 (15)	0.91
mRS 5–6, n (%)	168 (58)	88 (63)	0.41
Mortality, n (%)	99 (34)	65 (47)	0.069

*Indicates significance.
ASPECTS, Alberta Stroke Programme Early CT Score; mRS, modified Rankin Scale; MT, mechanical thrombectomy; mTICI, modified Thrombolysis in Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale; sICH, symptomatic intracranial hemorrhage.

Good functional outcome (mRS 0–2), very poor functional outcome (mRS 5–6), and sICH served as the dependent variables.

Subsequently, we investigated the impact of vessel recanalization status and number of retrieval attempts on functional outcome separately for patients with and without IVT. A subgroup analysis of patients with ASPECTS 0–4 was performed. Finally, a subgroup analysis including patients with ASPECTS 3–5 was performed to investigate the impact of bridging IVT versus direct MT on outcome in an effort to reduce a possible selection bias regarding patients initially presenting with extensive signs of ischemia (ASPECTS 0–2) and for comparability with the protocols of ongoing trials[22] (online supplemental material).

The significance level was set at $p<0.05$. Statistical analyses were carried out using Medcalc (version 11.5.1.0; Mariakerke, Belgium) and Stata/SE 13.0 (StataCorp, College Station, TX, USA)

Data availability statement

The data that support the findings of this study are available on reasonable request after approval of the ethics committee and all participating centers.

RESULTS

Study cohort

A total of 429 patients fulfilled the inclusion criteria. Patient characteristics are displayed in table 1. A flow chart diagram of patient inclusion can be found in the supplemental material (online supplemental figure 2).

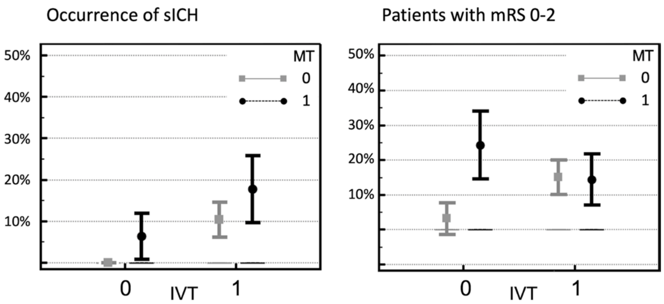

Figure 1 Proportion of patients with sICH (symptomatic intracerebral hemorrhage; left) according to treatment with intravenous thrombectomy with alteplase (IVT) and mechanical thrombectomy (MT), and proportion of patients with good functional outcome, defined as a modified Rankin Scale score (mRS) 0–2 at day 90 (right). Points/brackets indicate means and 95% confidence intervals.

The median ASPECTS was 4 (IQR 3–5), the median time from symptom onset to imaging was 119 min (IQR 79–157 min), and the median NIHSS was 18 (IQR 15–22). A total of 290 patients (68%) received IVT and 168 patients (39%) underwent MT. Of these, 90 (21%) received IVT before MT, while 78 (18%) underwent direct MT. Sixty-one patients (14%) received neither IVT nor MT and 200 patients (47%) received IVT only. Sixty-four patients showed good functional outcome at day 90 (15%), 112 patients had a 3-month mRS score of 3–4 (26%), and 253 patients were assigned an mRS score of 5–6 (59%). A total of 164 patients died (38%) and 42 had sICH (9.8%). Online supplemental figure 1 shows the impact of IVT on functional outcome according to MT success, and online supplemental table 1 shows the proportion of patients with good functional outcome and sICH stratified by IVT and MT. Online supplemental table 2 shows functional outcome with regards to treatment.

Impact of IVT and MT on functional outcome and sICH

Patients who received IVT (n=290, 68%) and those who did not (n=139, 32%) showed similar median times from symptom onset to imaging (119 vs 139 min, p=0.32) and a similar median ASPECTS of 4 (IQR 3–5). There were no significant differences in sex (p=0.31) or NIHSS (median 19 vs 18, p=0.36). Patients who received IVT were slightly younger (72 vs 75 years, p=0.02) and underwent MT less frequently (31% vs 56%, p<0.001). The proportion of patients in whom MT was successful (mTICI 2b-3) was similar between the groups (76% vs 68%, p=0.36). Looking at the entire cohort, the rate of sICH was higher in patients who received IVT (13% vs 4%, p=0.004). These patients in turn exhibited a significantly worse mRS score at day 90 (median mRS 6, IQR 5–6 vs 5, IQR 4–6, p=0.0005) (table 1, figure 1). Patients with direct MT showed a lower mRS score at day 90 compared with those who received bridging IVT; however, this was not significant (4.2, 95% CI 3.8 to 4.6 vs 4.6, 95% CI 4.2 to 4.9). The rate of good functional outcome was 14.4% (95% CI 7.1% to 21.8%) for patients with bridging IVT and 24.4% (95% CI 16.5% to 32.2%) for patients with direct MT. Patients without either IVT or MT had a mean mRS score at day 90 of 5.2 (95% CI 4.8 to 5.7). The rate of sICH was higher in patients with bridging IVT compared with those undergoing direct MT (17.8% vs 6.4%). No cases of sICH were observed in untreated patients, while the rate of sICH for IVT-only patients was 10.4% (95% CI 6.4% to 14.4%).

Following IPWA, the average treatment effect of IVT on functional independence was −16.8 (95% CI −27.4 to −6.2, p=0.002). IVT significantly increased the risk of sICH after regression adjustment, with a mean effect coefficient of 16.9% (95% CI 9.6% to 19.4%, p<0.0001). Online supplemental table 3 compares the effect coefficients of the present analyses with a comparable model including all patients of the study cohort after disintegration of the variable 'number of passes' and replacing 'mTICI' with 'MT'.

Multivariable logistic regression analysis

A multivariable logistic regression analysis with good functional outcome (mRS 0–2) as the dependent outcome and age, sex, NIHSS, ASPECTS, atrial fibrillation, time from onset to imaging, mTICI in a stepwise approach, and number of passes as independent variables was performed. Age (OR 0.92, 95% CI 0.89 to 0.96, p<0.001), mTICI (OR 1.93, 95% CI 1.11 to 3.35, p=0.02), and number of attempts (OR 0.59, 95% CI 0.39 to 0.91, p=0.02) were all significant independent predictors of good functional outcome. IVT was also associated with a reduced likelihood of good outcome (OR 0.38, 95% CI 0.14 to 1.02), with a borderline significance value of p=0.05.

In a multivariable logistic regression analysis including patients undergoing MT with very poor functional outcome as the dependent variable, IVT was found to be significantly and independently associated (OR 2.22, 95% CI 1.05 to 4.72, p=0.04). Further significant and independent predictors of very poor outcome were age (OR 1.09, 95% CI 1.05 to 1.12, p<0.001; figure 2) and mTICI (OR 0.63, 95% CI 0.43 to 0.89, p=0.01; figure 3). Table 2 shows the logistic regression model compared with a model including all patients. IVT was significantly associated with sICH (OR 4.89, 95% CI 1.84 to 13.03, p=0.001), while the degree of reperfusion was not significantly associated with sICH. Figure 4 illustrates the impact of IVT and MT on functional outcome.

Online supplemental table 4 compares the OR and 95% CI of these analyses with a comparable model including all patients of the study cohort after disintegration of the variable 'number of passes' and replacing 'mTICI' with 'MT'.

Impact of recanalization success and number of passes

The impact of IVT on functional outcome according to recanalization success and the number of passes was analyzed. The highest rates of functional outcome were observed in patients with direct MT and first pass mTICI 2b–3 (mean mRS 3.1, 95% CI 2.3 to 3.9). Patients with bridging IVT and first pass mTICI 2b–3 had a correspondingly worse mRS score (mean 4.4, 95% CI 3.8 to 5.0) at day 90. The rate of sICH was higher in patients with bridging IVT with mTICI ≥2b–MT compared with direct MT (14.7% vs 3.7%). Conversely, in patients without successful recanalization, IVT application resulted in similar outcomes (mean mRS 4.9; 95% CI 4.1 to 5.6) compared with patients without IVT (mean mRS 4.8; 95% CI 4.1 to 5.6). A detailed presentation of the subanalysis can be found in the supplemental material (online supplemental table 1).

Subanalysis including patients with ASPECTS 0–4

A total of 268 patients (63%) evidenced an ASPECTS of 0–4 on baseline CT. In this patient cohort, IVT was independently associated with sICH in multivariable logistic regression analysis utilizing the aforementioned model (adjusted OR (aOR) 4.57, 95% CI 1.29 to 16.09, p=0.02). In contrast, a higher degree of reperfusion was associated with lower probability for sICH (aOR per mTICI 0.49, 95% CI 0.28 to 0.87, p=0.02). Regarding functional outcome (ie, mRS 0–2), IVT was no significant predictor (aOR 0.65, 95% CI 0.16 to 2.64, p=0.55), while

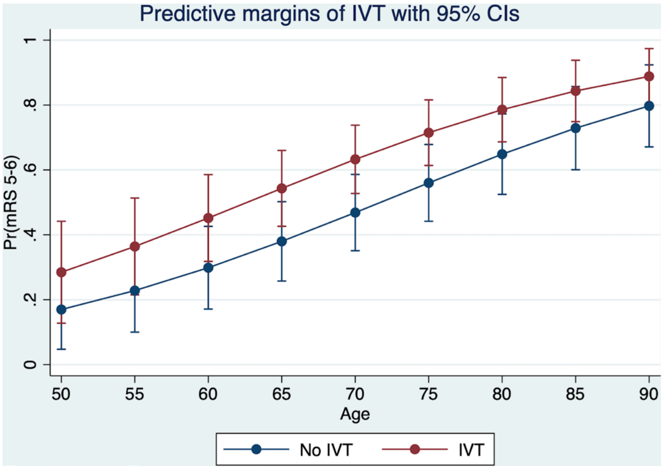

Figure 2 Multivariable logistic regression analysis displaying the impact of age (x axis) according to the application of intravenous alteplase (IVT; blue/red) on functional outcome with 95% CIs including all patients. mRS, modified Rankin Scale.

a higher degree of reperfusion was independently associated with better outcomes (aOR 2.88, 95% CI 1.09 to 7.61, p=0.03). Further predictors of functional outcome were age (aOR 0.87, 95% CI 0.79 to 0.95, p=0.002) and NIHSS (aOR 0.87, 95% CI 0.78 to 0.98, p=0.02). A subanalysis only including patients with an ASPECTS of 3–5 is shown in the supplemental material.

DISCUSSION

This international, real-world observational multicenter study investigating the impact of IVT on patients with AIS and low ASPECTS revealed the following main findings: (1) bridging IVT was independently associated with the occurrence of sICH and (2) very poor functional outcome at day 90 (figure 3); (3) in patients with successful reperfusion after MT, higher frequencies of sICH and lower rates of good functional outcome were observed in patients with bridging IVT, (4) the best functional outcome rates were observed in patients who underwent direct MT with a successful first pass mTICI 2b–3 reperfusion.

This multicenter study aimed to investigate the impact of IVT in patients with low ASPECTS in the context of MT by

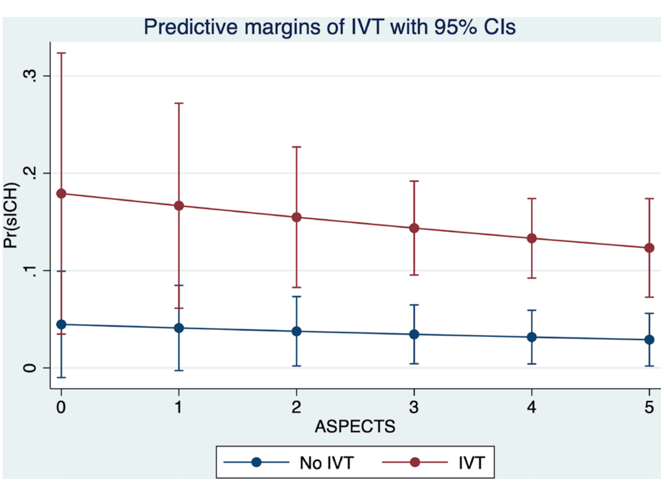

Figure 3 Multivariable logistic regression analysis displaying the impact of IVT (intravenous thrombolysis; blue/red) and ASPECTS (Alberta Stroke Programme Early CT Score; x axis) on the probability of sICH (symptomatic intracranial hemorrhage; y axis) including all patients.

comparing the functional outcomes of patients with direct MT veruss those with bridging IVT, only including patients with CT as the primary imaging modality. The choice of imaging modality in the evaluation of treatment effects in extensive baseline stroke may be of high importance considering that in the HERMES meta-analysis, a benefit of MT in pateints with low ASPECTS was only observed after MRI-based inclusion.[23 24] In contrast, no treatment effect for CT-selected cases was observed, which also highlights that CT-based versus MRI-DWI-based ASPECTS have a poor inter-modality agreement,[25] which explains substantial differences in outcome prediction.[16 26 27]

Although numerous studies investigating the relationship between signs of early ischemia and response to IVT exist, these data are mainly derived from the pre-thrombectomy era.[28–30] In addition, the study protocols of previous IVT landmark trials were heterogenous with regard to the treatment of early ischemic changes and often excluded patients who showed early extensive signs of ischemia. For example, the ECASS trial specifically excluded patients with signs of ischemia in more than a third of the MCA territory, which can be translated to an ASPECTS of ≤7.[5 31] A post hoc analysis of the ECASS study showed that the extent of hypoattenuation on the initial CT is predictive of the response to IVT.[32 33] The authors of the IST-3 trial concluded that their study might not have had enough statistical power to ascertain whether alteplase treatment in patients with an ASPECTS of 0–7 was of clinical benefit, although early ischemic changes were observed to be associated with reduced functional independence at 6 months and an increased risk of symptomatic hemorrhage. This relationship between early ischemic changes and the occurrence of secondary hemorrhage has been corroborated by other IVT studies.[30] Accordingly, we observed lower rates of sICH in patients with direct MT (6.4%) compared with those treated either with IVT only (10.4%) or bridging IVT (17.8%). The lowest rates of sICH (3.7%) were found in the subgroup of direct successful MT, significantly lower compared with successful MT with bridging IVT (14.7%). Because the occurrence of sICH after stroke is strongly correlated with very poor outcome, these findings suggest that IVT may carry a substantial harmful treatment effect in the subgroup of patients with low ASPECTS, especially if administered before MT.[34]

The majority of patients included in the thrombectomy landmark trials received IVT, ranging from 72% to 100%.[27] Recently, the DIRECT-MT study, the first of several ongoing direct to MT randomized controlled trials, reported non-inferiority of direct MT compared with MT preceded by IVT within 4.5 hours after stroke onset, despite the formal non-inferiority margin being relatively high at 20%.[35] Similarly, direct MT met the predefined thresholds for non-inferiority for the outcome at 90 days in the SKIP and DEVT trial,[36 37] with similar rates of reperfusion (mTICI 2b–3: 88.5% vs 87.2% after bridging)[37] and similar mRS scores (mRS 0–2: 54.3% vs 46.6% after bridging).[37] More lately, a meta-analysis of randomized controlled trials indicated a non-inferiority of direct MT with a 4% margin of confidence.[38] However, there is still a lack of data on direct MT versus bridging IVT in patients with lower ASPECTS. The SKIP trial specifically excluded patients with ASPECTS 0–5, while the study protocol of DIRECT-MT does not include ASPECTS as a selection variable. However, the IQR in both patient groups in the DIRECT-MT cohort was 7–10, strongly indicating the ASPECTS distribution of the included subjects. The DEVT trial also considered patients with all ASPECTS, but the median ASPECTS was 8 (IQR 7–9) in both groups, also indicating the lack of patients with low ASPECTS.[37] SWIFT DIRECT (NCT03192332) specifically excluded patients with an ASPECTS 0–3, and is hence also

Table 2 Multivariable logistic regression analysis for independent predictors of very poor outcome (modified Rankin Scale (MRS) 5–6) at 90-day follow-up

	All patients			MT patients		
Characteristics	**aOR**	**95% CI**	**P Value**	**aOR**	**95% CI**	**P Value**
Age (years)	1.07	1.04 to 1.09	<0.001*	1.09	1.05 to 1.12	<0.001*
Sex (male)	0.82	0.49 to 1.38	0.46	0.75	0.33 to 1.65	0.47
Atrial fibrillation	1.11	0.66 to 1.85	0.69	0.87	0.37 to 2.02	0.75
NIHSS on admission	1.02	0.98 to 1.07	0.37	1.04	0.98 to 1.10	0.17
ASPECTS on admission	0.78	0.63 to 0.98	0.03*	0.88	0.58 to 1.32	0.53
Intravenous thrombolysis	1.68	0.85 to 3.32	0.13	2.22	1.05 to 4.73	0.037*
mTICI score after thrombectomy†	X	X	X	0.63	0.43 to 0.89	0.01*
Number of passages†	X	X	X	1.21	0.98 to 1.50	0.08

*Indicates significance.
†Excluded variables to incorporate all patients.
ASPECTS, Alberta Stroke Programme Early CT Score; mRS, modified Rankin Scale; MT, mechanical thrombectomy ; mTICI, modified Thrombolysis In Cerebral Infarction; NIHSS, National Institutes of Health Stroke Scale.

expected to represent mainly cases with higher ASPECTS. A recent retrospective study observed that bridging IVT was associated with increased risk of sICH, but this study included patients mainly based on MRI as the primary imaging modality; this is an important limitation in contrast to the present study, which only includes patients with CT imaging at baseline.[39]In line with this study, we also observed a trend towards improved functional outcomes in this subgroup of patients. Highlighting the possible effectiveness of MT in patients with large baseline infarcts (ie, low ASPECTS), we observed the most favorable results for the subgroup who underwent successful mTICI ≥2b-MT without previous IVT (mean mRS 3.9, 95% CI 3.4 to 4.4). This was especially present in cases with fewer retrieval attempts (OR 0.62, 95% CI 0.41 to 0.92, p=0.02) or first pass mTICI 2b–3 (mean mRS 3.1, 95% CI 2.3 to 3.9). IVT, however, was a significant predictor of very poor outcome, together with advanced age, as previously reported.[40]

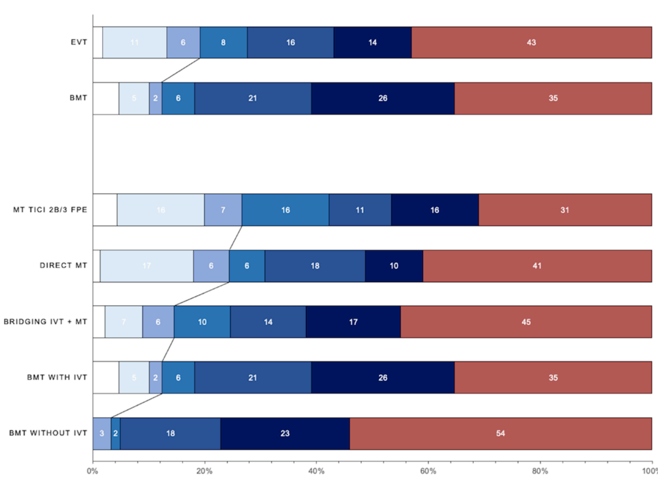

Figure 4 Bar graph showing the distribution of modified Rankin Scale (MRS) scores at 90 days according to the application of intravenous alteplase (IVT) and mechanical thrombectomy (MT). The upper bar graphs show outcome for patients with endovascular treatment (EVT) vs without treatment (BMT). The lower bar graphs show functional outcome for patients with successful MT after the first pass (mTICI 2b–3) for all direct MT patients, MT patients who received bridging IVT, BMT patients with and without IVT, respectively.

According to the current AHA guidelines, the application of alteplase is recommended 'in the setting of early ischemic changes on CT of mild to moderate extent'. However, IVT is not recommended in patients with extensive regions of 'clear hypoattenuation'.[41] This highlights a twofold problem: (1) how can early hypoattenuation of moderate extent be safely distinguished from clear hypoattenuation in the absence of any objectifiable threshold, (2) how high is the impact of the known poor inter-rater reliability of early ischemic changes and does this in turn lead to substantial differences in the decision-making for or against IVT in patients with low ASPECTS in daily clinical practice?[13 42] More importantly, the uncertain impact of IVT in patients with low ASPECTS may affect outcomes of the currently ongoing trials on MT in patients with low ASPECTS, to the extent of potentially even causing failure of these trials. Therefore, the standardized application of IVT in patients with low ASPECTS should be further evaluated, in particular in light of the availability of better treatment selection tools.[43] First, the scoring of ASPECTS could be improved by the use of standardized automated tools that are already available and are known to be precise in their prediction of the true final infarct volume compared with subjective ASPECTS reading.[44–46] Second, objective quantitative parameters could complement ASPECTS, such as quantitative lesion water uptake.[47–49] Indeed, it is important to note that the ASPECTS rating itself is based on binary subjective rating criteria (hypoattenuation yes/no). Therefore, it does not further quantify the degree of hypoattenuation. Early infarct of brain tissue is defined by net water uptake which, in turn, is directly related to lesion hypodensity and volume increase (ie, extracellular edema). The physics behind the decrease of CT attenuation of ischemic tissue requires a net influx of water (ie, edema), which has been illustrated in previous in vitro and in vivo experiments.[49] Therefore, such an additional quantitative parameter could improve the interpretation of the current guidelines in the more accurate differentiation of early ischemic hypoattenuation from frank hypodensity to better select patients with low ASPECTS for IVT administration. Furthermore, the specific degree of hypoattenuation could be predictive of the response to IVT in patients with low ASPECTS or could be used as a tool for early risk estimation of sICH.[47 50]

Limitations

Based on the retrospective design and the absence of randomization, several sources of potential bias have to be considered.

The decision of whether to apply IVT or not was left to the discretion of the treating physician. The present study did not analyze center-specific differences in IVT application, which might constitute a bias with regards to different institutional guidelines. Even in the absence of significant differences between the different cohorts in our analysis, we cannot rule out smaller differences that may have been obscured by the limited sample size. Moreover, without randomization, unknown risk factors for a poor outcome are not accounted for. Furthermore, no follow-up vessel imaging was available to compare the impact of reperfusion in the best medical treatment cohort.

CONCLUSION

The application of IVT before MT in patients with low ASPECTS was associated with an increased risk of sICH and a higher likelihood for very poor functional outcome. Therefore, IVT in extensive baseline infarctions should be considered with caution until evidence from randomized trials is available to support (or discredit) the application of IVT in this particular subgroup. Future research is necessary to identify objective selection criteria for IVT in patients with low ASPECTS.

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REFERENCES

1 Lees KR, Emberson J, Blackwell L, *et al*. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. *Stroke* 2016;47:2373–9.
2 Thomalla G, Simonsen CZ, Boutitie F, *et al*. Mri-Guided thrombolysis for stroke with unknown time of onset. *N Engl J Med* 2018;379:611–22.
3 Broocks G, Leischner H, Hanning U, *et al*. Lesion age imaging in acute stroke: water uptake in CT versus DWI-FLAIR mismatch. *Ann Neurol* 2020;88:1144–52.
4 Ma H, Campbell BCV, Parsons MW, *et al*. Thrombolysis guided by perfusion imaging up to 9 hours after onset of stroke. *N Engl J Med* 2019;380:1795–803.
5 Hacke W, Kaste M, Bluhmki E, *et al*. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008;359:1317–29.
6 Wahlgren N, Ahmed N, Dávalos A, *et al*. Thrombolysis with alteplase 3-4.5 H after acute ischaemic stroke (SITS-ISTR): an observational study. *Lancet* 2008;372:1303–9.
7 Powers WJ, Rabinstein AA, Ackerson T, *et al*. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2019;50:e344–418.
8 Bendszus M, Bonekamp S, Berge E, *et al*. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. *Int J Stroke* 2019;14:87–93.
9 (TESLA). TTTTfESoLACIS. Available: https://clinicaltrials.gov/ct2/show/NCT03805308
10 IEIEM-LH, 2020. Available: https://www.inextremis-study.com
11 Bendszus M, Fiehler J, Thomalla G. New interventional stroke trials. *Clin Neuroradiol* 2019;29:1.
12 Sarraj A, Hassan AE, Abraham M, *et al*. A randomized controlled trial to optimize patient's selection for endovascular treatment in acute ischemic stroke (SELECT2): study protocol. *Int J Stroke* 2021:17474930211035032.
13 Schröder J, Thomalla G. A critical review of Alberta stroke program early CT score for evaluation of acute stroke imaging. *Front Neurol* 2016;7:245.
14 Alegiani AC, Dorn F, Herzberg M, *et al*. Systematic evaluation of stroke thrombectomy in clinical practice: the German stroke Registry endovascular treatment. *Int J Stroke* 2019;14:372–80.
15 Wollenweber FA, Tiedt S, Alegiani A, *et al*. Functional outcome following stroke thrombectomy in clinical practice. *Stroke* 2019;50:2500–6.
16 Kaesmacher J, Chaloulos-Iakovidis P, Panos L, *et al*. Mechanical thrombectomy in ischemic stroke patients with Alberta stroke program early computed tomography score 0-5. *Stroke* 2019;50:880–8.
17 Rangaraju S, Haussen D, Nogueira RG, *et al*. Comparison of 3-month stroke disability and quality of life across modified Rankin scale categories. *Interv Neurol* 2017;6:36–41.
18 Broocks G, Flottmann F, Schönfeld M, *et al*. Incomplete or failed thrombectomy in acute stroke patients with Alberta Stroke Program Early Computed Tomography Score 0-5 - how harmful is trying? *Eur J Neurol* 2020;27:2031–5.
19 Broocks G, Kniep H, Schramm P, *et al*. Patients with low Alberta stroke program early CT score (aspects) but good collaterals benefit from endovascular recanalization. *J Neurointerv Surg* 2020;12:747–52.
20 Broocks G, Hanning U, Flottmann F, *et al*. Clinical benefit of thrombectomy in stroke patients with low aspects is mediated by oedema reduction. *Brain* 2019;142:1399–407.
21 Hacke W, Kaste M, Fieschi C, *et al*. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). second European-Australasian acute stroke study Investigators. *Lancet* 1998;352:1245–51.

22 Bendszus M, Bonekamp S, Berge E, *et al*. A randomized controlled trial to test efficacy and safety of thrombectomy in stroke with extended lesion and extended time window. *Int J Stroke* 2019;14:1747493018798558.
23 Meyer L, Bechstein M, Bester M, *et al*. Thrombectomy in extensive stroke may not be beneficial and is associated with increased risk for hemorrhage. *Stroke* 2021;52:3109–17.
24 Berkhemer OA, Fransen PSS, Beumer D, *et al*. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med* 2015;372:11–20.
25 McTaggart RA, Jovin TG, Lansberg MG, *et al*. Alberta stroke program early computed tomographic scoring performance in a series of patients undergoing computed tomography and MRI: reader agreement, modality agreement, and outcome prediction. *Stroke* 2015;46:407–12.
26 Bracard S, Ducrocq X, Mas JL, *et al*. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol* 2016;15:1138–47.
27 Román LS, Menon BK, Blasco J, *et al*. Imaging features and safety and efficacy of endovascular stroke treatment: a meta-analysis of individual patient-level data. *Lancet Neurol* 2018;17:895–904.
28 Wardlaw JM, von Kummer R, Carpenter T, *et al*. Protocol for the perfusion and angiography imaging sub-study of the third International stroke trial (IST-3) of alteplase treatment within six-hours of acute ischemic stroke. *Int J Stroke* 2015;10:956–68.
29 Dzialowski I, Pexman JHW, Barber PA, *et al*. Asymptomatic hemorrhage after thrombolysis may not be benign: prognosis by hemorrhage type in the Canadian alteplase for stroke effectiveness study registry. *Stroke* 2007;38:75–9.
30 Hirano T, Sasaki M, Tomura N, *et al*. Low Alberta stroke program early computed tomography score within 3 hours of onset predicts subsequent symptomatic intracranial hemorrhage in patients treated with 0.6 mg/kg alteplase. *J Stroke Cerebrovasc Dis* 2012;21:898–902.
31 Demaerschalk BM, Silver B, Wong E, *et al*. ASPECT scoring to estimate >1/3 middle cerebral artery territory infarction. *Can J Neurol Sci* 2006;33:200–4.
32 Bluhmki E, Chamorro A, Dávalos A, *et al*. Stroke treatment with alteplase given 3.0-4.5 H after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol* 2009;8:1095–102.
33 IST-3 collaborative group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International stroke trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet Neurol* 2015;14:485–96.
34 Ögren J, Irewall A-L, Bergström L, *et al*. Intracranial hemorrhage after ischemic stroke: incidence, time trends, and predictors in a Swedish nationwide cohort of 196 765 patients. *Circ Cardiovasc Qual Outcomes* 2015;8:413–20.
35 Yang P, Zhang Y, Zhang L, *et al*. Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020;382:1981–93.
36 Suzuki K, Matsumaru Y, Takeuchi M, *et al*. Effect of mechanical thrombectomy without vs with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021;325:244–53.
37 Zi W, Qiu Z, Li F, *et al*. Effect of endovascular treatment alone vs intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021;325:234–43.
38 Podlasek A, Dhillon PS, Butt W, *et al*. Direct mechanical thrombectomy without intravenous thrombolysis versus bridging therapy for acute ischemic stroke: a meta-analysis of randomized controlled trials. *Int J Stroke* 2021;16:621–31.
39 Kaesmacher J, Meinel TR, Nannoni S, *et al*. Bridging may increase the risk of symptomatic intracranial hemorrhage in thrombectomy patients with low Alberta stroke program early computed tomography score. *Stroke* 2021;52:1098–104.
40 Meyer L, Schönfeld M, Bechstein M, *et al*. Ischemic lesion water homeostasis after thrombectomy for large vessel occlusion stroke within the anterior circulation: the impact of age. *J Cereb Blood Flow Metab* 2021;41:20915792.
41 Powers WJ, Rabinstein AA, Ackerson T, *et al*. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American heart Association/American stroke association. *Stroke* 2018;49:e46–110.
42 von Kummer R, Allen KL, Holle R, *et al*. Acute stroke: usefulness of early CT findings before thrombolytic therapy. *Radiology* 1997;205:327–33.
43 McDonough R, Elsayed S, Faizy TD, *et al*. Computed tomography-based triage of extensive baseline infarction: aspects and collaterals versus perfusion imaging for outcome prediction. *J Neurointerv Surg* 2021;13:869–74.
44 Austein F, Wodarg F, Jürgensen N, *et al*. Automated versus manual imaging assessment of early ischemic changes in acute stroke: comparison of two software packages and expert consensus. *Eur Radiol* 2019;29:6285–92.
45 Kuang H, Najm M, Chakraborty D, *et al*. Automated aspects on noncontrast CT scans in patients with acute ischemic stroke using machine learning. *AJNR Am J Neuroradiol* 2019;40:33–8.
46 Sundaram VK, Goldstein J, Wheelwright D, *et al*. Automated aspects in acute ischemic stroke: a comparative analysis with CT perfusion. *AJNR Am J Neuroradiol* 2019;40:2033–8.
47 Nawabi J, Kniep H, Schön G, *et al*. Hemorrhage after endovascular recanalization in acute stroke: lesion extent, collaterals and degree of ischemic water uptake mediate tissue vulnerability. *Front Neurol* 2019;10:569.
48 Minnerup J, Broocks G, Kalkoffen J, *et al*. Computed tomography-based quantification of lesion water uptake identifies patients within 4.5 hours of stroke onset: a multicenter observational study. *Ann Neurol* 2016;80:924–34.
49 Broocks G, Flottmann F, Ernst M, *et al*. Computed tomography-based imaging of Voxel-Wise lesion water uptake in ischemic brain: relationship between density and direct volumetry. *Invest Radiol* 2018;53:207–13.
50 Nawabi J, Flottmann F, Kemmling A, *et al*. Elevated early lesion water uptake in acute stroke predicts poor outcome despite successful recanalization - When "tissue clock" and "time clock" are desynchronized. *Int J Stroke* 2021;16:1747493019884522.