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Safety and clinical outcomes of endovascular therapy versus medical management in late presentation of large ischemic stroke

Adnan Mujanovic[1], Daniel Strbian[2], Jelle Demeestere[3,4], João Pedro Marto[5], Volker Puetz[6,7], Raul G Nogueira[8,9], Mohamad Abdalkader[10,11], Simon Nagel[12,13], Jean Raymond[14], Marc Ribo[15], Patrik Michel[16], Shinichi Yoshimura[17], Osama O Zaidat[18], Simon Winzer[6,7], Santiago Ortega-Gutierrez[19], Sunil A Sheth[20], James E Siegler[21], Anne Dusart[22], Diogo C Haussen[23], Hilde Henon[24], Bettina L Serrallach[1], Mahmoud H Mohammaden[23], Markus A Möhlenbruch[25], Marta Olive-Gadea[15], Ajit S Puri[26], Nobuyuki Sakai[27], Piers Klein[10,11], Liisa Tomppo[2], Francois Caparros[24], João Nuno Ramos[28], Mouhammad Jumaa[29], Syed Zaidi[29], Tomas Dobrocky[1], Nicolas Martinez-Majander[2], Stefania Nannoni[30], Flavio Bellante[22], Aaron Rodriguez-Calienes[19], Sergio Salazar-Marioni[20], Pekka Virtanen[31], Daniel PO Kaiser[7,32], Rita Ventura[5], Jessica Jesser[25], Alicia C Castonguay[29], Muhammad M Qureshi[9,33], Hesham E Masoud[34], Milagros Galecio-Castillo[19], Manuel Requena[15], Riikka Lauha[31], Wei Hu[35], Eugene Lin[18], Zhongrong Miao[36], Daniel Roy[14], Hiroshi Yamagami[37], David J Seiffge[38], Davide Strambo[16], Peter A Ringleb[13], Robin Lemmens[3,4], Urs Fischer[38,39], Thanh N Nguyen[11,40]* and Johannes Kaesmacher[1]*

Abstract

Introduction: The benefit of endovascular therapy (EVT) among stroke patients with large ischemic core (ASPECTS 0–5) in the extended time window outside of trial settings remains unclear. We analyzed the effect of EVT among these stroke patients in real-world settings.

Patients and methods: The CT for Late Endovascular Reperfusion (CLEAR) study recruited patients from 66 centers in 10 countries between 01/2014 and 05/2022. The extended time-window was defined as 6–24 h from last-seen-well to treatment. The primary outcome was shift of the 3-month modified Rankin scale (mRS) score. Safety outcomes included symptomatic intracranial hemorrhage (sICH) and mortality. Outcomes were analyzed with ordinal and logistic regressions.

Results: Among 5098 screened patients, 2451 were included in the analysis (median age 73, 55% women). Of patients with ASPECTS 0–5 ($n = 310$), receiving EVT ($n = 209/310$) was associated with lower 3-month mRS when compared to medical management (median 4 IQR 3–6 vs 6 IQR 4–6; aOR 0.4, 95% CI 0.2–0.7). Patients undergoing EVT had higher sICH (11.2% vs 4.0%; aOR 4.1, 95% CI 1.2–18.8) and lower mortality (31.6% vs 58.4%, aOR 0.4; 95% CI 0.2–0.9) compared to medically managed patients. The relative benefit of EVT was comparable between patients with ASPECTS 0 and 5 and 6–10 in the extended time window (interaction aOR 0.9; 95% CI 0.5–1.7).

Conclusion: In the extended time window, patients with ASPECTS 0–5 may have preserved relative treatment benefit of EVT compared to patients with ASPECTS 6–10. These findings are in line with recent trials showing benefit of EVT among real-world patients with large ischemic core in the extended time window.
Trial registration number: clinicaltrials.gov; Unique identifier: NCT04096248

Keywords
Endovascular therapy, mechanical thrombectomy, best medical treatment, large ischemic core, extended time-window

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[1]Diagnostic and Interventional Neuroradiology, University Hospital Bern, University of Bern, Bern, Switzerland
[2]Neurology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[3]Neurology, UZ Leuven, Leuven, Belgium
[4]Laboratory for Neurobiology, KU Leuven, Leuven, Belgium
[5]Neurology, Hospital de Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisbon, Portugal
[6]Neurology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[7]Dresden Neurovascular Center, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[8]Neurology, University of Pittsburgh Medical Center, Pittsburgh, USA
[9]Neurosurgery, University of Pittsburgh Medical Center, Pittsburgh, USA
[10]Neurology, Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, USA
[11]Radiology, Boston Medical Center, Boston University Chobanian & Avedisian School of Medicine, USA
[12]Neurology, Klinikum Ludwigshafen, Ludwigshafen, Germany
[13]Neurology, Heidelberg University Hospital, Heidelberg, Germany
[14]Interventional Neuroradiology, Centre Hospitalier de l'Universite de Montreal, Radiology, Montreal, Canada
[15]Neurology, Hospital Vall d'Hebron, Barcelona, Spain
[16]Neurology, Lausanne University Hospital and University of Lausanne, Lausanne, Switzerland
[17]Neurosurgery, Hyogo Medical University, Japan
[18]Neuroscience and Stroke Program, Bon Secours Mercy Health St. Vincent Hospital, Toledo, USA
[19]Neurology, University of Iowa, Iowa City, USA
[20]Neurology, UTHealth McGovern Medical School, Neurology, Houston, USA
[21]Neurology, University of Chicago, Chicago, USA
[22]Neurology, Hôpital Civil Marie Curie, Charleroi, Belgium
[23]Neurology, Grady Memorial Hospital, Atlanta, USA
[24]Neurology, Centre Hospitalier Universitaire de Lille, Lille, France
[25]Radiology, Heidelberg University Hospital, Heidelberg, Germany
[26]Division of Interventional Neuroradiology, University of Massachusetts Memorial Medical Center, Worcester, USA
[27]Neurosurgery, Seijinkai Shimizu Hospital, Kyoto, Japan
[28]Neuroradiology, Hospital de Egas Moniz, Centro Hospitalar Lisboa Occidental, Lisbon, Portugal
[29]Neurology, University of Toledo, Toledo, USA
[30]Clinical Neurosciences, University of Cambridge, Cambridge, UK
[31]Radiology, Helsinki University Hospital, University of Helsinki, Helsinki, Finland
[32]Institute of Neuroradiology, Faculty of Medicine and University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany
[33]Radiation Oncology, Boston Medical Center, USA
[34]Neurology, State University of New York, Syracuse, USA
[35]Neurology, The First Affiliated Hospital of USTC, China
[36]Interventional Neuroradiology, Beijing Tiantan Hospital, Beijing, China
[37]Division of Stroke Prevention and Treatment, University of Tsukuba, Tsukuba, Japan
[38]Neurology, University Hospital Bern, University of Bern, Bern, Switzerland
[39]Neurology, University Hospital Basel, University of Basel, Basel, Switzerland
[40]Neurology, Boston Medical Center, Boston, USA

*These authors contributed equally to this work.

Corresponding authors:
Johannes Kaesmacher, University Institute of Diagnostic and Interventional Neuroradiology, University Hospital Bern Inselspital, Freiburgstrasse 10, Bern 3001, Switzerland.
Email: johannes.kaesmacher@insel.ch

Thanh N Nguyen, Neurology, Boston Medical Center, Boston University Chobanian and Avedisian School of Medicine, Boston, MA 02118, USA.
Email: Thanh.nguyen@bmc.org

Introduction

Present stroke treatment guidelines recommend endovascular therapy (EVT) as the standard of care for patients with acute ischemic stroke due to large vessel occlusion (LVO).[1–3] Patients presenting with small ischemic core on admission, defined as Alberta Stroke Program Early CT Score (ASPECTS) 6–10, are routinely treated with EVT; however, the ASPECTS threshold below which there is no clinical benefit from EVT is not established as most pivotal EVT trials excluded patients presenting with large ischemic core (ASPECTS 0–5).[4]

Recent randomized controlled trials (RCT) enrolled patients with large ischemic core to receive either best medical treatment (BMT) or EVT. Five of these trials (Recovery by Endovascular Salvage for Cerebral Ultra-Acute Embolism–Japan Large Ischemic Core Trial [RESCUE-Japan LIMIT], Endovascular Therapy in Acute Anterior Circulation Large Vessel Occlusive Patients with a Large Infarct Core [ANGEL-ASPECT], A Randomized Controlled Trial to Optimize Patient's Selection for Endovascular Treatment in Acute Ischemic Stroke [SELECT2], Efficacy, Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window [TENSION] and LArge Stroke Therapy Evaluation [LASTE]) reported benefit of EVT over BMT in patients with low ASPECTS, while one RCT (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke [TESLA]) did not show superiority of EVT over BMT in this subpopulation.[5–10] However, the majority of patients included in these RCTs presented ⩽6 h of symptom onset and with ASPECTS 3–5. Moreover, patients included into RCTs usually present a highly selected subpopulation and may not be representative of real-world settings.[11] Some observational studies using multi-center data have also shown benefit of EVT among patients with ASPECTS 3–5 presenting >6 h.[12,13] However, other observational studies in the extended time window showed disparate results with limited sample size.[14–17] Therefore, it still remains unclear if patients with ASPECTS 0–5 who present in the extended time-window (6–24 h after symptom onset) might benefit from EVT in a real-world setting. This multicenter study aimed to evaluate the clinical outcomes and safety of EVT among acute ischemic stroke patients presenting with low ASPECTS in the extended time window.

Methods

CT for Late Endovascular Reperfusion (CLEAR) was a multicenter study of consecutive acute ischemic stroke patients undergoing EVT or BMT for LVO in the extended time window (clinicaltrials.gov, NCT04096248).[18] CLEAR recruited patients from 15 centers in 5 countries that were treated from January 2014 until December 2020. After the initial paper, there was an expansion to a total of 66 sites, of whom 21 sites contributed consecutive data on patients with large ischemic core up to May 2022.[18] The extended time window was defined as 6–24 h from last-seen-well (TLSW) to treatment. Rating of ASPECTS was based on either the last non-contrast CT or diffusion-weighted MRI before intervention. The study period was during a time before and after the DAWN and DEFUSE-3 trial results when EVT was not routinely offered at centers in Europe in the extended window. Selection criteria and neuroimaging protocols were site-adjudicated.[18] Institutional Research Board or ethics committees' approval were obtained from all enrolling sites. This study was conducted according to the Declaration of Helsinki and reported according to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines. Anonymized study data are available from the corresponding author upon reasonable request and presented research plan.

Population and outcomes

Inclusion criteria for the present study were: (1) prestroke modified Rankin Scale (pre-mRS) score 0–3; (2) baseline National Institutes of Health Stroke Scale (NIHSS) score ⩾ 6; (3) TLSW-to-Treatment time within 6–24 h; (4) LVO of the internal carotid artery or middle cerebral artery; (5) available data on the 3-month modified Rankin Scale (mRS) score. For the primary analysis, we included only patients presenting with ASPECTS 0–5, and for the secondary analysis we included patients across all ASPECTS (0–10).

The primary outcome of interest was the ordinal shift of the mRS score at 3 months. Secondary outcomes were independent ambulation, defined as mRS score 0–3 at the 3 month follow-up. Safety outcomes included rates of symptomatic intracranial hemorrhage (sICH), defined as intracranial hemorrhage associated with deterioration in NIHSS ⩾ 4, and mortality at 3 months.

Statistical analysis

Descriptive statistics were used to summarize patient characteristics, with continuous data reported as median (interquartile range) and categorical data reported as counts (%). The Mann-Whitney *U* test was used for continuous and Fisher exact test for categorical variables. Mixed effects regression models were used to account for the heterogeneity between study sites by using random-intercept adjusted for clustering at the site level. Independent ambulation at 3 months was estimated by both ordinal and logistic regressions. Regression analyses were adjusted for baseline and potential pathophysiological covariates which could influence patient outcome: age, sex, NIHSS on admission, prestroke mRS, occlusion site, hypertension, atrial fibrillation, diabetes mellitus, TLSW-to-treatment time, intravenous thrombolysis and treatment modality. For the secondary

analysis, which included patients with ASPECTS 0–10, we added a multiplicative interaction term between the ASPECTS (dichotomized as 0–5 vs 6–10) and treatment (EVT vs BMT). The odds ratios of the interaction term describe the change of the association between EVT versus BMT and outcome if ASPECTS 0–5. In the logistic regression analysis, an odds ratio < 1 for the interaction term indicates the association is less strong than expected when considering only the main effects, while odds ratio > 1 indicates the association is stronger than expected. Only patients with all available data were included in the analysis (complete case analysis). For sensitivity purposes, we used multiple imputations (Multivariate Imputation by Chained Equations, MICE method) to account for missing data, after which the whole dataset was included in the regression analysis. Results are reported as adjusted odds ratios (aOR) with corresponding 95% confidence intervals (CI). All statistical analyses were conducted in R (v4.0.0 R Foundation for Statistical Computing, Vienna, Austria).

Results

Among 5098 patients assessed for eligibility, we included 2451 patients in our analysis (Figure S1). For the primary analysis only patients with ASPECTS 0–5 were considered ($n = 310$). The median age of this cohort was 72 years (IQR 59–82), 53.5% were female and 67% underwent EVT. When stratified across treatment arms, those who underwent EVT were younger (68 years vs 80 years, $p < 0.001$), less likely to have hypertension (61.2% vs 79.2%, $p = 0.002$) or atrial fibrillation (33.1% vs 47.5%; $p = 0.03$), have lower pre-mRS (0, IQR 0–1 vs 1, IQR 0–3; $p < 0.001$), more likely to be transfer patients (57.7% vs 15.8%, $p < 0.001$), have an ICA occlusion (41.6% vs 21.8%, $p = 0.003$), shorter TLSW-to-Treatment time (11 h 30 min vs 14 h 5 min, $p = 0.001$) and were more likely to have received IVT (19.6% vs 4.0%, $p < 0.001$) as shown in Table 1. Patients in the BMT arm were more likely to undergo CT on admission, while EVT-treated patients more often had MRI on admission (CT vs MRI rates per treatment arms: 97% vs 3%; 61% vs 39%; respectively). The distribution of ASPECTS across treatment arms is shown in Table S1.

Main outcomes

Patients with low ASPECTS who underwent EVT were more likely to achieve independent ambulation at 3 months compared to patients undergoing BMT (mRS 0–3: 40.7% vs 11.9%, $p < 0.001$). After adjustment for the prespecified confounders, there was a significant association between mRS ordinal shift and EVT (aOR 0.4, 95% CI 0.2–0.7; Figures 1 and 2). The aOR for independent ambulation at 3 months was 5.0, 95% CI 2.2–12.6. Sensitivity analysis with imputed data showed comparable results (Table S2). Patients with low ASPECTS undergoing EVT had higher likelihood for sICH (aOR 4.1, 95% CI 1.2–18.8) and lower likelihood for mortality at 3 months (aOR 0.4, 95% CI 0.2–0.9). Comparable results were obtained with imputed data (Table S3).

Interaction effect

Patients with both low and high ASPECTS ($n = 2451$) were included in the secondary analysis. When comparing patients with low versus high ASPECTS, patients with lower ASPECTS were younger (72 years vs 73 years, $p = 0.04$), had higher NIHSS score at baseline (19, IQR 15–22 vs 16, IQR 11–20; $p < 0.001$), were directly admitted to the treating center (56.3% vs 45.1%; $p < 0.001$), had an ICA occlusion (35.2% vs 24.6%; $p < 0.001$) and received BMT (32.6% vs 9.9%; $p < 0.001$, Table S4). In the adjusted analysis, the interaction term ASPECTS × Treatment was neither associated with mRS shift at 3 months (aOR 0.9, 95% CI 0.5–1.7, Figure 3), nor with independent ambulation at 3 months (aOR 1.9, 95% CI 0.9–4.4, Figure 4). Analysis with multiple imputations for missing data showed comparable results (Table S5). The interaction term remained non-significant for both safety outcomes (aOR 0.6, 95% CI 0.1–3.2 and 0.7, 95% CI 0.4–1.5 for sICH and mortality, respectively; Table S6).

Discussion

The main findings of this study are: (1) In routine clinical practice, EVT is associated with higher rates of independent ambulation among acute ischemic stroke patients presenting with anterior large vessel occlusion and low ASPECTS. (2) In comparison to patients with low ASPECTS receiving BMT, patients undergoing EVT had lower mortality rates but increased rates of symptomatic intracranial hemorrhage. (3) Although the overall outcome of patients with low ASPECTS is poor, the relative benefit of endovascular therapy may be preserved among patients with low ASPECTS.

Treatment benefit of EVT

The RESCUE Japan Limit trial showed higher likelihood of achieving independent ambulation in the EVT versus BMT group (RR 2.4, 95% CI 1.3–4.4).[5] The same results were shown by the ANGEL ASPECT and SELECT2 trials (RR 1.5, 95% CI 1.2–1.9 and RR 2.1, 95% CI 1.4–2.9, respectively).[6,7] The TENSION trial was stopped prematurely for efficacy and reported comparable results for mRS 0–3 (aOR 2.8, 95% CI 1.5–5.5).[9] Meta-analyses showed that EVT was significantly associated with reduced disability (OR 1.7, 95% CI 1.4–2.1) and higher rates of independent ambulation (RR 1.8, 95% CI 1.3–2.5).[17] Preliminary results from the TESLA trial did not show superiority of EVT over BMT,[8] whereas the LASTE trial demonstrated

Table 1. Baseline characteristics of patients with low ASPECTS.

Variable		Overall	BMT	EVT	*p*	Missing (%)
N (%)		310	101	209		
BASELINE						
Age (median [IQR])		72 [59, 82]	80 [68, 85]	68 [55, 79]	<0.001	0
Female Sex (%)		166 (53.5)	60 (59.4)	106 (50.7)	0.188	0
Hypertension (%)		208 (67.1)	80 (79.2)	128 (61.2)	0.002	0
Atrial fibrillation (%)		99 (38.8)	48 (47.5)	51 (33.1)	0.029	17.7
Diabetes mellitus (%)		58 (18.7)	23 (22.8)	35 (16.7)	0.263	0
NIHSS at admission (median [IQR])		19 [15, 22]	19 [16, 24]	18 [15, 22]	0.158	0
pre-mRS (median [IQR])		0 [0, 1]	1 [0, 3]	0 [0, 1]	<0.001	0
Patient arrival (%)	Direct admission	170 (56.3)	85 (84.2)	85 (42.3)	<0.001	2.6
	Transfer	132 (43.7)	16 (15.8)	116 (57.7)		
Occlusion site (%)	ICA	109 (35.2)	22 (21.8)	87 (41.6)	0.003	0
	M1 MCA	178 (57.4)	67 (66.3)	111 (53.1)		
	M2 MCA	21 (6.8)	11 (10.9)	10 (4.8)		
	M3 MCA	2 (0.6)	1 (1.0)	1 (0.5)		
Imaging on admission (%)	CT	126 (40.9)	73 (73.7)	53 (25.4)	<0.001	0.6
	CTP	97 (31.5)	23 (23.2)	74 (35.4)		
	MRI	85 (27.6)	3 (3.0)	82 (39.2)		
ASPECTS (median [IQR])		5 [3, 5]	4 [2, 5]	5 [4, 5]	<0.001	0
Last known well to CT time (h) (median [IQR])		11.35 [8.63, 14.80]	13.95 [9.63, 16.63]	10.60 [8.05, 13.70]	<0.001	0
Last known well to treatment time (h) (median [IQR])		11.87 [9.08, 15.56]	14.08 [8.86, 17.15]	11.50 [8.85, 14.18]	0.001	0
TREATMENT						
Intravenous thrombolysis (%)		45 (14.5)	4 (4.0)	41 (19.6)	<0.001	0.0
OUTCOME						
NIHSS at discharge (median [IQR])		14 [8, 21]	15 [10, 24]	14 [8, 21]	0.308	31.6
sICH (%)		27 (8.9)	4 (4.0)	23 (11.2)	0.066	1.6
mRS, ordinal at 3 months (median [IQR])		4 [3, 6]	6 [4, 6]	4 [3, 6]	<0.001	0
mRS 0–3 at 3 months (%)		97 (31.3)	12 (11.9)	85 (40.7)	<0.001	0
mRS 0–2 at 3 months (%)		52 (16.8)	7 (6.9)	42 (21.5)	0.002	
mRS 0–1 at 3 months (%)		18 (5.8)	2 (2.0)	16 (7.7)	0.081	
Mortality (%)		125 (40.3)	59 (58.4)	66 (31.6)	<0.001	0

BMT: best medical therapy; EVT: endovascular therapy; NIHSS: National Institutes of Health Stroke Scale; pre-mRS: pre-stroke modified Rankin Scale score; ICA: internal carotid artery; MCA: middle cerebral artery; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; sICH: symptomatic intracranial hemorrhage.

superiority of EVT over BMT for patients with ASPECTS 0–5 presenting in the 7-h window, most of whom were selected by MRI.[10]

However, the number of patients presenting in the extended time window across these trials varies. In RESCUE Japan Limit, only 30% of patients were admitted within 6–24 h after TLSW.[5] In ANGEL ASPECT and SELECT2, these numbers were higher (60%–70%); however, these two trials enrolled patients with ASPECTS 3–5, and ANGEL ASPECT enrolled ASPECTS 0–2 with 70–100 ml core volume.[5–7] On the other hand, the median onset-to-groin-puncture time in TENSION was 4 h 12 min and the median onset-to-randomization time was 2 h. Similarly, the LASTE trial only enrolled patients in the early window (onset-to-last-known-well < 7 h) with median onset-to-imaging time of 2 h 50 min.[9,10] Moreover, there was heterogeneity across the design of these trials.[19] Selection criteria differed according to the imaging modality; some trials used automated volumetric methods, two trials enrolled patients mainly by assessing MRI mismatch, only three trials had international recruitment, mortality in the control groups differed and deviations from the intended intervention were common.[19,20] Additionally, patients with large ischemic core are thought to be fast progressors, and the potential benefit of EVT among patients who present in an extended window with potentially more established infarct has not been fully explored in real-world setting yet.

In the present analysis, we observed preserved beneficial association of EVT with better outcomes among patients with low and high ASPECTS in the extended time window. Our data suggest a potentially beneficial effect which was reported in RCTs that spanned a heterogeneous

Variable	mRS shift at 3 months	
	aOR (95% CI)	P-value
Age	1.06 (1.04 – 1.09)	**<0.001**
Sex (Male)	1.34 (0.79 – 2.29)	0.278
NIHSS on admission	1.18 (1.12 – 1.24)	**<0.001**
pre-mRS	0.91 (0.67 – 1.23)	0.540
Occlusion site (M1)	0.98 (0.82 – 1.72)	0.354
Occlusion site (M2+)	0.85 (0.42 – 2.57)	0.236
Hypertension	1.43 (0.81 – 2.49)	0.211
Atrial fibrillation	1.08 (0.59 – 2.01)	0.787
Diabetes mellitus	2.14 (1.12 – 4.16)	**0.023**
Last known well to treatment time (h)	0.99 (0.93 – 1.05)	0.718
Intravenous Thrombolysis	1.21 (0.58 – 2.59)	0.614
Treatment (EVT)	0.41 (0.23 – 0.72)	**0.002**

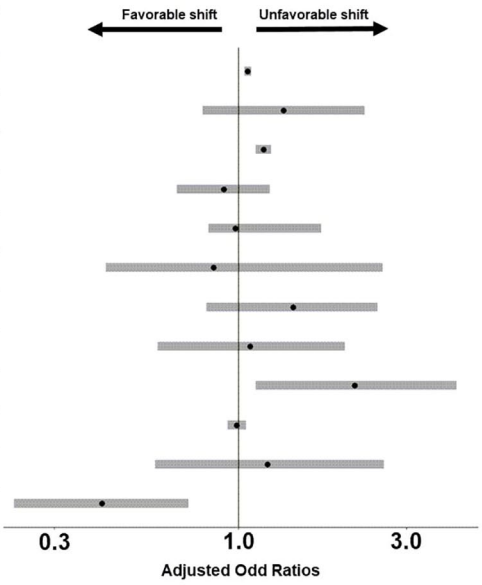

Figure 1. Adjusted ordinal regression among patients with low ASPECTS.
mRS: modified Rankin Scale; aOR: adjusted odds ratios; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; pre-mRS: pre-stroke modified Rankin Scale score; EVT: endovascular therapy. Odds ratios in ordinal regression > 1 indicate an unfavorable shift on the mRS, while odds ratios < 1 indicate a favorable shift on the mRS.

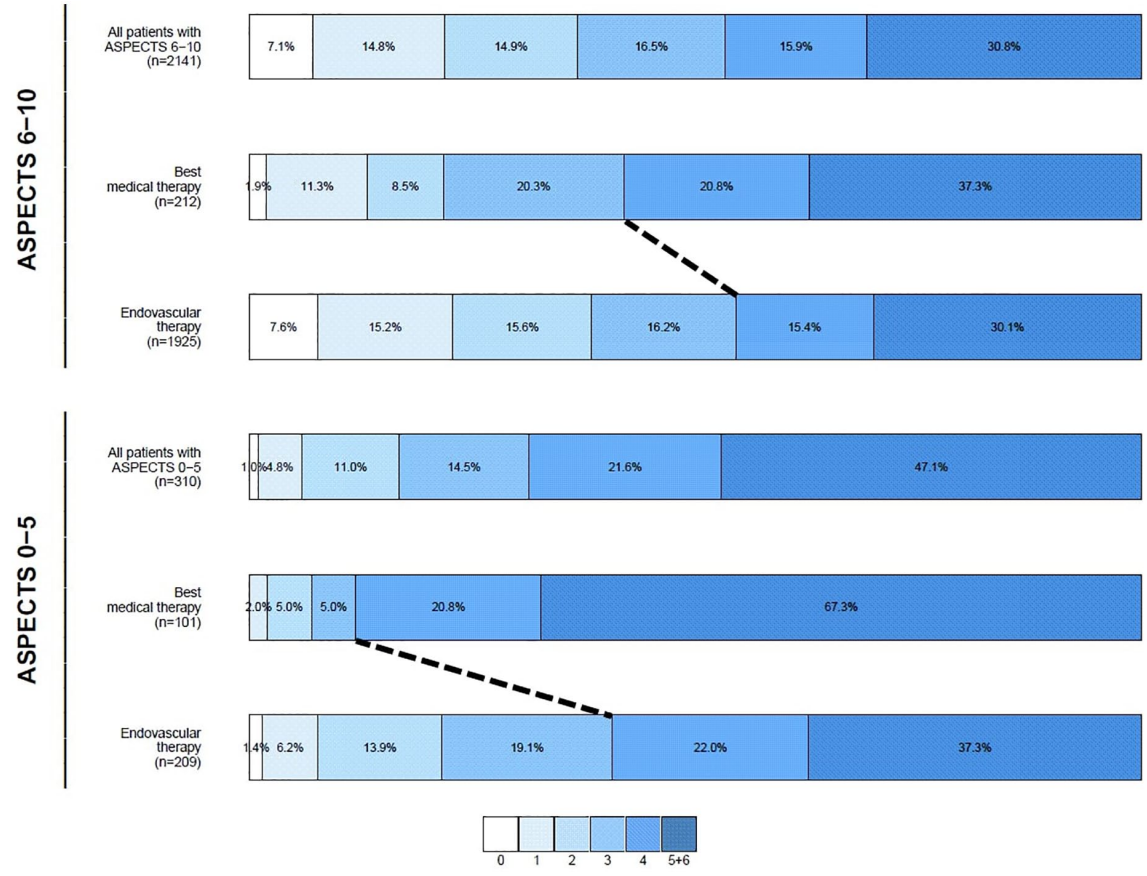

Figure 2. Modified Rankin Scale score shift at 3-month follow-up.
ASPECTS: Alberta Stroke Program Early Computed Tomography Score. Ordinal shift on the mRS (dashed black line for independent ambulation) was observed among patients with both high and low ASPECTS. After adjustment, the association between endovascular therapy and independent ambulation remained (ordinal regression aOR 0.4, 95% CI 0.2–0.7).

Variable	mRS shift at 3 months	
	aOR (95% CI)	P-value
Age	1.03 (1.02 – 1.03)	**<0.001**
Sex (Male)	1.01 (0.87 – 1.19)	0.864
NIHSS on admission	1.12 (1.10 – 1.14)	**<0.001**
pre-mRS	1.46 (1.34 – 1.58)	**<0.001**
Occlusion site (M1)	1.05 (0.82 – 1.21)	0.112
Occlusion site (M2+)	0.81 (0.69 – 0.97)	**0.015**
Hypertension	1.08 (0.91 – 1.29)	0.397
Atrial fibrillation	1.01 (0.85 – 1.20)	0.904
Diabetes mellitus	1.21 (1.01 – 1.45)	0.064
Last known well to treatment time (h)	1.01 (0.99 – 1.03)	0.150
Intravenous Thrombolysis	0.89 (0.74 – 1.09)	0.295
ASPECTS (0-5)	1.99 (1.23 – 3.31)	**0.006**
Treatment (EVT)	0.53 (0.41 – 0.69)	**<0.001**
ASPECTS (0-5)*Treatment (EVT)	0.95 (0.53 – 1.68)	0.868

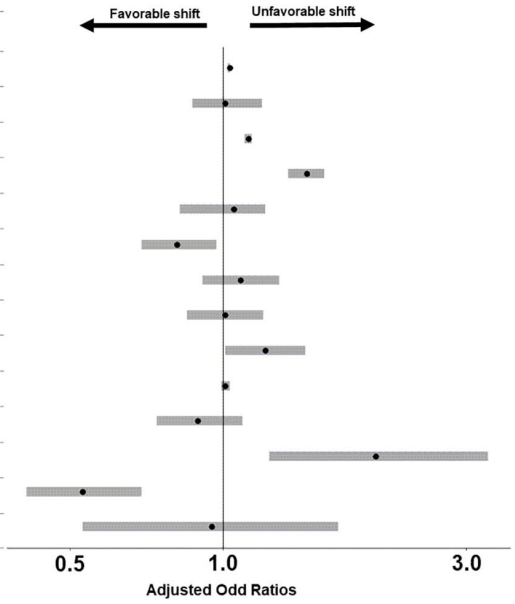

Figure 3. Adjusted ordinal regression among all patients.
mRS: modified Rankin Scale; aOR: adjusted odds ratios; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; pre-mRS: pre-stroke modified Rankin Scale score; ASPECTS: Alberta Stroke Program Early Computed Tomography Score; EVT: endovascular therapy. Odds ratios in ordinal regression > 1 indicate an unfavorable shift on the mRS, while odds ratios < 1 indicate a favorable shift on the mRS.

Variable	mRS 0-3 at 3 months	
	aOR (95% CI)	P-value
Age	0.96 (0.96 – 0.98)	**<0.001**
Sex (Male)	1.08 (0.89 – 1.30)	0.422
NIHSS on admission	0.90 (0.88 – 0.92)	**<0.001**
pre-mRS	0.75 (0.68 – 0.83)	**<0.001**
Occlusion site (M1)	1.21 (0.96 – 1.51)	0.103
Occlusion site (M2+)	1.49 (1.12 – 1.99)	**0.007**
Hypertension	0.89 (0.72 – 1.11)	0.300
Atrial fibrillation	0.98 (0.79 – 1.20)	0.835
Diabetes mellitus	0.85 (0.68 – 1.06)	0.144
Last known well to treatment time (h)	0.98 (0.96 – 1.00)	0.053
Intravenous Thrombolysis	1.02 (0.79 – 1.29)	0.901
ASPECTS (0-5)	0.32 (0.15 – 0.63)	**0.001**
Treatment (EVT)	2.00 (1.44 – 2.79)	**<0.001**
ASPECTS (0-5)*Treatment (EVT)	1.93 (0.88 – 4.44)	0.106

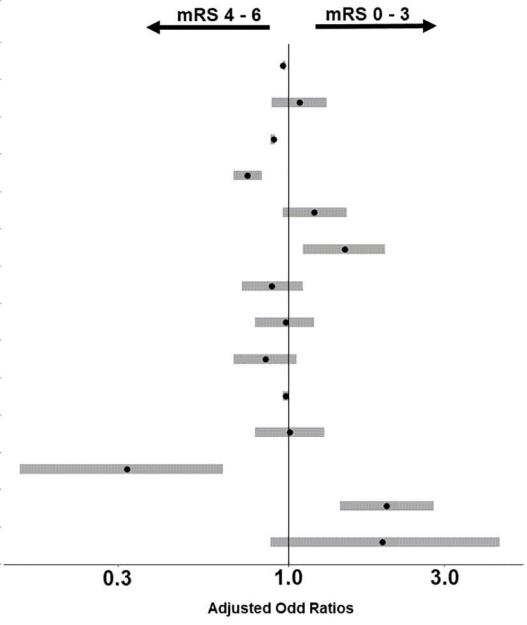

Figure 4. Adjusted logistic regression among all patients.
mRS: modified Rankin Scale; aOR: adjusted odds ratios; CI: confidence interval; NIHSS: National Institutes of Health Stroke Scale; pre-mRS: pre-stroke modified Rankin Scale score; EVT: endovascular therapy. After adjustment for the prespecified confounders, the interaction term ASPECTS × Treatment was not associated with independent ambulation at 3 months (aOR 1.9, 95% CI 0.9–4.4).

population with variable definitions of "large core" in various time windows. This finding is consistent with the increasing evidence that support EVT treatment in different ischemic stroke patient subpopulations. Concurrently, rates of independent ambulation seemed lower in large ischemic core patients who received BMT only.

Ischemic penumbra could also be a potentially relevant factor when deciding to pursue EVT among this patient subpopulation. The SELECT2 trial showed no heterogeneity of EVT treatment effect among patient with and without penumbra, across different mismatch profiles ($p > 0.5$ for all thresholds).[21] The beneficial effect of EVT was preserved even among late-presenting patients with no or minimal penumbra. While the presence of penumbra increases the probability of independent ambulation, it should not be the determining factor for pursuing EVT. Ischemic core volume, on the other hand, seems to be an important indicator for treatment outcome, especially among patients with volume > 150 ml.[21] Results from the upcoming pooled analysis of individual patient-level data from large core trials (MAGNA collaboration) will likely provide more data on these associations.[22]

Observational data

An analysis of the German Stroke Registry showed that patients with low ASPECTS who achieve successful reperfusion might benefit from EVT even when receiving it up to 17 h from symptom onset.[12] Subanalysis of the STAR registry reported that both low ASPECTS and extended window were independently associated with a lower odds of achieving good outcome.[13] In the present analysis, we observed that patients with low ASPECTS who received EVT had higher likelihood of achieving independent ambulation when compared to BMT. We also noticed a tendency by the treating team to choose younger patients with less comorbidities to undergo EVT. The percentage of patients with ASPECTS 4–5 were 93% and 55% in the EVT and BMT group, respectively. These differences between patients undergoing EVT and BMT are expected in the real-world setting and underline true differences in management and patient selection across centers before RCT data became available. To mitigate this selection bias, we adjusted our analysis for differences in baseline status. Even after adjustment for these differences, an association between EVT and favorable mRS shift was preserved showing potential efficacy of EVT in this subgroup of real-world stroke patients. Association between older age, preexisting comorbidities and poor outcome could be linked with an already compromised state of general health and overall decreased functional reserve in older age.[15,16]

EVT also seems to be cost-effective for patients with large ischemic core.[23,24] Data from several European countries, United States and China have shown that incremental cost-effectiveness can range up to US$11,000 per quality-adjusted life-years gained.[23,24] This association on cost-effectiveness was preserved even at different thresholds of willingness to pay, providing additional evidence of beneficial EVT effect across different healthcare systems.

Safety concerns

In four large-core RCTs (RESCUE Japan Limit, ANGEL ASPECT, SELECT2 and TENSION), rates of sICH at 24–48 h and all-cause mortality at 90 days were comparable between the two treatment arms. In the meta-analysis of the first three trials, there was a higher risk of sICH in the EVT arm (RR 1.9, 95% CI 1.1–3.7) and no difference in 3-month mortality (RR 0.9, 95% CI 0.8–1.1).[17] According to another study-level meta-analysis, sICH risk was higher in the EVT- compared to the BMT-arm (RR 1.8, 95% CI 0.9–3.5, $p = 0.07$).[17] In the sub-analysis of observational studies only, patients undergoing EVT had lower 3-month mortality risk (RR 0.6, 95% CI 0.5–0.7; $p < 0.001$).

We also observed a higher risk for sICH among patients with low ASPECTS undergoing EVT. This could be due to reperfusion injury with the sudden restoration of blood flow in a large infarct area, which subsequently leads to blood extravasation around the ischemic tissue. It could also be due to other individual factors that can mediate higher sICH risk (e.g. poor status at admission, older age, presence of edema, worse collateral status).[25,26] Despite the beneficial treatment effect of EVT, the prognosis of patients with low ASPECTS remains overall poor. Two thirds of patients with low ASPECTS were treated with EVT; however, only one-third achieved independent ambulation. This implies that most patients will remain disabled despite receiving treatment. Therefore, selection criteria for EVT in this subgroup of stroke patients should not be based purely on ASPECTS. ASPECTS are based on anatomical structures and this results in unequal coverage of brain tissue by individual ASPECT regions.[27] Further, this leads to disparity in weighing different brain regions without consideration on their eloquence.[27] ASPECTS should be considered only as a part of a broader diagnostic approach alongside other imaging and clinical characteristics that are used for EVT selection. This could maximize benefits over general treatment-related risks.

Limitations

The retrospective study design limits the generalization of our results. Patients undergoing EVT were in general younger, had better pre-stroke independence, fewer comorbidities and were more likely to receive intravenous thrombolysis. However, this selection bias is reflective of real-world management of large-core patients before RCT data were available. Even after adjustment for these confounders, the relative treatment benefit of EVT was still preserved. We cannot exclude that our analyses were adjusted for all relevant confounders and it remains unclear

if these adjustments appropriately mitigated the present selection bias. Multiple centers included in this study used different imaging tools, scanners and protocols which likely contributed to selection bias. This heterogeneity is reflective of real-world practice and differences between the centers were adjusted for in the analysis. The number of patients with ASPECTS 0–2 in our analyses was small; therefore we advise caution when extrapolating our results to these subgroups.[28] As our study was conducted prior to the results of multiple large core trials, changes in selection treatment paradigms may incur differing results as patients with larger ischemic core are considered for EVT.

Conclusion

In this multi-center study of real-world patients with large ischemic score who underwent endovascular therapy in the extended time window, there was a preserved relative treatment benefit of endovascular therapy comparable to patients with small ischemic core. Patients with large ischemic core in the extended time window might be a subpopulation of ischemic stroke patients who would benefit from endovascular therapy.

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This study received ethics committee approval from all enrolling sites.

Informed consent

Written informed consent was waived because of the retrospective nature of this study and because the research was considered no more than minimal risk.

Guarantor

T.N. Nguyen and J. Kaesmacher.

Contributorship

A. Mujanovic contributed to conception and design, analysis and interpretation of data, and writing of the original draft. D. Strbian

contributed to conception and design, analysis and interpretation of data. J. Demeestere contributed to conception and design, analysis of data, and writing of the original draft. J.P. Marto contributed to design and critical revision of the manuscript for important intellectual content. U. Fischer contributed to conception and design, critical revision of the publication for important intellectual content. T.N. Nguyen contributed to conception and design, critical revision of the publication for important intellectual content, and supervision. J. Kaesmacher contributed to conception and design, critical revision of the publication for important intellectual content, and supervision. All other authors contributed substantially to data acquisition, interpretation, and critical revision of the manuscript for important intellectual content. All authors approved the final version of the manuscript.

ORCID iD

Adnan Mujanovic https://orcid.org/0000-0002-6839-7134
Daniel Strbian https://orcid.org/0000-0001-9095-2344
Jelle Demeestere https://orcid.org/0000-0001-8186-0237
João Pedro Marto https://orcid.org/0000-0003-2277-5950
Markus A Möhlenbruch https://orcid.org/0000-0002-5075-704X
Nobuyuki Sakai https://orcid.org/0000-0002-3289-1210
Piers Klein https://orcid.org/0000-0001-7468-137X
Liisa Tomppo https://orcid.org/0000-0002-9369-5846
João Nuno Ramos https://orcid.org/0000-0001-9678-3422
Nicolas Martinez-Majander https://orcid.org/0000-0001-8489-7051
Flavio Bellante https://orcid.org/0000-0002-8718-9250
Sergio Salazar-Marioni https://orcid.org/0000-0002-2722-7542
Pekka Virtanen https://orcid.org/0000-0002-9547-4940
Jessica Jesser https://orcid.org/0000-0002-1236-8828
Manuel Requena https://orcid.org/0000-0002-5671-6484
David J Seiffge https://orcid.org/0000-0003-3890-3849
Thanh N Nguyen https://orcid.org/0000-0002-2810-1685

Supplemental material

Supplemental material for this article is available online.

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