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ORIGINAL COMMUNICATION

Endovascular stroke treatment's impact on malignant type of edema (ESTIMATE)

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Abstract
Background and purpose In patients with acute ischemic stroke and large vessel occlusion, the prognosis has improved tremendously since the implementation of endovascular thrombectomy (EVT). The effect of EVT on the incidence of malignant middle cerebral artery infarctions (MMI) has not been studied before.
Methods ESTIMATE, a multicenter retrospective study, evaluates data of ischemic stroke patients with occlusion in the anterior circulation in the years of 2007–2015 comparing three treatment options (no therapy; IV-TPA; IV-TPA plus EVT or EVT only). Primary endpoint of the study was the incidence of MMI on follow-up imaging and mortality rates. Secondary endpoints were functional outcome, further clinical and imaging data. Logistic and Cox-regression models with a propensity score weighting approach were applied to evaluate differences between treatment groups.
Results In 2161 patients over 9 years, EVT reduced the MMI rates significantly: patients without acute stroke treatment had increased odds for MMI of 1.57 [95% confidence interval (CI) 1.49–1.65]. In contrast, after treatment with IV-TPA, only we observed an OR of 0.88 (95% CI 0.83–0.94, $p<0.001$), and after EVT an OR of 0.80 (95% CI 0.76–0.85, $p<0.001$). This was more pronounced in larger pretreatment infarctions (ASPECTS < 5, $p<0.01$). IV-TPA also lowers the MMI rates but not to the same extent. EVT-treated patients had increased survival rates ($p<0.05$) and the best functional outcome at discharge.
Conclusions The findings of this study illustrate that occurrence of MMI and mortality rates was significantly reduced in patients treated with EVT.

Keywords Infarction · Middle cerebral artery · Stroke · Brain ischemia · Thrombectomy · Treatment outcome

Introduction

The prognosis for patients with acute ischemic stroke and large vessel occlusion of the anterior circulation has dramatically improved since the introduction of endovascular thrombectomy (EVT) using stent-retriever devices [11, 22, 29]. In cases of unsuccessful recanalization or prolonged hypoperfusion, large infarctions may occur leading to "malignant middle cerebral artery infarctions (MMI)" [30]. Randomized controlled trials (RCTs) were not designed to detect a significant effect of EVT on the MMI incidence, particularly not in large pretreatment infarctions [9]. Subgroup analyses from MR-CLEAN and further retrospective case series suggest that patients with large infarction cores may benefit regarding functional outcome [8, 10]. Rates of decompressive hemicraniectomy did not differ compared to usual care [5, 7, 24]. To elucidate the effect of EVT on MMI one retrospective single-center study found a significant frequency reduction of decompressive hemicraniectomy attributing this to the treatment with EVT [15]. However, the design of their study did not allow proving causality.

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The effect of EVT on the incidence of MMI should be addressed in a large multicenter study, rather comparing MMI rates than surrogate parameters, such as numbers of hemicraniectomies. Because such retrospective analyses are prone to confounding by indication [3], sophisticated statistical methods are crucial to avoid major bias, i.e., propensity score methods [26]. Therefore, the Endovascular Stroke Treatment´s Impact on Malignant Type of Edema (ESTIMATE) study aims to assess treatment effects in acute stroke patients with large vessel occlusion on MMI rates.

Methods

In a retrospective multicenter study, we gathered data from patients with acute ischemic stroke in the period between 2007 and 2015 who met the following inclusion criteria: (1) acute ischemic stroke in the anterior circulation and (2) large vessel occlusion of the anterior circulation, i.e., occlusion of the internal carotid artery (ICA), middle cerebral artery (MCA), a combination of both, or occlusion of the ICA terminus (ICAT). Patients' diagnostics and treatment were performed according to international guidelines [11] and local in-house protocols. All five participating centers were Neurological Departments at University Hospitals with comprehensive stroke centers and access to neurointerventional and neurosurgical facilities on a 24/7 basis with adequate expertise in the treatment of stroke, including decompressive hemicraniectomy.

We gathered time metrics data regarding symptom onset, time of admission, and length of hospital stay. Revascularization success using the thrombolysis in cerebral infarction (TICI) classification was obtained [28]. The completion of decompressive hemicraniectomy was noted, if applicable. The following imaging data were collected: infarction size on admission (Alberta stroke program early CT score, ASPECTS), site of vessel occlusion, incidence of MMI, and presence of intracranial hemorrhage (using the Heidelberg bleeding classification, HBC if follow-up CT was performed) [1]. We evaluated demographic and clinical data, including the National Institutes of Health-Stroke Scale (NIHSS) score on admission and discharge, and the frequencies of other co-morbidities (prior stroke, atrial fibrillation, and cardiovascular risk factors). Infarction etiology was classified according to the trial of ORG 10,172 in acute stroke treatment (TOAST) criteria which could be attributed to atherosclerosis, cardioembolism, small-vessel occlusion, other determined and undetermined etiology [12]. Functional outcome was obtained according to available data either as modified Rankin Scale (mRS)- or NIHSS scores at discharge, or the type of residence (rehabilitation, hospital, nursing home, and other hospital) following the primary hospital stay.

Primary and secondary endpoints were prespecified prior to data collection in a consensus meeting of the Initiative of German Neurointensive Trial Engagement (IGNITE)-study group. Primary endpoint was the incidence of MMI based on imaging criteria: (1) infarction size > 66% of MCA territory on CT, or > 50% in CT plus 145 ml lesion on MR-diffusion-weighted imaging; (2) with or without additional infarction of the anterior or posterior cerebral artery; and (3) at least partial infarction of the basal ganglia [20]. Secondary endpoints were the rates of decompressive hemicraniectomy and mortality, functional outcome, and imaging data (ASPECTS, HBC). We planned a subgroup analysis of large pretreatment infarctions (ASPECTS 0–4 points).

The aim was to evaluate differences in endpoints between the three treatment groups (no acute stroke therapy, intravenous thrombolysis (IV-TPA) only, EVT ± IV-TPA). We report mean values and standard deviations (continuous outcomes), and relative and absolute frequencies (categorical variables), then descriptive *p* values stemming from a univariate ANOVA for continuous and from a Chi-squared-test for categorical outcomes. To compensate for possible group differences with respect to main potential confounders (age, NIHSS at admission and the year of treatment) inverse propensity score weighting was applied. We implemented a Generalized Boosted Model to estimate the propensity score [23]. Up to 5000 regression trees were used to iteratively estimate the average treatment effect with the stopping rule based on the average absolute standardized mean difference and shrinkage of 0.01. Five cross-validation folds were used to prevent overfitting (with a fraction of 0.6 as training and 0.4 as validation set). After the weighting procedure, we checked whether the variables were well-balanced.

A logistic regression model on the weighted data set was used to model the influence of the different treatments on MMI; logistic regression models or Cox proportional hazard models to model the influence of the secondary outcomes. Odds or hazard ratios, depending on the scale level, are reported.

Sensitivity analyses were performed with respect to the matching algorithm including a simple multinomial logit score and covariance-balancing propensity scores [6].

A *p* value less than 0·05 was considered as significant. Since this being an exploratory trial, the *p* values are interpreted only in a descriptive way and no adjustment for multiple testing was performed. All analyses were implemented using R, version 3·4·0 [13], and its extensions 'twang', 'CBPS', 'survminer', and 'ggplot2'.

Results

Patients' characteristics, diagnostics, and treatment

2161 patients matched the inclusion criteria of this study; demographic and clinical data are summarized in Tables 1 and 2. From 2007 to 2015, absolute numbers of stroke patients and EVT procedures increased continuously. Pretreatment median ASPECTS was seven points in all groups, with small-to-middle-sized infarctions (ASPECTS 5–10) present in 1281 (82.2%) patients and large infarctions (ASPECTS 0–4) in 277 (17.8%) and a significantly difference between treatment groups ($p < 0.01$). Recanalization by EVT was successful (TICI 2b/3) in 597 patients (71.3%).

Table 1 Baseline demographic, clinical characteristics, and group differences

Characteristic	No therapy ($N = 511$)	IV-TPA ($N = 543$)	EVT ± IV-TPA ($N = 1107$)	p value
Demographic characteristics				
Age—yr; mean (SD)	73.9 (14.3)	76.1 (13.5)	71.8 (13.2)	< 0.0001
Female sex—no. (%)	260 (60.2)	266 (56.4)	557 (56)	0.32
Premedication—no. (%)				
Antiplatelets	135 (28.9)	180 (35·4)	301 (28.1)	< 0.01
Oral anticoagulants	68 (15)	51 (10)	165 (15.4)	
None	386 (18.9)	423 (20.6)	836 (40.8)	
Statin[a]	83 (17.6)	85 (16.7)	237 (22.1)	0.02
Vascular risk factors—no. (%)				
Hypertension	378 (74)	409 (75.3)	852 (77)	0.38
Diabetes mellitus	130 (25.4)	120 (22.1)	243 (22)	0.27
Hyperlipidemia	146 (28.9)	149 (27.4)	322 (29.8)	0.62
Smoking	100 (21.7)	71 (14.1)	238 (24)	< 0.01
Atrial fibrillation	255 (50)	272 (50.1)	539 (48.7)	0.82
Prior stroke	97 (19)	78 (14.4)	159 (14.4)	0.04
Pretreatment imaging—no. (%)				
ASPECTS[b]—no. (%)				< 0.0001
5–10	239 (60)	282 (88.4)	760 (90.4)	
0–4	159 (40)	37 (11.6)	81 (9.6)	
Mean (SD)	5.5 (3)	7.4 (2.2)	7.4 (2.1)	
Scores on admission				
NIHSS on admission[c]—no. (%)	499 (23.4)	541 (25.3)	1096 (51.3)	
Median (IQR)	16 (10;20)	15 (11;19)	16 (13;20)	< 0.0001
Occlusion—no. (%)				< 0.01
MCA	195 (38.2)	332 (61.4)	588 (53.2)	
ICA	168 (32.9)	57 (10.5)	49 (4.4)	
ICA + MCA	58 (11.4)	85 (15.7)	159 (14.4)	
ICAT + MCA	89 (17.4)	67 (14.4)	309 (28)	
Occlusion side right	253 (49.6)	262 (48.4)	547 (49.5)	0.90
Onset-to-door [min] (SD)	512.3 (782)	125.6 (134.1)	170.5 (190.1)	< 0.0001

ASPECTS Alberta Stroke Program Early CT Score; *CCT* computed tomography; *EVT* endovascular stroke treatment; *ICA* internal carotid artery; *ICAT* terminus of internal carotid artery, *IQR* interquartile range, *IV-TPA* intravenous thrombolysis; *MCA* middle cerebral artery; *MRI* Magnetic resonance imaging; *NIHSS* National Institutes of Health-Stroke Scale; *N/no.* number; *SD* standard deviation; *yr* years

[a]Smaller sample size (469 in the no therapy, 508 IV-TPA and 1073 in the EVT ± IV-TPA-treatment group)

[b]The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is a measure of the extension of stroke. Score ranges from 0 to 10, higher scores indicating fewer early ischemic changes. ASPECTS were assessed manually in 76% patients based on CT and in 24% based on MRI data

[c]The NIHSS classifies neurological deficit from 0 (no deficit) to 42 (most severe deficit)

Table 2 Outcome results

Variable	No therapy (N = 511)	IV-TPA (N = 543)	EVT ± IV-TPA (N = 1107)	p value
Outcomes				
NIHSS at discharge, median (IQR)[a]	12 (4;16)	6 (2;12)	6 (2;13)	0.04
mRS at discharge, median (IQR)[b]	5 (4;6)	4 (2;5)	4 (2;5)	< 0.0001
0–3	112 (5.7)	183 (9.3)	436 (22.1)	< 0.01
4–6	361 (18.3)	298 (15.2)	581 (29.5)	
6	133 (28.1)	95 (19.8)	98 (9.6)	
Substantial reperfusion (TICI)—no. (%)[c]			838	
0–1			122 (14.6)	
2a			119 (14.2)	
2b			283 (33.8)	
3			314 (37.5)	
Logistics: mean (SD)				
Door-to-IV-TPA (min)[d]	NA	150.4 (91.2)	150.9 (124.6)	0.28
Door-to-groin (min)	NA	NA	243.2 (222.9)	
Subtypes of ischemic stroke				< 0.01
TOAST– no. (%)[e]				
1 (atherosclerosis)	88 (17.2)	84 (15.5)	214 (19.4)	
2 (cardioembolism)	213 (41.7)	273 (50.3)	567 (51.3)	
3 (small-vessel occlusion)	0	0	0	
4 (other determined etiology)	24 (4.7)	10 (1.8)	55 (5)	
5 (undetermined etiology)	186 (36.4)	176 (32.4)	270 (24.4)	

ASPECTS Alberta Stroke Program Early CT Score; *IV-TPA* intravenous thrombolysis; *NIHSS* National Institutes of Health-Stroke Scale; *EVT* endovascular stroke treatment; *IQR* interquartile range; *mRS* modified Rankin Scale; *N*/*no.* number; *SD* standard deviation; *TICI* thrombolysis in cerebral infarction scale; *TOAST* The Trial of Org 10172 in Acute Stroke Treatment

[a]Smaller sample size (342 in the no therapy, 426 IV-TPA and 905 in the EVT ± IV-TPA-treatment group)

[b]Smaller sample size (473 in the no therapy, 481 IV-TPA and 1017 in the EVT ± IV-TPA-treatment group)

[c]TICI; range 0 to 3; with 0 no antegrade flow beyond the occlusion, 1 minimal perfusion, 2a perfusion of < 50% of the vascular distribution of the occluded artery, 2b perfusion of ≥ 50 of the vascular distribution of the occluded artery, 3 complete perfusion; smaller sample size (838 patients)

[d]Smaller sample size (428 in the IV-TPA and 673 in the EVT ± IV-TPA treatment group)

[e]The Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification denotes five subtypes of ischemic stroke: (1) large-artery atherosclerosis, (2) cardioembolism, (3) small-vessel occlusion, (4) stroke of other determined etiology (nonatherosclerotic vasculopathies, hypercoagulable states, or hematologic disorders), and (5) stroke of undetermined etiology; smaller sample size (511 in the no therapy, 543 IV-TPA and 1106 ind the EVT ± IV-TPA-treatment group); the test was performed excluding TOAST = 3 as there are no patients in this category in any of the treatment groups

Primary outcome

In the raw data, MMI occurred in 691 (32.1%) patients. MMI rates differed significantly between treatment groups (no treatment: 256 (50.1%) of 511 patients, IV-TPA: 175/543 (32.2%) and EVT 263/1107 (23.8%); $p < 0{\cdot}01$). Propensity scores were estimated to adjust for differences between treatments. The main prognostic parameters age, NIHSS on admission, and year of treatment were significantly unbalanced in the raw data set ($p < 0.001$). The inverse of the propensity score was then used to balance the data (online supplement Table I).

Patients without recanalization treatment had increased odds for MMI of 1.57 [95% confidence interval (CI) 1.49–1.65]. Any treatment lowered the odds for experiencing MMI: after treatment with IV-TPA, we observed a reduced OR of 0.88 (95% CI 0.83–0.94, $p < 0.001$), and even a greater reduction after treatment with EVT with OR of 0.80 (95% CI 0.76–0.85, $p < 0.001$).

We further evaluated the risks of MMI in pretreatment subgroups for high ASPECTS (≥ 5) and low ASPECTS (< 5). In patients with low ASPECTS, we observed a non-significant reduction of the odds in the IV-TPA group with OR 0.85 (95% CI 0.71–1.01, $p = 0.07$). EVT lowered the odds significantly compared to no acute stroke treatment with OR of 0.73 (95% CI 0.64–0.82, $p < 0.01$). In contrast, we could not observe a decreased MMI risk in patients with high ASPECTS: compared to no acute therapy IV-TPA has an OR of 1.03 (95% CI 0.95–1.11, $p=0.50$) and EVT an OR of 0.98 (95% CI 0.92–1.04, $p=0.53$).

Secondary outcomes

In-house mortality was the lowest in the EVT group (157 patients; 19.4%). 88 (27%) of IV-TPA patients died, whereas 151 (35.9%) patients without acute treatment deceased. Death was attributed to MMI in 218 patients (10.1% of all 2161 patients; 55.1% of all patients who died during their hospital stay). 146 patients (6.8% of all; 36.9% of the deceased) died because of documented other reasons, which were: palliative treatment (90 patients; 22.7% of patients who died), second cerebral ischemia or hemorrhage (10 patients; 2.5%), and other medical cause (reanimation, sepsis and others; 46 patients, 11.6%). In 32 (8.1%) patients, the reason of death was declared unknown. There was no significant difference between groups whether death occurred due to MMI or not ($p=0.12$).

Decompressive hemicraniectomy was rarely performed with a rather constant rate over the years (112/ 5.2% patients in total, with 2–28 operations/year, relative frequency of 0.00–0.01%). There was no significant difference between groups regarding rates of hemicraniectomy ($p=0.93$): 25 (4.9%) patients without acute treatment received hemicraniectomy, 28 (5.2%) treated with IV-TPA, and 59 (5.3%) treated with EVT. Figure 1 shows frequencies of MMI and hemicraniectomy per year.

The effect of treatment on functional outcome reflected by mRS levels at discharge was best with a favorable outcome (mRS 0–3) in 436 (42.9%) in the EVT group. It differed significantly between groups ($p<0.01$). Only 183 (38.0%) of IV-TPA patients and 112 (23.7%) of patients without acute therapy were discharged with a mRS 0–3. EVT patients also showed a lower NIHSS at discharge ($p<0.05$) and were more often discharged home (128, 15.8%).

Cox-regression analysis (Fig. 2) demonstrated that any treatment prolonged the time from stroke to discharge being a reflection of survival rate. This effect was significant in patients treated with EVT ($p<0.05$). The hazard ratio of being discharged after treatment with IV-TPA compared to no therapy is exp (− 0.246; − 0.38 to 0.11) = 0.782. For EVT treatment compared to no therapy, the hazard ratio amounts to 0.514 with exp (− 0.67; − 0.81 to 0.53).

In regards to complications, there were 686/1284 (53.4%) patients showing no intracerebral hemorrhage analyzing follow-up imaging during hospital stay. 238/1284 (18.5%) patients had bleeding incidents (PH, SAH, IVH, remote bleedings) and 360/1284 (28.0%) hemorrhagic transformations (type HT1 and HT2). Comparing treatment groups, there was a significant difference between these incidents (any bleeding and hemorrhagic transformation) and no hemorrhage ($p<0.01$) with the highest number in patients receiving IV-TPA ± EVT.

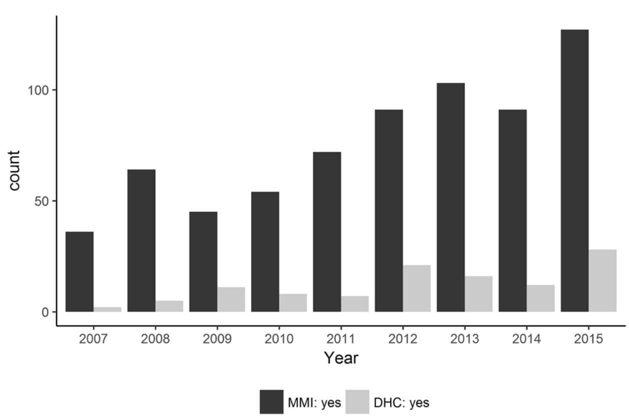

Fig. 1 Frequency of malignant media infarction and decompressive hemicraniectomy during the years 2007 and 2015. *MMI* malignant media infarction; *DHC* decompressive hemicraniectomy. Patients treated per year: 2007: in total 91 (no therapy: 41, IV-TPA only: 26, EVT ± IV-TPA 24), 2008: 99 (46/22/31), 2009: 45 (18/22/5), 2010: 81 (25/36/20), 2011: 125 (38/27/60), 2012: 180 (39/44/97), 2013: 206 (46/50/110), 2014: 228 (66/42/120), 2015: 306 (91/36/179)

Discussion

This study represents the largest multicenter cohort of patients with acute ischemic stroke and large vessel occlusion of the anterior circulation over the period from 2007 to 2015 and reports several important findings. First, increased utilization of EVT significantly reduces the rate of MMI. The effect of EVT in preventing MMI may be more pronounced in patients with large pretreatment infarctions. Second, any recanalization treatment lowers the mortality rate. In contrast, decompressive hemicraniectomy was performed constantly over the years independently from

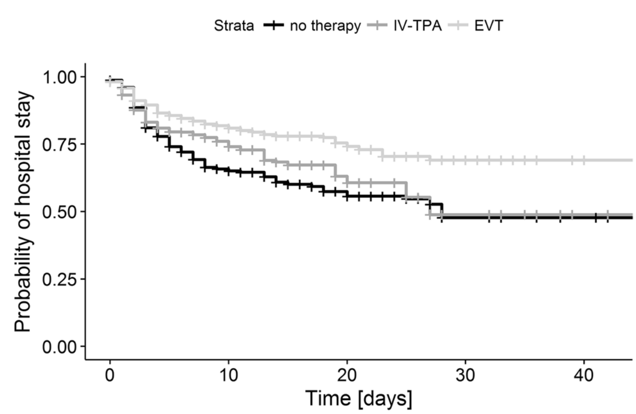

Fig. 2 Analysis of length of hospital stay between the different groups (no therapy, IV-TPA only and EVT ± IV-TPA). *IV-TPA* tissue plasminogen activator; *EVT* endovascular therapy

treatment measures. Furthermore, functional outcome differed between groups with patients benefitting most from EVT, even though hemorrhagic complications were the highest in patients receiving treatment with IV-TPA ± EVT. As balance with respect to potential confounders (age, NIHSS on admission, year of treatment) could not be achieved in these subgroups and sizes of the groups differed, these results are regarded as highly explorative.

MMI was present in 32.1% in our patient population. Former studies report on MMI incidence in 10–78% [16]. Some of the recent RCTs on patients treated with IV-TPA ± EVT mostly excluded patients with large pretreatment infarction. They report on lower MMI rates: 10.7% of the REVASCAT population [17] experienced an MMI and only 4.8% in the ESACPE trial [9].

In our study, the diagnosis of MMI was made in a semi-quantitative way based on results of former studies using imaging criteria as prognostic factors [20]; volumetric analysis was not feasible in such a large patient cohort. The imaging MMI criteria does not demand an infarction of the entire MCA territory as MMI was traditionally defined [30] but according to large RCTs, an MCA lesion of at least 66% [20, 25]. However, due to our semiquantitive imaging analysis approach, it is possible that smaller space occupying infarctions, with a size of at least > 50% of the territory, were classified as MMI. Therefore, the MMI rate could be overrated in our patient cohort, and the potential treatment effect of EVT may be underestimated, because some patients would never develop an MMI.

An initial lesion of 50% MCA territory is a strong and independent risk factor to develop MMI, and a 66% lesion accounts as a stronger predictor [OR 7.5 (CI 95%; 3.9–14.3)] [16]. An initial low ASPECTS < 7 and a lesion > 82 ml likely determine a progression to MMI [9, 10, 20]. In an MR-CLEAN-subgroup analysis of 28 patients with ASPECTS 1–4, EVT did improve the clinical outcome, but had no effect on mortality or hemicraniectomy rate [29]. Our unadjusted subgroup analyses suggested a positive effect of treatment options in patients with an initial ASPECTS ≤ 4 (but none with ASPECTS > 4): MMI rates seemed to be significantly lower in the EVT group ($p < 0{\cdot}01$) than in patients treated with IV-TPA only (not significant, $p = 0.324$) when compared to no therapy at all. Therefore, it can be speculated that patients benefit from EVT regarding MMI rates even if initial infarction is large (ASPECTS < 4). These results are supported by a retrospective analysis which could detect positive effects on a favorable functional outcome of EVT on patients with ASPECTS < 5 [21]. In our ASPECTS subgroup cohorts (ASPECTS 1–4 versus 5–10), age was significantly different in treatment groups with the youngest age average in the EVT group (of 68.1 and 72.3 years, respectively).

Despite pretreatment infarction size, age in general is a strong independent predictor for outcome in acute stroke patients; younger patients' functional outcome is better even in large initial infarction cores > 70 ml [7]. Further studies on outcome prediction were done and are so far non-conclusive. A recent study detected clinical signs of brain swelling and heavy smoking as independent predictors for experiencing an MMI [2].

Since there are no former studies on treatment effects on MMI rates, we can only associate secondary outcomes, such as hemicraniectomy rates, mortality, and functional outcome, to a possible occurrence of MMI.

The results of a single-center study report that the hemicraniectomy rate decreased since the implementation of EVT. They described a total number of 64 procedures (in 497 patients) [15]. The frequency of patients treated with hemicraniectomy was lower in our cohort (in total 112 patients over the period of 9 years, relative frequency of 0.00–0.01%) and we were not able to show any treatment effects. The study by Sporns et al. does not report on correction for potential confounders. So far, the differences of hemicraniectomy rates cannot be explained evoking the need to further trials: Compared to our patient, cohort EVT patients in the study of Sporns et al. showed smaller initial infarctions and lower median NIHSS on admission (5 versus 16 points in our cohort) [24]. Most importantly, the rate of decompressive hemicraniectomy does not reflect incidence of MMI. The decision to execute the operation is not only driven by hard facts but rather by soft facts such as personal attitudes, especially in older patients, and hemicraniectomy is underutilized [14].

Overall mortality in patients receiving EVT was 19.4% in our patient cohort. A meta-analysis of 8 large RCTs on EVT showed a trend towards reduced mortality with OR of 0.84 (0.67–1.05, $p = 0.12$) [4]. In our patient, cohort death was attributed to MMI in 52·3% of all deceased patients. This is significantly lower than the initially reported 80% death rate. Up until today, MMI patients still have a poor prognosis with a mortality rate of 33–53% despite maximal NICU treatment [15, 18, 25]. Age was higher in our patients (mean 73·4 years) compared to that in RCTs on decompressive hemicraniectomy (mean range 43–52 years in the DECIMAL-, DESTINY-, HAMLET trials; 70 years in the DESTINY II trial) [18, 27], or former RCTs on EVT (mean range 65–71 years). Higher age is associated with greater brain atrophy which can be protective regarding MMI and death [19]. In addition, the inclusion of patients with smaller infarction due to the selection by imaging criteria used in our trial for MMI diagnosis may have led to a lower mortality rate.

The results of RCTs showed positive effects of EVT on functional outcome (mRS of 0–2 after 90 days) with an OR of 1.71 (CI 95%; 1.18–2.48) [4]. Along with these results, we showed that EVT patients experience a favorable functional outcome at discharge. Our data, however, does not include a long-term follow-up without possible data balancing.

We analyzed data of a large multicenter patient cohort over the period of 9 years with rigorous statistical means to correct for bias due to three known confounders. Nevertheless, we acknowledge that our data interpretation is limited due to the retrospective study design and its collection in various centers; confounding due to additional variables cannot be excluded. We only included acute ischemic stroke leading to hospitalization into a comprehensive stroke center. Although propensity weighting minimized confounding by indication, residual bias of parameters were not investigated, as well as healthy cohort and center effects may not be fully excluded. Volumetric analysis of imaging data was not feasible in our large retrospective cohort. For MMI diagnosis, a semiquantitative imaging interpretation was used. This may have influenced the results with leading to a larger MMI rate, but still showed highly significant results regarding treatment effects on MMI development. Mortality was lower in our patient cohort compared to others. This could be due to data collected in comprehensive stroke centers only.

Summary/conclusions

In conclusion, our findings illustrate that MMI and mortality rates are significantly reduced in stroke patients treated with EVT and that even patients with a large pretreatment infarction (ASPECTS < 5) may benefit from EVT but this fact should be addressed in future studies. Furthermore, the effect of EVT on hemicraniectomy rates remains uncertain. EVT patients showed a higher rate of a favorable outcome at discharge.

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Compliance with ethical standards

Ethical approval This study was carried out in accordance with the declaration of Helsinki and the recommendations and approval of the protocol of the leading ethics committee, Germany (University of Ulm, EK64/16, 10.03.2016), and the local committees of the other participating centers. As ESTIMATE is a retrospective study, the boards waived the need for patient consent.

Conflicts of interest Dr. Beck has nothing to disclose. Dr. Fuhrer has nothing to disclose. Dr. Gerner has nothing to disclose. Dr. Huttner has nothing to disclose. Dr. Kieser has nothing to disclose. Dr. Meckel reports personal fees from Acandis GmbH, other from Covidien/Medtronic; Microvention; Stryker, grants from Bracco S.p.A., outside the submitted work; Dr. Meyne reports non-financial support from Boehringer Ingelheim, non-financial support from Daiichi Sankyo, outside the submitted work; Dr. Möhlenbruch reports personal fees from Board Membership, grants and personal fees from Consultancy, grants from Grant, grants and personal fees from Payment for lectures including Đervice on speakers bureaus, outside the submitted work; Dr. Neugebauer has nothing to disclose. Dr. Niesen has nothing to disclose. Dr. Ringleb reports personal fees from Boehringer Ingelheim, personal fees from Bayer, personal fees from Pfizer, personal fees from BMS, outside the submitted work; Dr. Schocke has nothing to disclose. Dr. Schönenberger has nothing to disclose. Svenja Seide has nothing to disclose. Christoph Vollmuth has nothing to disclose. Dr. Wodarg has nothing to disclose.

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