THERAPEUTIC ADVANCES in
Neurological Disorders

Original Research

The pivotal role of timing of intravenous thrombolysis bridging treatment prior to endovascular thrombectomy

Ther Adv Neurol Disord

2023, Vol. 16: 1–13

DOI: 10.1177/17562864231216637

Jeremy Molad, Hen Hallevi, Estelle Seyman, Einor Ben-Assayag, Tali Jonas-Kimchi, Udi Sadeh, Ofer Rotschild, Naaem Simaan, Anat Horev, Jose Cohen, Ronen R. Leker and Asaf Honig

Abstract

Background: The role of intravenous thrombolysis (IVT) as bridging treatment prior to endovascular thrombectomy (EVT) is under debate and better patient selection is needed.

Objectives: As the efficacy and safety of IVT diminish with time, we aimed to examine the impact of bridging treatment within different time frames from symptom onset.

Design: A retrospective registry study.

Methods: Data were extracted from ongoing prospective EVT registries in two large tertiary centers. The current study included IVT-eligible patients with onset to door (OTD) < 4 h. We examined the efficacy and safety of bridging treatment through a comparison of the IVT + EVT group with the direct-EVT group by different time frames.

Results: In all, 408 patients (age 71.1 ± 14.6, 50.6% males) were included, among them 195 received IVT + EVT and 213 underwent direct EVT. Both groups had similar characteristics. In the IVT + EVT group only, longer OTD was associated with lower rates of favorable outcome ($p = 0.021$) and higher rates of hemorrhagic transformation (HT; $p = 0.001$). In patients with OTD $\leqslant 2$ h, IVT + EVT compared to direct EVT had higher rates of TICI 2b-3 (86.2% *versus* 80.7%, $p = 0.038$). In patients with OTD > 2 h, IVT + EVT had lower rates of favorable outcome (33.3% *versus* 56.9%, $p = 0.021$), worse discharge National Institutes of Health Stroke Scale [7 (2–13) *versus* 3 (1–8), $p = 0.024$], and higher rates of HT (34.0% *versus* 8.5%, $p < 0.001$).

Discussion: In this study, we found OTD times to have a significant effect on the impact of IVT bridging treatment. Our study shows that among patients with OTD < 2 h bridging treatment may be associated with higher rates of successful recanalization. By contrast, in patients with OTD > 2 h, bridging treatment was associated with worse outcomes. Further time-sensitive randomized trials are needed.

Keywords: bridging treatment, endovascular thrombectomy, thrombolysis

Received: 16 September 2023; revised manuscript accepted: 9 November 2023.

Correspondence to:
Jeremy Molad
Department of Stroke and Neurology, Tel-Aviv Sourasky Medical Center, 6 Weizmann Street, Tel-Aviv 64239, Israel
jeremymolad@gmail.com

Hen Hallevi
Einor Ben-Assayag
Department of Stroke and Neurology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Faculty of Medicine, Tel-Aviv University, Tel-Aviv, Israel

Estelle Seyman
Ofer Rotschild
Department of Stroke and Neurology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Tali Jonas-Kimchi
Udi Sadeh
Department of Radiology, Tel-Aviv Sourasky Medical Center, Tel-Aviv, Israel

Naaem Simaan
Department of Neurology, Ziv Medical Center, Safed, Israel

Anat Horev
Asaf Honig
Department of Neurology, Soroka Medical Center, Beer-Sheva, Israel

Jose Cohen
Department of Neurosurgery, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Ronen R. Leker
Department of Neurology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel

Introduction

Endovascular thrombectomy (EVT) is considered the most beneficial reperfusion therapy for acute ischemic stroke (AIS) due to large vessel occlusion (LVO) in the anterior circulation.[1] The role of intravenous thrombolysis (IVT) as a bridging treatment prior to EVT is still debatable. Although current guidelines advocate for IVT treatment in all eligible LVO cases,[1] studies examining bridging treatment, including six randomized control trials and several meta-analyses,[2–4] have demonstrated inconclusive results. Finding subpopulations that may benefit or conversely be harmed by the IVT + EVT approach may allow better patient selection that could potentially lead to improved outcomes.

The efficacy of IVT is time dependent on diminishing effects depending on the time from symptoms onset.[5] Moreover, the longer the brain parenchyma is subjected to ischemia, it is more susceptible to hemorrhagic transformation (HT) in the setting of LVO.[6] Therefore, our primary goal was to examine the impact of bridging-IVT treatment within different time frames from symptom onset.

Methods

Study population

This observational study was conducted in two large academic centers. Both centers prospectively enroll all patients with LVO who underwent EVT. The study was approved by the institutional review boards of the participating centers with a waiver of informed consent.

In the current study, we analyzed data from patients that presented within 4 h of symptoms onset, in the years 2017–2021 (Supplemental Figure 1). We compared clinical and radiological outcomes, between the IVT + EVT group (all patients were treated with alteplase) and the direct-EVT group. We examined the impact of both treatment strategies in accordance with symptoms onset to door times (OTD). Further analysis compared bridging treatment to direct EVT in patients with OTD below 2 h and in those with OTD between 2 and 4 h (As arrival after 4 h precludes thrombolysis administration within 4.5 h). The institutional protocols of our two academic centers allow patients presenting in the early stage of AIS who have an Alberta Stroke Program Early CT Score (ASPECTS)[7] $\geqslant$6 to undergo direct-EVT without bridging-IVT treatment if the neuroendovascular team is present at the hospital.

To minimize potential bias, we excluded from our study patients who were not eligible to receive IVT, including patients treated with oral anticoagulants. In addition, patients who showed major improvement with a resolution of their main deficits following IVT and were not taken to digital subtraction angiography if repeat CTA showed resolution of the previously seen vessel occlusion were excluded from the primary analysis. Data from the two centers for patients treated between 01 January 2016 and 31 December 2021 who met the inclusion criteria were pooled for retrospective analysis.

EVT treatment algorithm

All included patients underwent EVT using any approved device or approach at the discretion of the treating endovascular team. Data on procedural variables, including modified thrombolysis in cerebral infarction (mTICI) score[8] at the end of the procedure and the number of passes needed to achieve the best possible recanalization, were also studied. mTICI2b-3 was considered a successful target vessel recanalization. All patients were admitted to intensive care stroke units and treated with similar institutional protocols. Treatment protocols included intensive care unit admissions post-procedure maintaining a fixed systolic blood pressure below 140 mmHg for all patients who achieved target recanalization and below 180 mmHg for those who received IVT and did not achieve successful recanalization.

Data collection

Neurological deficits were measured using the National Institutes of Health Stroke Scale (NIHSS)[9] at admission and discharge. Time metrics were routinely measured at predefined definitions. Stroke etiology was classified with the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification.[10] All patients underwent CT angiography (CTA) upon admission and a repeat non-contrast head CT (NCCT) 24 h post-procedure. Imaging variables, including admission CTA and repeated NCCT, were routinely assessed by vascular neurologists and neuroradiologists blinded to the clinical scenario. Collateral status was assessed on admission CTA according to the Alberta stroke programme early CT score (ASPECT) collateral grading scale,[11] with a score of 4–5 defined as good collaterals. HT was assessed both radiologically and clinically according to the European Cooperative Acute Stroke Study 2 (ECASS-2) criteria.[12] We used post-EVT NCCT data to classify HT into petechial hemorrhagic infarction and parenchymal hematoma type 1 or 2, defined as confluent hemorrhage covering less or more than 1/3 of the infarct volume, respectively.[13] A dual-energy CT protocol was used to enable distinction between HT and contrast extravasation due to blood–brain barrier damage. Further clinical division was made into asymptomatic and symptomatic ICH (sICH). sICH was defined as any apparent extravascular blood in the brain or within the cranium that was associated with clinical deterioration (defined as an increase of 4 points or more in the score on the NIHSS), or

led to death, and was identified as the predominant cause of the neurologic deterioration.[14]

Functional outcome was assessed with the modified Rankin Score (mRS)[15] prior to stroke, upon discharge, and 90 days after stroke. A favorable functional outcome was defined based on mRS-90 as either mRS ≤ 2 for patients with baseline mRS ≤ 2 or mRS 3 in patients who had baseline mRS 3 prior to admission.

Statistical analysis

Statistical analysis was performed using the SPSS software (version 27.0, IBM, Chicago, IL, USA). $p < 0.05$ was considered significant. Continuous variables were reported as a mean value ($\pm$SD), ordinal variables as median and interquartile range (IQR), and dichotomous variables as a percentage of the total. Comparisons or distributions between categories were assessed using Student's *t*-test for continuous variables, the chi-square test for qualitative variables, and the Mann–Whitney or to compare differences between two independent groups when the dependent variable is either ordinal or continuous, but not normally distributed. Multivariate regression models that included age, sex, and predictors who were found significant in the univariate analysis were used to outline modifiers of outcome.

Results

In all, 408 patients (age: 71.1 ± 14.6, 50.6% males) were included in the study, among them 299 patients had symptoms to door time (OTD) of less than 2 h (average 56 ± 28 min) and 109 had OTD between 2 and 4 h (173 ± 37 min). No significant between groups differences were found in baseline characteristics, percent of bridging therapy, and outcome measures (Table 1).

Table 1. Patients' characteristics by symptoms to door.

Characteristics	OTD < 2 h *N* = 299	OTD > 2 h *N* = 109	*p* Value
Age (SD)	69.3 (14.9)	71.1 (14.6)	0.273
Sex: male (%)	152 (50.8)	55 (50.5)	0.946
Hypertension (%)	194 (64.9)	81 (74.3)	0.072
Diabetes (%)	91 (30.4)	37 (33.9)	0.499
Hyperlipidemia (%)	147 (49.2)	51 (46.8)	0.671
Smoking (%)	82 (27.4)	31 (28.4)	0.839
Atrial fibrillation (%)	103 (34.4)	35 (32.1)	0.659
Ischemic heart disease (%)	97 (32.4)	34 (31.2)	0.811
Valvular disease (%)	15 (5.0)	7 (6.4)	0.578
Congestive heart failure (%)	32 (10.7)	9 (8.3)	0.280
Chronic renal failure (%)	17 (5.7)	11 (10.2)	0.115
Prior stroke (%)	47 (15.7)	14 (12.8)	0.471
Malignancy (%)	32 (11.6)	14 (13.5)	0.610
Statins (%)	82 (29.3)	29 (27.6)	0.748
Antiplatelets (%)	86 (29.0)	28 (26.2)	0.583
Vessel lesion (%)			0.145
ICA	64 (21.4)	26 (25.2)	
M1 MCA	160 (53.5)	52 (47.7)	

(Continued)

Table 1. (Continued)

Characteristics	OTD < 2 h *N* = 299	OTD > 2 h *N* = 109	*p* Value
M2 MCA	44 (14.7)	21 (19.3)	
Basilar	16 (5.4)	3 (2.8)	
ACA	3 (1.0)	1 (0.9)	
PCA	1 (0.3)	0 (0)	
Tandem lesion	43 (14.4)	22 (20.1)	0.168
Side, right (%)	141 (47.2)	50 (45.9)	0.567
TOAST (%)			0.961
Cardioembolism	163 (54.5)	57 (52.3)	
Large artery atherosclerosis	59 (19.7)	29 (26.6)	
Other determined etiology	18 (6.0)	4 (3.7)	
Undetermined	44 (14.7)	12 (11.0)	
Collaterals, good (%)	121 (40.5)	50 (45.9)	0.296
Symptom to door (SD)	56.4 (27.7)	173.6 (36.7)	**<0.001**
Door to groin puncture (SD)	155.4 (157.0)	166.6 (187.0)	0.552
tPA (%)	145 (48.5)	50 (45.9)	0.463
Number of passes (IQR)	1 (1–3)	1 (1–3)	0.878
TICI 2b-3 (%)	242 (85.5)	89 (88.1)	0.514
First pass (%)	114 (38.1)	45 (41.3)	0.407
Stent (%)	46 (15.4)	15 (13.8)	0.766
HT (%)	52 (17.4)	22 (20.2)	0.460
HT PH (%)	23 (7.7)	16 (14.7)	**0.031**
HT PH2 (%)	14 (4.7)	4 (3.7)	0.678
Symptomatic HT (%)	7 (2.3)	1 (0.9)	0.368
NIHSS on admission (IQR)	16 (11–20)	14 (10–19)	0.662
NIHSS on discharge (IQR)	4 (1–9)	4 (1–9)	0.887
NIHSS, delta (IQR)	9 (2–14)	6 (2–11)	0.204
mRS baseline (IQR)	0 (0–1)	0 (0–2)	0.835
mRS discharge (IQR)	3 (2–5)	3 (2–5)	0.124
mRS 90 (IQR)	3 (1–5)	3 (1–4)	0.625
Mortality (%)	41 (13.7)	10 (9.2)	0.220
Outcome, favorable (%)	138 (49.6)	44 (45.8)	0.520

ACA, anterior cerebral artery; HT, hemorrhagic transformation; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery; PH, parenchymal hemorrhagic transformation.
p value < 0.05 was marked as bold.

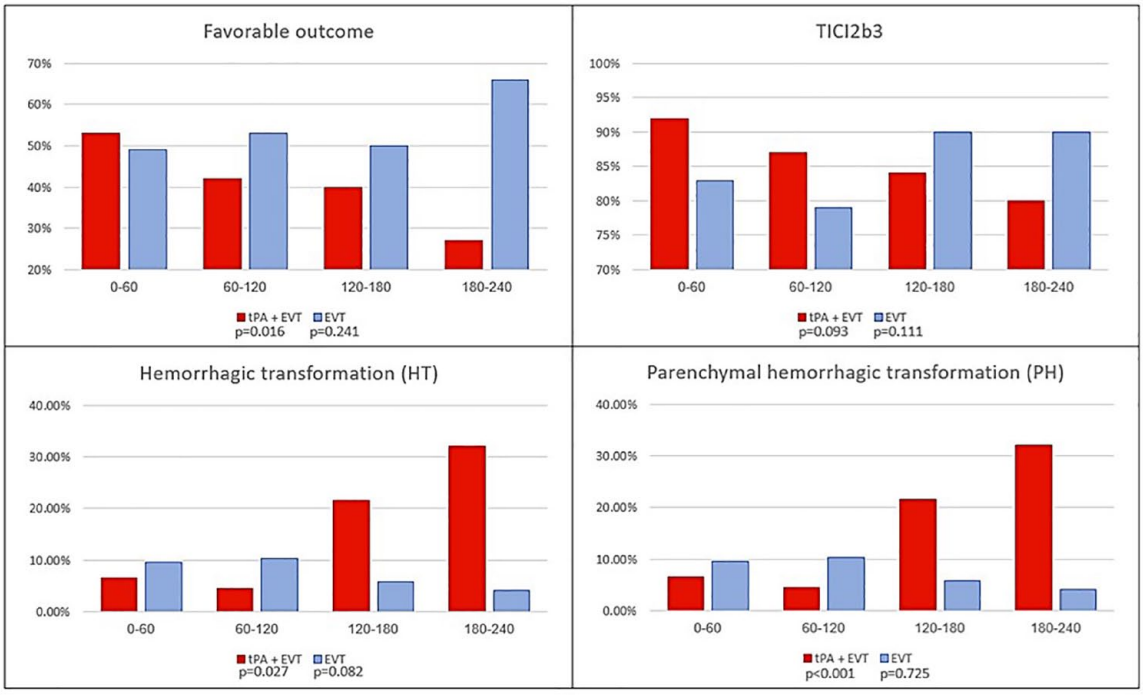

Figure 1. Changes in rates of favorable outcome, HT, parenchymal hemorrhagic transformation, and TICI-2b3 according to OTD by hours.
HT, hemorrhagic transformation; OTD, onset to door; TICI, thrombolysis in cerebral infarction.

The IVT + EVT cohort ($n = 195$, age: 71.1 ± 13.7, 53.8% male) and the direct-EVT group ($n = 213$, age: 68.6 ± 15.6, 47.9% male) had similar stroke etiology and comparable OTD and symptoms onset to EVT (OTE) times (Supplemental Table 1). Direct-EVT patients had higher rates of statins and antiplatelet treatment (32.4% *versus* 21.5%, $p = 0.041$, 34.1% *versus* 21.5%, $p = 0.006$, respectively), tandem lesions (18.8% *versus* 12.8%, $p = 0.024$), and carotid stent deployment during EVT procedure (23.0% *versus* 6.2%, $p < 0.001$). No differences were observed in outcome, mortality, HT, and discharge NIHSS. We further performed a sub-analysis including four patients in whom EVT was aborted due to significant clinical improvement after IVT administration. This analysis demonstrated similar results.

Bridging treatment outcome by OTD

Among patients treated with IVT + EVT, longer OTD was associated with lower rates of favorable outcome ($p = 0.021$), worse mRS-90 ($p = 0.013$), higher rates of HT ($p = 0.004$), and higher rates of parenchymal hemorrhagic transformation ($p < 0.001$). Figure 1 illustrates the changes in rates of favorable outcome, HT, and TICI-2b3 according to OTD by hours. Moreover, when comparing patients admitted in the very early time frame (OTD < 90 min) with those arriving in the delayed time frame (OTD 180–240 min), patients who arrived at the emergency department within 90 min were more likely to have favorable outcome [OR 2.81 (CI: 1.05–7.56), $p = 0.024$], and less likely to develop HT [OR 0.35 (CI: 0.14–0.9), $p = 0.029$].

On the contrary, among direct-EVT patients with OTD < 4 h, no significant association was found between OTD and favorable outcome, mRS-90, HT, or TICI 2b-3 rates (Figure 1).

Bridging treatment versus *direct-EVT in OTD < 2 h*

In all, 299 patients had arrived at the emergency department within 120 min of symptoms onset or last well time. Direct-EVT ($n = 154$, age 68.3 ± 15.2, 47.4% males) and IVT + EVT patients ($n = 145$, age: 70.4 ± 14.5, 54.5% males) had similar thrombus location, stroke etiology, OTD, or OTE time frames (Table 2). Direct-EVT patients

Table 2. Direct-EVT *versus* IVT + EVT in patients with symptoms to door <2 h.

Characteristics	Direct-EVT *N* = 154	IVT + EVT *N* = 145	*p* Value
Age (SD)	68.3 (15.2)	70.4 (14.5)	0.212
Sex: male (%)	73 (47.4)	79 (54.5)	0.221
Hypertension (%)	108 (70.1)	86 (59.3)	**0.05**
Diabetes (%)	49 (31.8)	42 (29.0)	0.592
Hyperlipidemia (%)	79 (51.3)	68 (46.9)	0.447
Smoking (%)	44 (28.6)	38 (26.2)	0.647
Atrial fibrillation (%)	53 (34.4)	50 (34.5)	0.614
Ischemic heart disease (%)	52 (33.8)	45 (31.0)	0.811
Valvular disease (%)	6 (3.9)	7 (6.4)	0.360
Congestive heart failure (%)	15 (9.7)	17 (11.7)	0.897
Chronic renal failure (%)	10 (6.5)	7 (4.8)	0.525
Prior stroke (%)	27 (17.5)	20 (13.8)	0.375
Malignancy (%)	20 (12.9)	12 (8.3)	0.081
Statins (%)	55 (35.7)	27 (18.6)	**0.004**
Antiplatelets (%)	53 (34.6)	33 (22.9)	**0.026**
Vessel lesion (%)			0.159
ICA	37 (24.0)	27 (18.6)	
M1 MCA	81 (52.6)	79 (54.5)	
M2 MCA	20 (13.0)	24 (16.6)	
Basilar	7 (4.5)	9 (6.2)	
ACA	2 (1.3)	1 (0.7)	
PCA	0 (0)	1 (0.7)	
Tandem lesion	26 (16.8)	17 (11.7)	0.074
Side, right (%)	75 (48.7)	66 (45.5)	0.384
TOAST (%)			0.748
Cardioembolism	83 (53.9)	80 (55.2)	
Large artery atherosclerosis	34 (22.1)	25 (17.2)	
Other determined etiology	7 (4.5)	11 (7.6)	
Undetermined	24 (15.6)	20 (13.8)	
Collaterals, good (%)	61 (45.2)	59 (56.2)	0.177
Symptom to door (SD)	54.6 (31.7)	58.4 (22.5)	0.246

(Continued)

Table 2. (Continued)

Characteristics	Direct-EVT *N* = 154	IVT + EVT *N* = 145	*p* Value
Door to groin puncture (SD)	149.2 (189.4)	161.7 (115.1)	0.501
Number of passes (IQR)	1 (1–3)	1 (13)	0.691
TICI 2b-3 (%)	117 (80.7)	125 (86.2)	**0.038**
PH (%)	15 (9.7)	8 (5.5)	0.161
First pass (%)	65 (42.2)	49 (33.8)	0.855
Stent (%)	35 (22.7)	11 (7.6)	**<0.001**
HT (%)	29 (18.8)	23 (15.8)	0.553
HT PH (%)	15 (10)	8 (5.6)	0.161
HT PH2 (%)	9 (5.9)	5 (3.5)	0.328
Symptomatic HT (%)	5 (3.2)	2 (1.4)	0.295
NIHSS on admission (IQR)	16 (11–20)	15 (10–20)	0.197
NIHSS on discharge (IQR)	4 (1–11)	4 (1–7)	0.122
NIHSS, delta (IQR)	9 (3–14)	8 (2–13)	0.218
mRS baseline (IQR)	0 (0–2)	0 (0–1)	0.568
mRS discharge (IQR)	3 (2–5)	3 (2–5)	0.845
mRS 90 (IQR)	3 (1–5)	3 (2–4)	0.886
Mortality (%)	19 (12.3)	22 (15.2)	0.476
Outcome, favorable (%)	71 (50.7)	67 (48.6)	0.718

ACA, anterior cerebral artery; HT, hemorrhagic transformation; ICA, internal carotid artery; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery; PH, parenchymal hemorrhagic transformation.
p value < 0.05 was marked as bold.

had higher rates of hypertension (70.1% *versus* 59.3%, $p=0.05$), statins and antiplatelet treatment (35.7% *versus* 18.6%, $p=0.004$, 34.6% *versus* 22.9%, $p=0.026$, respectively), and carotid stent deployment during EVT procedure (22.7% *versus* 7.6%, $p<0.001$) compared with IVT + EVT patients.

IVT + EVT patients had higher rates of TICI 2b-3 compared to direct-EVT (86.2% *versus* 80.2%, $p=0.038$). In a multivariate analysis, bridging treatment remained the only significant predictor for achieving TICI-2b3 [OR 2.89 (1.24–6.78), $p=0.014$] (Supplemental Table 2). No differences were found in the rates of favorable outcome, mortality, and HT.

Bridging treatment versus *direct-EVT in OTD of 2–4 h*

In all, 109 patients had arrived at the emergency department 2–4 h of symptoms onset or last well time. Direct-EVT ($n=59$, age: 69.5 ± 16.9, 49.2 males) and IVT + EVT patients ($n=50$, age: 72.4 ± 11.3, 52% males) had similar baseline characteristics, thrombus location, stroke etiology, OTD, or STE time frames (Table 3). Direct-EVT patients had lower rates of previous stroke (6.8% *versus* 20%, $p=0.04$) and higher rates of carotid stent deployment during EVT procedure (23.7% *versus* 2.0%, $p<0.001$) compared with IVT + EVT patients.

In patients with OTD of 2–4 h, patients receiving bridging treatment in comparison to direct-EVT

Table 3. Direct-EVT *versus* IVT + EVT in patients with symptoms to door time of 2–4 h.

Characteristics	Direct-EVT *N* = 59	IVT + EVT *N* = 50	*p* Value
Age (SD)	69.5 (16.9)	72.4 (11.3)	0.319
Sex: male (%)	29 (49.2)	26 (52.0)	0.767
Hypertension (%)	41 (69.5)	40 (80.0)	0.211
Diabetes (%)	19 (32.2)	18 (36.0)	0.677
Hyperlipidemia (%)	27 (45.8)	24 (48.0)	0.816
Smoking (%)	18 (30.5)	13 (26.0)	0.603
Atrial fibrillation (%)	20 (33.9)	15 (30.0)	0.664
Ischemic heart disease (%)	18 (30.5)	16 (32.0)	0.867
Valvular disease (%)	3 (5.1)	4 (8.0)	0.536
Congestive heart failure (%)	5 (8.5)	4 (8.0)	0.752
Chronic renal failure (%)	5 (8.5)	6 (12.0)	0.563
Prior stroke (%)	4 (6.8)	10 (20.0)	**0.04**
Malignancy (%)	6 (10.2)	8 (16.0)	0.465
Statins (%)	14 (23.7)	15 (30.0)	0.375
Antiplatelets (%)	19 (32.2)	9 (18.0)	0.092
Vessel lesion (%)			0.744
ICA	15 (25.4)	11 (22.0)	
M1 MCA	26 (44.1)	26 (52.0)	
M2 MCA	10 (16.9)	11 (22.0)	
Basilar	2 (3.4)	1 (2.0)	
ACA	1 (1.7)	0 (0)	
PCA	0 (0)	0 (0)	
Tandem lesion	14 (23.7)	8 (16.0)	0.179
Side, right (%)	29 (49.2)	21 (42.0)	0.702
TOAST (%)			0.767
Cardioembolism	30 (50.8)	27 (54.0)	
Large artery atherosclerosis	19 (32.2)	10 (20.)	
Other determined etiology	3 (5.1)	1 (2.0)	
Undetermined	3 (5.1)	9 (18.0)	
Collaterals, good (%)	30 (50.8)	20 (40.0)	0.501
Symptom to door (SD)	168.8 (36.9)	178.9 (36.1)	0.160

(Continued)

Table 3. (Continued)

Characteristics	Direct-EVT *N* = 59	IVT + EVT *N* = 50	*p* Value
Door to groin puncture (SD)	172.8 (220.7)	161.9 (143.1)	0.773
tPA (%)	144 (48.5)	47 (44.3)	0.463
Number of passes (IQR)	1 (1–3)	1 (1–3)	0.659
TICI 2b-3 (%)	50 (84.7)	39 (78.0)	0.136
First pass (%)	28 (47.4)	17 (34.0)	0.437
Stent (%)	14 (23.7)	1 (2.0)	**<0.001**
HT (%)	5 (8.5)	17 (34.0)	**<0.001**
HT PH (%)	3 (5.2)	13 (27.1)	**0.002**
HT PH2 (%)	1 (1.7)	3 (6.0)	0.224
Symptomatic HT (%)	0 (0)	1 (2.0)	0.259
NIHSS on admission (IQR)	12 (7–19)	14 (11–19)	0.168
NIHSS on discharge (IQR)	3 (1–8)	7 (2–13)	**0.024**
NIHSS, delta (IQR)	6 (2–11)	5 (2–11)	0.586
MRS baseline (IQR)	0 (0–1)	0 (0–2)	0.205
MRS discharge (IQR)	3 (1–4)	4 (3–5)	**0.007**
MRS 90 (IQR)	2 (1–4)	3 (2–4)	0.423
Mortality (%)	7 (11.9)	3 (6.0)	0.291
Outcome, favorable (%)	29 (56.9)	15 (33.3)	**0.021**

ACA, anterior cerebral artery; HT, hemorrhagic transformation; ICA, internal carotid artery; IQR, Interquartile range; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institute of Health Stroke Scale; PCA, posterior cerebral artery; PH, parenchymal hemorrhagic transformation; tPA , tissue plasminogen activator.
p value < 0.05 was marked as bold.

patients had lower rates of favorable outcome (33.3% *versus* 56.9%, $p = 0.021$), higher rates of HT (34.0% *versus* 8.5%, $p < 0.001$), higher rates of parenchymal hemorrhagic transformation (27.1% *versus* 5.2%, $p = 0.002$), worse NIHSS on discharge [7 (2–13) *versus* 3 (1–8), $p = 0.024$], and worse mRS on discharge [4 (3–5) *versus* 3 (1–4), $p = 0.007$). In a multivariate analysis, bridging therapy remained significantly associated with HT [OR 6.25 (1.61–24.24), $p = 0.008$), parenchymal hemorrhagic transformation [OR 7.32 (1.26–42.51), $p = 0.027$], and had a nearly significant trend for unfavorable outcome [OR = 2.37 (0.95–5.93), $p = 0.064$, Supplemental Table 3).

Discussion

In this observational study, we demonstrated the pivotal impact of timing of bridging-IVT on the clinical, radiological, and EVT procedural outcomes. OTD times were associated with the rates of favorable outcome, mRS-90, and HT among patients receiving IVT + EVT but not in those treated with direct-EVT. We found that for patients presenting 0–2 h from onset, bridging-IVT was associated with a beneficial effect on procedural outcomes manifested by achieving higher rates of target recanalization. This finding is in agreement with the previously published meta-analyses showing the overall positive effect of bridging-IVT on successful recanalization

rates.[2,4] By contrast, in the 2–4 h OTD patients, IVT was not associated with higher rates of target recanalization and was associated with higher rates of HT and poor outcomes. We further demonstrated that the beneficial effect of thrombolysis is higher among patients with OTD below 90 min, and lowest among patients with OTD above 180 min. Our results are supported by the results of a recent study, which demonstrated that bridging-IVT efficacy was associated with IVT timing. However, that trial used door-to-needle times and not OTD and did not examine IVT timing impact on safety and HT.[16]

The beneficial effect of thrombolysis is known to decrease with the time passed since symptoms onset.[5] Previous studies have demonstrated that the help-to-harm ratio of thrombolysis is 18.1 for patients treated within 90 min *versus* 5.0 for patients treated 180–270 min from onset.[17] In a recent propensity score matching study compared with the non-IVT group, thrombolysis performed within 2 h significantly reduced the risk of 3-month mortality by 37%, whereas thrombolysis performed between 2 and 4.5 h significantly reduced the risk of 3-month mortality by only 26%.[18] It should also be noted that the beneficial effect of thrombolysis is lower in patients with LVO compared with more distal occlusions.[19] Moreover, the safety of IV tissue plasminogen acctivator (tPA) diminishes with time from symptom onset in the setting of large territory ischemic strokes that are more prone to undergo HT.[19] Indeed, in the current study, in patients presenting within the 2- to 4-h OTD timeframe, bridging-IVT was associated with higher rates of HT and ultimately worse functional outcomes. Furthermore, among direct-EVT patients, longer OTD times were not associated with worse outcomes or higher rates of HT. As most patients are being selected for EVT based on imaging findings, prolongation of times does not significantly impact EVT results. This was previously found in various studies including the randomized trials which demonstrated EVT to be beneficial in patients in the delayed time frame for intervention.[20,21] Therefore, the association found here between OTD and the impact of bridging treatment cannot be solely explained by the effect of time lapsed, rather it probably derives from IVT-related complications or toxicity.[6] Possibly, as previously suggested,[22] the worse outcome in the IVT + EVT group may be partially attributed to asymptomatic forms of HT. This may be supported by the higher rates of any parenchymal hemorrhagic transformation associated with bridging treatment in the current study.

Our study illuminates OTD as a possible simple parameter for patient selection for bridging-IVT treatment. We believe that our findings may also explain the conflicting results of previous trials. To date, six randomized control trials have been conducted to examine IVT bridging treatment, of those four reported beneficial effect[23–26] while two found non-inferiority of direct-EVT approach.[27,28] When examining these RCTs, a suggested association between time to randomization and IVT impact arises – IVT + EVT demonstrated favorable outcome in all trials with a median time to randomization of 151 min or less, while in trials supporting direct-EVT, the median time to randomization was 168 min and above. A similar trend is found when looking at the results of large registries. In the Italian registry, which reported bridging treatment has a beneficial effect, the median OTD was 95 min.[29] Whereas, in two other register cohorts that reported no benefit of thrombolysis, the median OTD values were 110 and 171 min.[30,31]

These findings support the results of our study and point out that OTD has a major role in patient selection for bridging treatment. Moreover, our study possibly suggests the superiority of direct-EVT among patients with OTD of 2–4 h and may suggest avoiding IVT among such patients, as it was associated with worse outcomes and higher rates of HT. However, these results should be interpreted with caution. Further studies are needed to better determine the selection for bridging treatment, including studies focusing on the inter-relation between bridging treatment and OTD in other large cohorts, as well as examining other factors such as imaging parameters. Only a few studies to date have focused on patient selection parameters for bridging therapy. These studies reported no association with the occlusion site, age, or the presence of atrial fibrillation.[32–34] A *post hoc* analysis of the MR-CLEAN-NO-IV trial has demonstrated an association with the first-line thrombectomy technique used.[35] Other parameters may include pre-treatment with antiplatelets or statins.[36] Pre-treatment with statins was previously reported to be associated with better outcomes among LVO patients.[37,38] However, in our cohort, higher rates of statins pre-treatment were found among direct-EVT patients and were not associated with outcome or recanalization rates after multi-variant analysis.

Study limitations include the observational nature of our study and the relatively small number of posterior circulation LVO cases. Second, as direct-EVT was allowed if the neuroendovascular team was present in the hospital and according to the discretion of the senior stroke neurologists, a potential selection bias cannot be excluded. However, it should be noted that no significant differences were found between groups. Third, we could not compare patients with witnessed onset to those with wake-up stroke due to insufficient data and small numbers. Finally, we did not include in our study time frames of achieving successful recanalization.

Conclusion

In this study, we found OTD times to have a significant effect on the impact of IVT bridging treatment. Our study shows that among patients in the earlier time frame of 0–120 min from symptom onset, bridging treatment may be associated with favorable effects. By contrast, in patients with OTD above 2 h, IVT was associated with poor outcomes, a finding that could suggest refraining from IVT in such patients. However, our findings should be viewed as hypothesis-generating and need corroboration in larger time-sensitive randomized clinical trials.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Review Boards of the Hadassah-Hebrew University Medical Center (HMO 18-0378) and the Tel-Aviv Sourasky Medical Center (18-0535). The need for patient consent was waived due to the retrospective design of this study.

Consent for publication

Not applicable.

Author contributions

Jeremy Molad: Conceptualization; Data curation; Formal analysis; Methodology; Project administration; Writing – original draft.

Hen Hallevi: Conceptualization; Supervision; Writing – review & editing.

Estelle Seyman: Data curation; Writing – review & editing.

Einor Ben-Assayag: Formal analysis; Writing – review & editing.

Tali Jonas-Kimchi: Data curation; Investigation; Writing – review & editing.

Udi Sadeh: Data curation; Writing – review & editing.

Ofer Rotschild: Data curation; Investigation; Writing – review & editing.

Naaem Simaan: Data curation; Investigation; Writing – review & editing.

Anat Horev: Data curation; Writing – review & editing.

Jose Cohen: Data curation; Writing – review & editing.

Ronen R. Leker: Methodology; Supervision; Writing – review & editing.

Asaf Honig: Conceptualization; Data curation; Methodology; Project administration; Writing – original draft.

Acknowledgements

None.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

Full data is available following a formal reasonable request and in compliance with state and participating centers' regulations.

ORCID iDs

Jeremy Molad https://orcid.org/0000-0001-6868-4849

Asaf Honig https://orcid.org/0000-0002-9489-0133

Supplemental material

Supplemental material for this article is available online.

References

1. 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–e418.
2. Trifan G, Biller J and Testai FD. Mechanical thrombectomy *versus* bridging therapy for anterior circulation large vessel occlusion stroke: systematic review and meta-analysis. *Neurology* 2022; 98: e1361–e1373.
3. Katsanos AH, Malhotra K, Goyal N, *et al*. Intravenous thrombolysis prior to mechanical thrombectomy in large vessel occlusions. *Ann Neurol* 2019; 86: 395–406.
4. Kobeissi H, Adusumilli G, Ghozy S, *et al*. Mechanical thrombectomy alone *versus* with thrombolysis for ischemic stroke: a meta-analysis of randomized trials. *Interv Neuroradiol* 2023; 0(0). doi:10.1177/15910199231154331
5. Lees KR, Bluhmki E, von Kummer R, *et al*. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet* 2010; 375: 1695–1703.
6. Honig A, Molad J, Horev A, *et al*. Predictors and prognostic implications of hemorrhagic transformation following cerebral endovascular thrombectomy in acute ischemic stroke: a multicenter analysis. *Cardiovasc Intervent Radiol* 2022; 45: 826–833.
7. Hill MD, Demchuk AM, Goyal M, *et al*. Alberta stroke program early computed tomography score to select patients for endovascular treatment: Interventional Management of Stroke (IMS)-III Trial. *Stroke* 2014; 45: 444–449.
8. Higashida RT, Furlan AJ, Roberts H, *et al*. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003; 34: e109–e137.
9. Brott T, Adams HP Jr, Olinger CP, *et al*. Measurements of acute cerebral infarction: a clinical examination scale. *Stroke* 1989; 20: 864–870.
10. Adams HP Jr, Bendixen BH, Kappelle LJ, *et al*. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993; 24: 35–41.
11. Menon BK, d'Esterre CD, Qazi EM, *et al*. Multiphase CT angiography: a new tool for the imaging triage of patients with acute ischemic stroke. *Radiology* 2015; 275: 510–520.
12. 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: 1245–1251.
13. Hacke W, Kaste M, Fieschi C, *et al*. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European Cooperative Acute Stroke Study (ECASS). *JAMA* 1995; 274: 1017–1025.
14. 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: 1317–1329.
15. Rankin J. Cerebral vascular accidents in patients over the age of 60. II. Prognosis. *Scott Med J* 1957; 2: 200–215.
16. Man S, Solomon N, Mac Grory B, *et al*. Shorter door-to-needle times are associated with better outcomes after intravenous thrombolytic therapy and endovascular thrombectomy for acute ischemic stroke. *Circulation* 2023; 148: 20–34.
17. Lansberg MG, Schrooten M, Bluhmki E, *et al*. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke* 2009; 40: 2079–2084.
18. Heo NH, Lee MR, Yang KH, *et al*. Short- and long-term mortality after intravenous thrombolysis for acute ischemic stroke: a propensity score-matched cohort with 5-year follow-up. *Medicine (Baltimore)* 2021; 100: e27652.
19. Honig A, Percy J, Sepehry AA, *et al*. Hemorrhagic transformation in acute ischemic stroke: a quantitative systematic review. *J Clin Med* 2022; 11: 1162.
20. Albers GW, Marks MP, Kemp S, *et al*. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med* 2018; 378: 708–718.
21. Nogueira RG, Jadhav AP, Haussen DC, *et al*. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med* 2018; 378: 11–21.

22. Dzialowski I, Pexman JH, 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: 75–79.

23. Mitchell PJ, Yan B, Churilov L, *et al.* Endovascular thrombectomy *versus* standard bridging thrombolytic with endovascular thrombectomy within 4.5 h of stroke onset: an open-label, blinded-endpoint, randomised non-inferiority trial. *Lancet* 2022; 400: 116–125.

24. Fischer U, Kaesmacher J, Strbian D, *et al.* Thrombectomy alone *versus* intravenous alteplase plus thrombectomy in patients with stroke: an open-label, blinded-outcome, randomised non-inferiority trial. *Lancet* 2022; 400: 104–115.

25. Suzuki K, Matsumaru Y, Takeuchi M, *et al.* Effect of mechanical thrombectomy without *versus* with intravenous thrombolysis on functional outcome among patients with acute ischemic stroke: the SKIP randomized clinical trial. *JAMA* 2021; 325: 244–253.

26. LeCouffe NE, Kappelhof M, Treurniet KM, *et al.* A randomized trial of intravenous alteplase before endovascular treatment for stroke. *N Engl J Med* 2021; 385: 1833–1844.

27. Yang P, Zhang Y, Zhang L, *et al.* Endovascular thrombectomy with or without intravenous alteplase in acute stroke. *N Engl J Med* 2020; 382: 1981–1993.

28. Zi W, Qiu Z, Li F, *et al.* Effect of endovascular treatment alone *versus* intravenous alteplase plus endovascular treatment on functional independence in patients with acute ischemic stroke: the DEVT randomized clinical trial. *JAMA* 2021; 325: 234–243.

29. Casetta I, Pracucci G, Saletti A, *et al.* Combined intravenous and endovascular treatment *versus* primary mechanical thrombectomy. The Italian Registry of Endovascular Treatment in Acute Stroke. *Int J Stroke* 2019; 14: 898–907.

30. Seker F, Bonekamp S, Rode S, *et al.* Impact of bridging thrombolysis on clinical outcome in stroke patients undergoing endovascular thrombectomy: a retrospective analysis of a regional stroke registry. *Neuroradiology* 2021; 63: 935–941.

31. Coutinho JM, Liebeskind DS, Slater LA, *et al.* Combined intravenous thrombolysis and thrombectomy *versus* thrombectomy alone for acute ischemic stroke: a pooled analysis of the SWIFT and STAR studies. *JAMA Neurol* 2017; 74: 268–274.

32. Zhou Y, Xing P, Li Z, *et al.* Effect of occlusion site on the safety and efficacy of intravenous alteplase before endovascular thrombectomy: a prespecified subgroup analysis of DIRECT-MT. *Stroke* 2022; 53: 7–16.

33. Honig A, Hallevi H, Simaan N, *et al.* Safety and efficacy of intravenous alteplase before endovascular thrombectomy: a pooled analysis with focus on the elderly. *J Clin Med* 2022; 11: 3681.

34. Mujanovic A, Kurmann CC, Dobrocky T, *et al.* Bridging intravenous thrombolysis in patients with atrial fibrillation. *Front Neurol* 2022; 13: 945338.

35. Rinkel LA, Treurniet KM, Nieboer D, *et al.* Effect of intravenous alteplase treatment on first-line stent retriever *versus* aspiration alone during endovascular treatment. *Stroke* 2022; 51: 2540–2543.

36. Tsivgoulis G, Goyal N, Kerro A, *et al.* Dual antiplatelet therapy pretreatment in IV thrombolysis for acute ischemic stroke. *Neurology* 2018; 91: e1067–e1076.

37. Malhotra K, Safouris A, Goyal N, *et al.* Association of statin pretreatment with collateral circulation and final infarct volume in acute ischemic stroke patients: a meta-analysis. *Atherosclerosis* 2019; 282: 75–79.

38. Tsivgoulis G, Katsanos AH, Sharma VK, *et al.* Statin pretreatment is associated with better outcomes in large artery atherosclerotic stroke. *Neurology* 2016; 86: 1103–1111.