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Thrombectomy in Acute Ischemic Stroke in the Extended Time Window: Real-Life Experience in a High-Volume Center

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Objectives: Selected patients with acute ischemic stroke (AIS) caused by proximal middle cerebral artery (MCA) or internal carotid artery occlusion benefit from endovascular thrombectomy (EVT) in extended time window (6−24 h from last seen well) based on two landmark randomized controlled trials (RCTs) DAWN and DEFUSE-3. We evaluated patients' outcome in the real-life with the focus on adherence to protocol of the two RCTs. *Materials and methods:* We included consecutive patients with AIS (excluding basilar artery occlusions) referred to EVT in our stroke center in the extended time window between January 2018 and December 2019 and compared the outcome of patients who fulfilled criteria of the RCTs with those who did not. *Results:* Of the total of 100 patients, 23 complied with RCT's criteria and 18 presented with minor non-adherence (lower NIHSS score or longer treatment delay), whereas 22 patients had large baseline ischemia (>1/3 MCA), 28 presented with M2 and more distal occlusions, and 9 patients did not undergo perfusion imaging prior to EVT. Good 3-month outcome (modified Rankin Scale 0-2) was observed in 54% of those who either met the RCT criteria or presented with lower NIHSS score or longer treatment delay, but only in 30% of M2 occlusions, and in none of the patients with large baseline ischemia. *Conclusions:* Our findings highlight the impact of mostly large baseline ischemia but also vessel status when selecting patients for EVT in the extended time window and emphasize the need for further data in these patient subgroups.

Keywords: Real-life—Outcome—Ischemic stroke—Endovascular thrombectomy

Introduction

In acute ischemic stroke (AIS), fast recanalization of the occluded artery is crucial in order to re-establish perfusion of ischemic brain tissue. Intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT) are used to achieve this goal. The treatment effect is time-dependent at least in the conventional time windows of 4.5 h for IVT and 6 h for EVT. Such data come mostly from studies in anterior circulation stroke. We have previously shown that patients with basilar artery occlusion (posterior circulation) can achieve good functional outcomes in much longer than conventional time windows.[1] The most important outcome predictor in that study was extent of baseline ischemia (most importantly in the brainstem).

In line, two landmark randomized controlled trials (RCTs) in anterior circulation showed that EVT is effective in selected patients with proximal middle cerebral artery (MCA) or internal carotid artery (ICA) occlusion beyond 6 h and up to 24 h from last seen well.[2,3] Every second patient achieved favorable clinical outcome in these trials,

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where the typical patient had a small ischemic core and a large penumbra. However, only a small portion of stroke patients can potentially fulfill the trial criteria.[4]

Our aim was to analyze the real-life experience with EVT in the extended time window in our high-volume stroke center after publication of the two landmark trials. We evaluated the adherence to treatment protocols and hypothesized that non-adherence translates into worse functional outcomes.

Methods

Patients

The study was carried out at the Helsinki University Hospital, Helsinki, Finland which has catchment area of 2.2 million inhabitants for EVT, also being the sole EVT center in the province with about 250 stroke thrombectomies annually. Our baseline cohort consists of all consecutive patients with AIS referred to EVT as part of the routine care between January 2018 and December 2019, i.e., within the first 2 years after publishing the 2 landmark RCTs.[2,3] From the baseline cohort, we identified the patients treated in the extended time window i.e., over 6 h from last seen well (LSW). Patients with basilar artery occlusion were excluded from the analysis, because of their specific treatment protocol in our institution.[1]

The stroke severity was assessed using The National Institutes of Health Stroke Scale (NIHSS) prior to EVT and at 24 h post EVT. The stroke classification was performed using the Trial of Org 10172 in Acute Stroke Treatment (TOAST) criteria.[5] Clinical parameters and demographic details were obtained from electronic medical charts. All patients were prospectively included into the database.

Imaging

The imaging protocol included non-contrast computed tomography (NCCT) of the brain, computed tomography angiography (CTA), and computed tomography perfusion imaging (CTP) at baseline. All the scans were reviewed by experienced neuroradiologist (PV).

The extent of baseline ischemia was evaluated from NCCT in two ways: a) ASPECTS scoring system and b) visual inspection of early ischemic changes including blurring of grey-white matter junction either cortically or in deep white matter or hypoattenuation of the parenchyma.[6] We determined whether the baseline ischemia covered >1/3 of the total volume of the MCA region or ASPECTS <6, as was done in the two RCTs.[2,3]

The thrombus location was assessed on the baseline CTA according to Tomsick et al.[7] CTP evaluation was based on RAPID™ (iSchema View, Inc., California).

All EVTs were performed by experienced interventional radiologists using SOLUMBRA or ADAPT methods or redefined version of SOLUMBRA.[8] (Re)perfusion status from pre EVT and post EVT digital subtraction angiography (DSA) was scored according to the modified Thrombolysis in Cerebral Infarction (mTICI). Successful reperfusion was defined as a mTICI scale score of 2B or 3 and complete reperfusion as an mTICI scale score of 3.[9]

Final ASPECTS score and hemorrhagic transformation was evaluated on CT (vast majority) or magnetic resonance imaging (MRI) obtained approximately at 24 h after EVT (1 patient had no control imaging due to his death). Three patients had large intracerebral hemorrhage (ICH) making post EVT ASPECTS evaluation impossible.

All radiological data were analyzed on a picture archiving and communication system workstation (AGFA IMPAX; Agfa HealthCare, Belgium and Syngo.plaza and Syngo.share, Siemens, Germany) and by using in-built multiplanar reconstruction software (AGFA IMPAX; Agfa HealthCare, Belgium) or 3rd party software (Vitrea, Vital Imaging, Vital Images, Canon, USA).

Safety and functional efficacy outcome measures

Primary functional outcome measure was modified Rankin Scale (0 to 6) at 3 months, which was assessed by certified stroke neurologist by personal appointment or by telephone interview of patient or their caregivers. Good outcome was defined as modified Rankin Scale (mRS) 0 to 2. Mortality means mRS of 6 at 3 months. Hemorrhagic transformation was defined as any hemorrhagic transformation in post EVT imaging. Symptomatic ICH (sICH) was rated according to the Safe Implementation of Thrombolysis in Stroke (SITS) and European Cooperative Acute Stroke Study II (ECASS-II) criteria.[10,11]

Patients' allocation according to the adherence with trial criteria

It is obvious that the inclusion and exclusion criteria were not identical in the DAWN and DEFUSE-3 trials.[2,3] That is why we focused on the major aspects of the adherence to be able to classify patients into meaningful categories. It was our aim not to end up with numerous categories of non-adherence to the protocol. Hence, we streamlined the classification process in the simplified hierarchical order: first, we evaluated whether the patient had large ischemia on baseline imaging or large core on perfusion imaging (criterion 1). This was defined as >1/3 of the MCA region or ASPECTS <6, large core on perfusion imaging or no target mismatch according to the DAWN (radiological-clinical) and DEFUSE-3 (radiological) criteria. Secondly, if the patient did not have large baseline ischemia, we checked if the level of vessel occlusion was adherent to trial criteria (ICA and/or M1 segment of MCA). M2 segment and more distal occlusions were considered as non-adherent vessel status.[2,3] The latter included posterior cerebral artery (PCA) (criterion 2). Thirdly, if the patient passed also this criterion, we identified the patients without perfusion imaging performed

(criterion 3). Finally, we considered slightly longer time delays and lower NIHSS as minor non-adherence (criterion 4) and for the purpose of this study, these patients were merged into one group together with the trial-adherent patients.

Statistical analysis

Continuous variables were analyzed with Mann-Whitney U test and dichotomous variables with Fisher's exact test. Two-sided values of $P < 0.05$ were considered statistically significant. We used IBM SPSS Statistics for Windows, Version 25.0 (Armonk, NY: IBM Corp.) for the analyses.

Standard protocol approvals, registrations, and patient consents

Ethical review was not required for a retrospective analysis of the data collected as a part of routine clinical care. Institutional review board permission was obtained.

Data availability statement

The anonymized data that support the findings of this study are available from the corresponding author upon reasonable request.

Results

Baseline characteristics

In total, 506 patients were referred to EVT due to AIS into our center between January 2018 and December 2019. After excluding patients with basilar artery occlusion, 101 patients were found to be treated in extended time window (>6 h from LSW). One patient was lost to follow up and was excluded from the analysis resulting in a cohort of 100 patients, of whom 30 patients were secondary transfers from primary stroke centers. Only two patients had pre-stroke mRS >2 (mRS 3).

Table 1 summarizes the baseline characteristics of the cohort. The median age was 72 (IQR 61-79) years and 55 were females. At baseline, the median NIHSS score was 13 (IQR 7-18) and the median ASPECTS-score was 9 (IQR 7-10).

Stratified analyses based on adherence to trial criteria

Fig. 1 depicts the hierarchical stratification of the patients into 4 subgroups. Large baseline ischemia was observed in 22 patients. Of 28 patients with non-adherent vessel status (and without large baseline ischemia), the majority had M2-occlusion (20 proximal, 2 distal), 4 had M3-, 1 ACA-, and 1 PCA occlusion.

We have not found any age-related non-adherence. One patient had adherence to all criteria except a slightly longer time window, whereas 17 patients had NIHSS <10.

Table 1. *Baseline characteristics.*

	Whole cohort $n = 100$
Sex (female)	55
pre-stroke mRS	
0	86
1	6
2	6
3	2
Onset	
Witnessed	14
Unwitnessed	27
Wake-up stroke	59
Secondary transfer	30
mTICI baseline	
0	85
1	9
2A	2
2B	4
3	0
TOAST classification	
Large artery atherosclerosis	23
Cardiac embolism	47
Other	2
Multiple	1
Not sufficient work-up	13
Unknown	14

Data presented as n or median (IQR). Abbreviations: mRS = modified Rankin Scale, LSW = last seen well, min = minutes, mTICI = modified Thrombolysis in Cerebral Infarction grade, TOAST = Trial of Org 10172 in Acute Stroke Treatment

These were considered minor non-adherence and were combined in the group of 23 fully adherent patients.

Table 2 outlines the baseline characteristics of patients according to the adherence/non-adherence groups. Patients with non-adherent vessel status were older than the trial-adherent patients. Otherwise, the groups were well balanced when considering age, sex and cardiovascular comorbidities. One patient in the trial-adherent group did not have data available on the cardiovascular comorbidities.

Table 3 describes baseline characteristics of the index stroke in each subgroup. Patients with large baseline ischemia had higher NIHSS at baseline compared with patients in the adherent group. Of note, visual inspection of baseline ischemia showed good correlation with the ASPECTS score. In particular, none of the patients with >1/3 MCA baseline ischemia had ASPECTS score >6 (median 6, IQR 5-6), whereas all the patients who did not meet this criterion, had ASPECTS score >6. Compared to the trial-adherent group, patients with non-adherent vessel status had fewer EVT attempts. In this subgroup, 4 patients did not have any attempt due to their DSA showing no EVT target anymore. For one patient in the

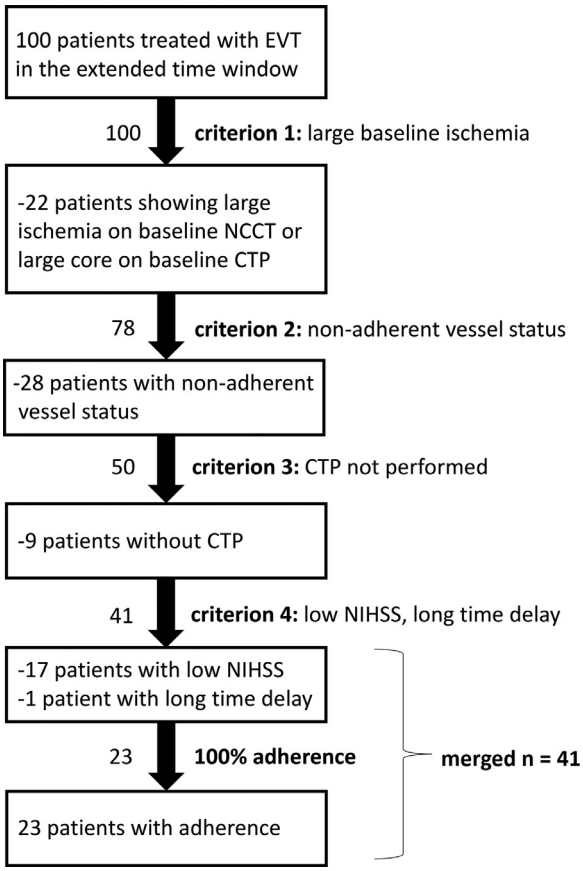

Fig. 1. *Flow chart describes patients' allocation to subgroups based on adherence / non-adherence to trial criteria. Abbreviations: EVT = endovascular thrombectomy, NCCT = non-contrast computed tomography, CTP = computed tomography perfusion, NIHSS = National Institutes of Health Stroke Scale.*

adherent group, the time of LSW was unknown, but the time from observation of symptoms to arrival was >6 h.

Finally, rates of reperfusion, NIHSS and ASPECTS at 24 h, hemorrhagic complications, and functional outcome are outlined in Table 4. The highest rates of good 3-month outcome were observed in the trial adherent group (54%). As expected, the patients in the large baseline ischemia group had the worst outcomes, and none of them achieved good outcome. In line, they had the highest frequency of any ICH, sICH, and mortality together with the lowest ASPECTS and highest NIHSS at 24 h. Ten patients with non-adherent vessel status achieved good 3-month outcome but none of them reached mRS 0-1. Moreover, of the 22 patients with M2-occlusion, 7 (30%) had mRS of 2 and 15 (70%) ended up with poor outcomes. Treatment complication (vessel perforation) was reported for one patient in this group.

Discussion

In this study of 100 consecutive AIS patients referred to EVT in the extended time window, of the patients who fully complied to RCT's inclusion criteria or presented with lower NIHSS score or longer treatment delay, more than a half achieved good outcome at 3 months. These results are comparable to DAWN (49%) and DEFUSE3 (45%) trials,[2,3] keeping in mind that our patients had lower NIHSS score. The rates of sICH and mortality at 3 months in this subgroup were also comparable to the RCTs.

In contrary, none of the patients with large baseline ischemia achieved good outcome at 3 months. Moreover, the rates of hemorrhagic complications that have previously been shown to be an independent predictor of poor outcome were much higher in this subgroup.[12,13] Our definition of large baseline ischemia on NCCT was identical to the one used in both DAWN and DEFUSE-3 trials.[2,3] Extent of ischemia >1/3 of the MCA showed good correlation with ASPECTS <7, which is in line with previous studies.[14]

Patients with lower ASPECTS have in general worse outcome.[15–17] In the REVASCAT study, patients were randomized up to 8 h from LSW if CT ASPECTS score was >6 or MRI ASPECTS score was >5.[18] In that study, less than 20% of patients presenting with ASPECTS score 6-7 ended up with good 3-month outcome if reperfusion was achieved more than 9 h from LSW.[18,19] In most previous large RCTs, low ASPECTS (i.e. <6-7) has been used as

Table 2. *Baseline characteristics per adherence to criteria.*

	Adherence to trial criteria* *n* = 41	Large baseline ischemia *n* = 22	Non-adherent vessel status *n* = 28	CTP not done *n* = 9
Age, years	67 (60−77) [48, 95]	72 (66−76) [52, 87]	77 (66−82) [38, 88] †	72 (61−81) [59, 83]
Sex, female	20 (48.8)	12 (54.5)	17 (60.7)	6 (66.7)
Diabetes	5 (12.5)	3 (13.6)	2 (7.1)	2 (22.2)
Atrial fibrillation	7 (17.5)	6 (27.3)	6 (21.4)	1 (11.1)
Hypertension	25 (62.5)	11 (50.0)	18 (64.3)	6 (66.7)
Hyperlipidemia	16 (40.0)	7 (31.8)	12 (42.9)	3 (33.3)
Previous ischemic stroke	6 (15.0)	4 (18.2)	6 (21.4)	2 (22.2)
Coronary heart disease	8 (20.0)	1 (4.5)	5 (17.9)	3 (33.3)

Data are presented as n (%) or median (IQR) [min, max]. * Including also patients with lower NIHSS or longer time delay. † P-value <0.05 compared to Adherence to trial criteria. Abbreviations: CTP = computed tomography perfusion imaging.

Table 3. *Stroke characteristics per adherence to trial criteria.*

	Adherence to trial criteria* $n = 41$	Large baseline ischemia $n = 22$	Non-adherent vessel status $n = 28$	CTP not done $n = 9$
NIHSS baseline	11 (6-18) [0, 26]	17 (14-20) [5, 38] †	10 (6-14) [0, 20]	16 (12-20) [6, 24]
ASPECTS baseline	9 (8-10) [7, 10]	6 (5-6) [0, 6] †	10 (9-10) [7, 10]	9 (7-10) [7, 10]
LSW to arrival, min	624 (482-922) [373, 1752]	630 (501-1005) [364, 1694]	726 (505-834) [400, 1288]	515 (428-784) [393, 981]
Arrival to end of EVT ‡, min	128 (102-166) [57, 470]	121 (93-182) [59, 301]	130 (98-161) [72, 413]	99 (78-171) [67, 260]
Number of attempts	2 (1-3) [0, 8]	2 (1-3) [1, 7]	1 (0-2) [0, 5] †	1 (1-3) [0, 7]
IVT	5 (12.2)	4 (18.2)	4(14.3)	3 (33.3)
IAT during EVT	1 (2.4)	3 (13.6)	2 (7.1)	2 (22.2)
Heparin during EVT	19 (46.3)	14 (63.6)	11 (39.3)	4 (44.4)

Data are presented as n (%) or median (IQR) [min, max]. * including also patients with lower NIHSS or longer time delay. † *P*-value < 0.05 compared to Adherence to trial criteria. ‡ Catheter removal. Abbreviations: CTP = computed tomography perfusion imaging, NIHSS = National Institutes of Health Stroke Scale, ASPECTS = The Alberta Stroke Programme Early CT Score, LSW = last seen well, EVT = endovascular thrombectomy, IVT = intravenous thrombolysis, IAT = intra-arterial thrombolysis.

Table 4. *Outcome according to trial adherence.*

	Adherence to trial criteria* $n = 41$	Large baseline ischemia $n = 22$	non-adherent vessel status $n = 28$	CTP not done $n = 9$
Successful reperfusion (mTICI 2b or 3)	30 (73.2)	16 (72.7)	16 (57.1)	7 (77.8)
Complete reperfusion (mTICI 3)	16 (39.0)	7 (31.8)	9 (32.1)	3 (33.3)
NIHSS 24h	6 (3-16) [0, 34]	17 (12-22) [7, 40] †	10 (7-13) [1, 31]	9 (3-22) [2, 31]
ASPECTS 24h	8 (7-9) [0, 10]	5 (4-5) [0, 6] †	7 (7-8) [5-10]	6 (3-9) [1, 10]
Any ICH	11 (26.8)	16 (72.7) †	12 (42.9)	4 (44.4)
ECASS II ICH	3 (7.3)	6 (27.3)	2 (7.1)	0 (0)
SITS sICH	1 (2.4)	3 (13.6)	2 (7.1)	0 (0)
mRS 0-2	22 (53.7)	0 (0) †	10 (35.7)	3 (33.3)
Death within 3 months	3 (7.3)	5 (22.7)	3 (10.7)	2 (22.2)

Data are presented as n (%) or median (IQR) [min, max]. * Including also patients with lower NIHSS or longer time delay. † *P*-value < 0.05 compared to Adherence to trial criteria. Abbreviations: CTP = computed tomography perfusion imaging, mTICI = modified Thrombolysis in Cerebral Infarction grade, NIHSS = National Institutes of Health Stroke Scale, ASPECTS = The Alberta Stroke Programme Early CT Score, ICH = intracerebral hemorrhage, ECASS = European Cooperative Acute Stroke Study, SITS sICH = Safe Implementation of Treatments in Stroke Symptomatic intracerebral hemorrhage, mRS = modified Rankin Scale.

an exclusion criterion.[2,3,20–23] Even though recent meta-analysis showed that also these studies included a small proportion of patients with more extensive baseline ischemia (ASPECTS 0-5), the benefits of EVT in this subgroup remain unclear.[24] RESCUE-Japan LIMIT -study randomized Japanese patients with large baseline ischemia (ASPECTS 3-5) into EVT or medical care. In the EVT group, 31% of patients achieved favorable 3-month outcome (defined as mRS 0-3 and not mRS 0-2 as in our study) compared to 13% in the medical care group. Of note, all the patients treated in the extended time window had baseline MRI and patients with acute ischemic changes on fluid-attenuated inversion recovery (FLAIR) were excluded.[25] There are several other ongoing trials evaluating safety and efficacy of EVT in patients with large ischemic core both in the conventional and extended time window which in the future will help to address treatment decisions in this patient population.

In our study, only 30% of the patients with M2 occlusions achieved good outcome. As an indirect comparison, of the M2-occlusion patients in the conventional time-window, good functional outcome was reported in almost 60% after EVT and in 40% after best medical treatment (this included alteplase).[26] Another study reported good recovery in as much as 70% of patients with M2 occlusion.[27] Furthermore, there are some reports of patients with M2 occlusions that have not received any recanalization treatment whatsoever. In particular, Lima et al reported that 54% of such patients had good recovery.[28] In another study of 90 isolated M2 occlusions, majority of whom (74%) did not receive revascularization treatment, 69% achieved good outcome.[29]

Thus, in our cohort patients with M2 occlusion treated with EVT in the extended time window end up with much worse outcome that expected. These patients were older, and though not reaching statistical significance,

also had lower recanalization rate compared to trial-adherent patients which might at least partially explain the high rate of poor functional outcome in this subgroup. Our findings highlight the need of further studies with larger sample sizes of M2 and more distal occlusions in the extended time window, preferably in the RCT setting.

A recent study reported that outcomes of patients selected for EVT in the extended time window based on NCCT were comparable to those selected with more advanced imaging.[30] In our cohort, the number of patients who were otherwise eligible for EVT but did not undergo CTP was too limited for drawing definite conclusions, but despite lack of significant ischemic changes on baseline NCCT, only 1/3 achieved favorable 3-month outcome.

We have not performed any multivariable regression model for several reasons. First, none of the patients with large baseline ischemia achieved good functional outcome, which is a robust finding per se, and this would be a challenging factor for conventional regression models. Second, it is not meaningful to compare the non-adherence groups among each other, as it is not a fair comparison. For example, we cannot compare outcome of patients with M2 or M3 occlusions to those with ICA/M1 occlusions and extensive baseline ischemia. However, we have discussed our findings in the light of the published data regarding the outcome of patients with M2 occlusion who have or have not received recanalization therapy. Third, we considered that the cohort size is not big enough for robust regression modeling.

Our study is a consecutive single center study of observational type. Our university hospital has a catchment area of 2.2 million inhabitants and is the sole provider of EVT in the province ensuring that our cohort represents unselected population. However, the observational nature, small sample size and heterogeneity of the cohort set limitations for the generalizability of our findings.

Our study highlights the fact that trial criteria should be followed until more data are available for specific subgroups of patients. For example, there are ongoing trials evaluating efficacy of thrombectomy in patients middle-size vessel occlusions or large baseline ischemia. To our knowledge, the present study is the first prospective real-life cohort with substantial number of patients collected after adaptation of the protocols of the two landmark RCTs into clinical practice.

Conclusion

Our study supports feasibility of EVT in the extended time window in carefully selected patients. However, non-adherence to trial protocol resulted into worse outcomes in our cohort. This highlights the need of further studies (with RCTs ongoing) to gain more understanding about outcomes of EVT in different patient subgroups including those with large baseline ischemia and M2 and more distal occlusions.

Declarations of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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None.

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