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The Endovascular Stroke Treatment Only (ESTO) Trial. A Phase 2 Open Label Multicenter Trial

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Abstract

Background and Aims— We performed a phase 2 trial to determine whether mechanical thrombectomy (MT) alone in acute ischemic stroke patients demonstrates "promise" or a lack thereof ("futility") compared with those treated with intravenous (IV) recombinant tissue plasminogen activator (rt-PA) (historical controls).

Methods— Subjects with a baseline National Institutes of Health Stroke Scale (NIHSS) score ≥6 who presented within 4.5 hours of symptom onset with documented occlusion of intracranial internal carotid artery, or M1 or M2 segment of the middle cerebral artery on computed tomographic angiography were treated with MT alone. The primary outcome was functional independence defined by a modified Rankin scale (mRS) of 0-2 at 90 days post recruitment.

Results— The 72 subjects (median baseline NIHSS score of 17) were treated with MT with a median time from symptom onset of 180 minutes with complete and partial angiographic recanalization observed in 45 and 27 patients, respectively. Symptomatic intracerebral hemorrhage (≥4 points NIHSS score increase) within 24 hours was observed in none of the 72 subjects. Overall, functional independence at 90 days was observed in 38 (52.8%) of 72 subjects. The rate was higher than the rate of functional independence in a comparable historical cohort of patients treated with IV rt-PA (52.8% versus 35.9%, p=0.032) enabling us to reject the futility hypothesis.

Conclusions— Due to the relatively high rates of functional independence at 90 days observed in this phase 2 trial, a randomized phase 3 comparing standard intravenous rt-PA followed by MT with primary MT is being planned.

Keywords— acute ischemic stroke; tissue plasminogen activator; tPA; mechanical thrombectomy

INTRODUCTION

The American Heart Association (AHA)/American Stroke Association (ASA) 2018 guidelines recommend intravenous (IV) recombinant tissue plasminogen activator (rt-PA) for selected ischemic stroke patients who can be treated within 4.5 hours of symptom onset[1] and additional mechanical thrombectomy (MT) for patients with occlusion of major cerebral arteries.[1] However, there is conflicting evidence as to whether IV rt-PA adds any benefit if MT is already indicated. There are four randomized trials that have been completed[2-5] which have been powered to detect large non-inferiority margins (10-15%).[6] However, due to limitations in existing data, the AHA/ASA 2015, 2018 and 2019 guidelines,[1,7,8] European Stroke Organization 2021 guidelines9, and European Society for Minimally Invasive Neurological Therapy guidelines,[10] the Multisociety Consensus Quality Improvement 2018,[11] and European Stroke Organisation-Karolinska Stroke Update Conference 2018[12] have continued to recommend IV rt-PA prior to MT. To provide additional data regarding this question, we performed a multicenter open label phase 2 trial to assess outcomes in patients who were candidates for both IV rt-PA and MT when treated with MT alone and identify factors that influence outcomes.

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METHODS

The primary objective of these phase 2 trial was to determine whether the MT alone without using IV rt-PA in acute ischemic stroke (AIS) patients demonstrates "promise" or a lack thereof ("futility") in deciding whether to proceed with a phase 3 trial. The trial was performed at 4 comprehensive stroke centers in Turkey: Eskisehir Osmangazi University Medical Faculty, Kartal Dr. Lütfi Kirdar City Hospital, Sakarya University Faculty of Medicine, and Samsun Training and Research Hospital. The protocol was approved by the Ethics Committee of Kartal Dr. Lütfi Kirdar City Hospital (Ethics Committee Ruling number: 2020/514/174/6). Each patient or next of kin provided written consent for participation in the study. The trial is registered at clinicaltrials.gov (NCT number: NCT04240470).

Patients

Patients aged 18 through 90 years who presented within 4.5 hours of onset of stroke symptoms and had a National Institutes of Health Stroke Scale (NIHSS) score ≥6 with an occlusion in the intracranial internal carotid artery (ICA), or M1 or M2 segment of the middle cerebral artery (MCA) confirmed by computed tomography (CT) angiography that was accessible to MT were eligible. Furthermore, MT could be initiated (groin puncture) within 6 hours of symptom onset as per AHA/ASA guidelines.[1] The exclusion criteria for IV rt-PA as per AHA/ASA guidelines[1] were used.

Patients with any intracerebral hemorrhage (ICH), significant mass effect with midline shift, and/or large (more than 1/3 of the MCA) regions of clear hypodensity on the baseline CT scan or Alberta Stroke Program Early CT Score (ASPECTS) of <4 on baseline CT scan were excluded. Perfusion CT scan was not considered a requirement for participation in the study.

Study intervention

Patients were assigned to proceed to MT without receiving any IV rt-PA. IV sedation or general anesthesia, as appropriate, was administered and an appropriately sized sheath (5F-7F) was placed into the accessed femoral artery. Appropriate guide catheter or guide sheath was placed in the internal (or common) carotid artery. Both contact aspiration and thrombectomy with stent retriever were acceptable due to comparable outcomes.[13-15] Intra-arterial thrombolytic was permissible during the thrombectomy procedure as a maximum dose of 22 mg of rt-PA. Patients were to be managed according to standard procedures for AIS patients who receive thrombectomy at the study center and AHA/ASA guidelines.[1]

Clinical and imaging assessments

Demographic and baseline history and physical examination data were collected on designated case report forms. Initial angiographic severity of the arterial occlusion was graded using a previously validated scale.[16-18] An NIHSS score was performed in every subject at 24±6 hours (by a physician who was blinded to the 24-hour CT scan results), and at 7 days or discharge from hospital after enrollment. CT scans were performed 24±6 hours after enrollment, and in cases of worsening neurological condition. Post-discharge follow-up was performed at 90 days (±14 days) in person by a qualified investigator (certified in assessment of mRS scores) who did not participate in the recruitment or treatment of the subject.

Outcomes ascertained

Primary outcome: Functional independence defined as a mRS score of 0-2 at 90 days after ischemic stroke (0, No symptoms at all; 1, No significant disability despite symptoms; able to carry out all usual duties and activities; 2, Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance) consistent with previous trials of MT in AIS.[19]

Secondary Outcomes

Angiographic recanalization: Ascertained on post procedure angiogram according to modified Thrombolysis in Cerebral Infarction (TICI) perfusion flow categories ranging from 0 = No perfusion to 3 = Full perfusion with filling of all distal branches (22).

Early neurological improvement: An improvement in the NIHSS score of ≥8 points or achieving a score of 0-1 at 24 hours post enrollment (23,24).

Safety endpoints

All serious adverse events (SAEs): Adverse event that led to death or serious deterioration in the health of a subject that resulted in a life-threatening illness or injury, permanent impairment of a body structure or a body function, hospitalization or prolongation of existing hospitalization, and/or medical or surgical intervention.

Symptomatic ICH at 27±3 hours post randomization: Any ICH within ischemic field with space occupying effect, or remote from the ischemic field, subarachnoid hemorrhage, or intraventricular hemorrhage associated with ≥4 points worsening on the NIHSS within 24 hours as used in previous trials (18-21).

Statistical considerations

The trial was designed as a single arm futility study using recommendations by Palesch et al.[20] similar to other AIS phase 2 futility studies.[21,22]

The proportion of patients who will achieve a primary outcome (mRS 0-2) at 90 days was estimated as 36% based on data from Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial[23] which served as our reference value (p0). We wanted to test whether a proportion, pN, is non-inferior/superior to a reference value, p0. The hypothesis was:

$H0: pN-p0 \leq \delta H0: pN-p0 \leq \delta$

$H1: pN-p0 > \delta H1: pN-p0 > \delta$

and δ, δ is the superiority or non-inferiority margin set at 2.5%.

TABLE 1: Proportion of subjects who achieved functional independence at 90 days (with 95% CI) based on CT angiography.

		SWIFT PRIME[23] IV rt-PA+MT (n=98)	SWIFT PRIME[23] IV rt-PA alone (n=93)	ESTO 1 (n=72)
Overall (ICA+M1+M2)	n	56/92	32/89	38/72
	95% CI	60.8% (50.9%-70.8%)	35.9% (26%-46.8%)	52.8% (40.7%-64.7%)
ICA	n	8/17	3/13	9/18*
	95% CI	47% (22.9%-72.2%)	23% (5%-53.8%)	50% (26.0%-74.0%)
M1 segment of MCA	n	41/62	27/71	21/41
	95% CI	66% (52.9%-77.7%)	38% (26.8%-50.3%)	51.2% (36.5%-65.7%)
M2 segment of MCA	n	7/13	2/5	8/13
	95% CI	53% (25%-80.8%)	40% (5.2%-85.3%)	61.5% (31.6%-86.1%)

Abbreviations: CI- confidence interval, ESTO- Endovascular Stroke Treatment Only trial, ICA-internal carotid artery, IMS- Interventional Management of Stroke trial, IV-intravenous, MCA-middle cerebral artery, MT- mechanical thrombectomy, rt-PA-recombinant tissue plasminogen activator.

*7 patients had an additional occlusion in M1 segment.

The sample size estimation was estimated to be 72 subjects with an alpha of 0.10 (one sided test)[20] and β of 0.20. We provided a comparison of proportion of patients with functional independence according to site of occlusion on CT angiogram for ESTO and SWIFT PRIME.[23,24]

RESULTS

Recruitment started on January 31 and was completed on October 23, 2021. The 72 subjects enrolled had a median baseline NIHSS score of 17. The median time to initiation of MT from symptom onset was 180 minutes (interquartile range [IQR] 131.25-230 minutes). The site of occlusion was intracranial ICA (n=18), M1 segment (n=41), single M2 segment (n=13) of MCA on cerebral angiography. The devices used included stent retriever (n=52), suction catheter (n=36), angioplasty (n=4), and/or intracranial stent placement (n=5). Early neurological improvement was seen 39 (54.2%) of 72 subjects. Symptomatic ICH was observed in none of the 72 subjects. Functional independence at 90 days was observed in 38 (52.8%) of 72 subjects with 1 death (1.39%). The rate was higher than the rate of functional independence in a comparable cohort of patients treated with IV rt-PA in SWIFT-PRIME (52.8% versus 35.9%, p=0.033) enabling us to reject the futility hypothesis (see Table 1).

A comparison of baseline characteristics of the subjects who did or did not achieve functional independence is presented in Tables 2 and 3. There were no differences in the mean age, median NIHSS score at baseline, and site of occlusion on CT angiography between the two groups. The proportion of subjects who were active cigarette smokers was higher in those with functional independence (p=0.037). The proportion of subjects with complete recanalization on post procedure angiogram was not different between the two groups. The proportion of subjects with early neurological improvement was higher among those with functional independence (81.58% versus 26.47%, p<0.001). Compared with subjects who achieved functional independence, the mean time interval between symptom onset and recruitment (133.6±75.9 versus 188.7±72.5 minutes, p=0.002) and between symptom onset and initiation of MT (161.3±53.3 versus 199.2±60.6 minutes, p=0.007) were significantly longer among subjects who did not achieve functional independence. There were no significant differences in the rates of SAEs, mortality at 7 days, in the rate of symptomatic ICH although proportion of any ICH on neuroimaging within 24 hours was higher in the among subjects who did not achieve functional independence (13.16% versus 38.24%, p=0.014). One patient had arterial perforation and subarachnoid hemorrhage but achieved functional independence at 90 days.

When subjects were stratified based on time interval between symptom onset and initiation of MT into four strata: 0-90 mins (n=5), 91-180 min (n=32), 181-240 min (n=23), and 241-290 min (n=12), the rate of favorable outcomes decreased as the time interval between symptom onset and initiation of MT increased (from 83.30% to 8.3%). The proportion of patients according to each time interval strata are presented in Figure 1.

DISCUSSION

We found that the MT alone without using IV rt-PA in AIS patients demonstrated "promise" or a lack thereof ("futility") in the study. The proportion of subjects who achieved functional independence at 90 days in our cohort treated without IV rt-PA was higher than that observed in patients with similar characteristics treated with IV rt-PA alone in SWIFT-PRIME trial.[23] Our analysis identified a prominent reduction in patients with favorable outcomes if MT was not initiated with 240 minutes of symptom onset. A total of 4 randomized trials have been performed.[2-5] Endovascular therapy with versus without intravenous tissue plasminogen activator in acute stroke with ICA and M1 occlusion randomized clinical trial (SKIP)[2] administered 0.6 mg/kg dose of IV rt-PA and other three trials used 0.9 mg/kg of IV rt-PA (3-5). The absolute difference in proportion of subjects who achieved

TABLE 2: Baseline characteristics of the patients.

		Overall(n=72)	Patients who achieved functional independence at 90 days(n=38)	Patients who did not achieve functional independence at 90 days(n=34)	P value
Demographics					
Age - mean±SD (yr)		66.7±13.0	65.5±14.2	68.0±11.7	0.425
Women		38 (52.8%)	19(50%)	19(55.9%)	0.618
Past Medical History					
Hypertension		52(72.2%)	25(65.8%)	27(79.4%)	0.198
Antihypertensive medication		46(63.9%)	20(52.6%)	26(76.5%)	0.036
Diabetes mellitus		23(31.9%)	9(23.7%)	14(41.2%)	0.112
Medication for diabetes mellitus		19(26.4%)	6(15.8%)	13(38.2%)	0.031
Hyperlipidemia		16(22.2%)	5(13.2%)	11(32.4%)	0.050
Atrial fibrillation		24(33.3%)	14(36.8%)	10(29.4%)	0.504
Cigarette smoking	Previous	15(20.8%)	9(23.7%)	6(17.6%)	0.529
	Current	8(11.1%)	7(18.4%)	1(2.9%)	0.037
Previous stroke		7(9.7%)	4(10.5%)	3(8.8%)	0.808
Previous myocardial infarction		5(6.9%)	2(5.3%)	3(8.8%)	0.553
Current antiplatelet use		21(29.2%)	13(34.2%)	8(23.5%)	0.320
Current anticoagulation use		7(9.7%)	4(10.5%)	3(8.8%)	0.808
Clinical Characteristics					
Initial systolic blood pressure- mean±SD		161.5±28.7	158.1±27.6	165.4±29.7	0.287
Initial diastolic blood pressure - mean±SD		88.0±16.2	84.9±18.3	91.4±12.8	0.081
INR - median (range)		1.03(0.87-2.43)	1.02(0.87-2.43)	1.06(0.9-1.41)	0.801
Serum creatine level - mean±SD		0.94±0.41	0.98±0.39	0.90±0.43	0.374
Baseline NIHSS – median (IQR)		17(14-19)	17(13.25-19)	17(14.25-18)	0.620
Baseline CT scan	No ischemic changes	60(83.33%)	33(86.8%)	27(79.4%)	0.398
	Ischemic changes <1/3 MCA	12(16.67%)	5(13.2%)	7(20.6%)	
Site of occlusion* (CT angiography)	ICA	18(25.0%)	9(23.7%)	9(26.5%)	0.785
	MCA-M1	41(56.9%)	21(55.3%)	20(58.8%)	0.761
	MCA-M2	13(18.1%)	8(21.1%)	5(14.7%)	0.485
Presumptive location of stroke	Left hemisphere	38(52.8%)	20(52.6%)	18(52.9%)	0.979
	Right hemisphere	34(47.2%)	18(47.4%)	16(47.1%)	0.979
Time interval between symptom onset and screening - mean±SD		**134.3±70.8**	**115.2±65.1**	**155.5±71.8**	**0.016**

Abbreviations: CT- computed tomography, DM- diabetes mellitus, DBP- diastolic blood pressure, HTN- hypertension, INR- international normalized ratio, ICA- internal carotid artery, IQR- interquartile range, IV- intravenous, MI- myocardial infarction, mRS- modified Rankin scale, NIHSS- National Institutes of Health Stroke Scale, SBP- systolic blood pressure, SD- standard deviation

***7 patients had an additional occlusion in M1 segment.**

TABLE 3: Procedural aspects and primary and secondary safety endpoints.

			Overall (n=72)	Patients who achieved functional independence at 90 days (n=38)	Patients who did not achieve functional independence at 90 days (n=34)	P value
Procedural aspects						
Primary site of occlusion on cerebral angiogram*	**ICA**		23(31.9%)	12(31.6%)	11(32.4%)	0.944
	M1		39(54.2%)	19(50.0%)	20(58.8%)	0.453
	M2		10(13.9%)	7(18.4%)	3(8.8%)	0.240
Initial severity of arterial occlusion	**Grade 1**		0(0%)	0(0%)	0(0%)	
	Grade 2		9(12.5%)	6(15.8%)	3(8.8%)	0.372
	Grade 3		42(58.3%)	21(55.3%)	21(61.8%)	0.576
	Grade 4		15 (20.8%)	8(21.1%)	7(20.6%)	0.961
	Grade 5		6 (8.3%)	3(7.9%)	3(8.8%)	0.887
Device	**Stent retriever**		52(72.2%)	26(68.4%)	26(76.5%)	0.446
	Suction catheter (manual)		30(41.7%)	18(47.4%)	12(35.3%)	0.300
	Suction catheter (mechanical)		6(8.3%)	4(10.5%)	2(5.9%)	0.477
	Angioplasty catheter		4(5.6%)	3(7.9%)	1(2.9%)	0.360
	Stent deployment		5(6.9%)	2(5.3%)	3(8.8%)	0.553
Medication used	**Intra-arterial rt-PA**		22(30.6%)	8(21.1%)	14(41.2%)	0.064
Time interval between symptom onset and recruitment - mean±SD			159.6±78.8	133.6±75.9	188.7±72.5	0.002
Time interval between symptom onset and MT - mean±SD			179.2±59.6	161.3±53.3	199.2±60.6	0.007
Final angiographic results	**Complete (TICI 3)**		45(62.5%)	24(63.2%)	21(61.8%)	0.903
	Partial (TICI 2)	**2a**	1(1.4%)	0(0%)	1(2.9%)	0.287
		2b	19(26.39%)	9(23.7%)	9(26.5%)	0.785
		2c	7(9.72%)	5(13.2%)	3(8.8%)	0.559
	None-minimal (TICI 1 or 0)		0	0	0	
Procedure time - mean±SD			56.3±37.1	55.4±37.5	58±37.2	0.808
Procedural complications						
Device-related complications	Vasospasm		6(8.3%)	5(13.2%)	1(2.9%)	0.117
	Arterial perforation/ dissection		1(1.39%)**	1(2.6%)	0	0.341
Endpoints						
Symptomatic intracerebral hemorrhage			0	0	0	0.472
Embolization to new or target vessel territory			1(1.4%)	0	1(2.9%)	0.287
ICH on neuroimaging within 24h			18(25%)	5(13.16%)	13(38.24%)	0.014
Early neurological improvement			39(54.2%)	31(81.6%)	8(23.5%)	<0.00001
NIHSS at 24 h - median (IQR)			7(2-12.25)	2(0-5)	13(9-15)	<0.00001

Abbreviations: CT- computed tomography, ICA- internal carotid artery, IQR-interquartile range, MT- mechanical thrombectomy, SD- standard deviation, TICI- Thrombolysis in Cerebral Infarction perfusion flow categories

*9 patients had an additional occlusion in M1 segment.

**Resulted in subarachnoid hemorrhage and classified as a serious adverse event.

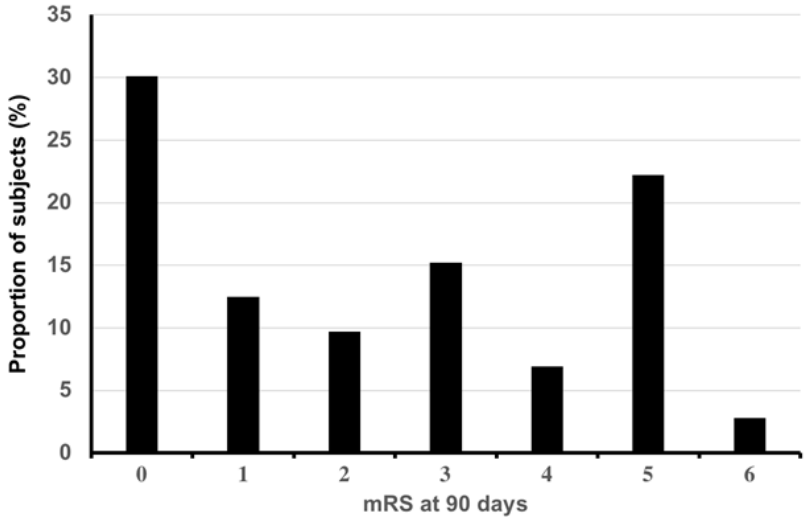


FIGURE 1: The proportion of subjects in various categories of modified Rankin scale at 90 days.

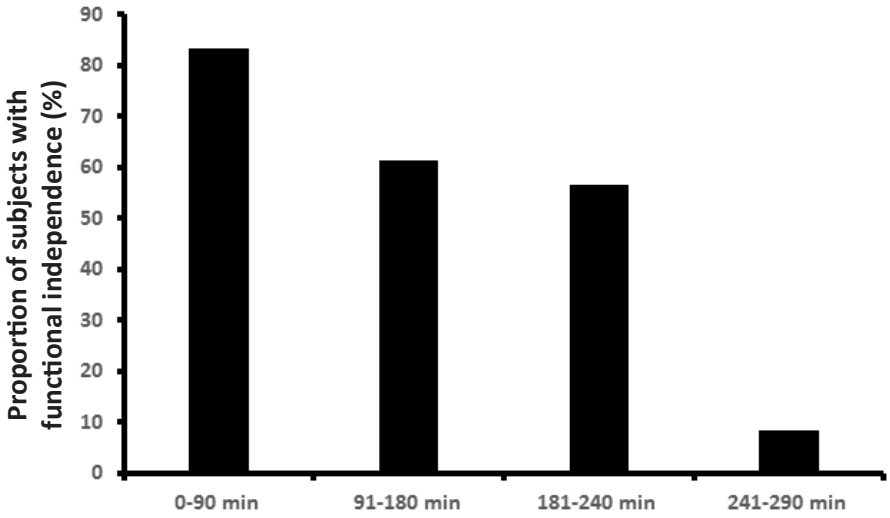


FIGURE 2: The proportion of subjects who achieved functional independence at 90 days according to time interval between symptom onset and initiation of mechanical thrombectomy. (min: minutes).

functional independence between patients treated with MT alone compared with IV rt-PA followed by MT was as follows: SKIP trial (2%), DEVT trial (7.7%), DIRECT-MT (0.4%), and MR CLEAN NO IV (2%). In a meta-analysis of these trials by Ishfaq et al.,[25] the proportion of subjects who achieved functional independence at 90 days was similar between patients who underwent MT with or without IV rt-PA (46.0% versus 45.5%) among the 1633 subjects randomized.

Potential advantages of administering IV rt-PA prior to MT include higher recanalization rates, shorter procedure time for MT, and lysis of thrombi in small arteries and in the microvasculature.[26] However, previous studies have not demonstrated any differences in recanalization rates or distal embolization in MT procedures with or without prior IV rt-PA.[27-29] The short half-life of IV rt-PA (3-5 minutes)[30] may contribute to the lack of any beneficial effect seen during MT as there is a time gap between IV rt-PA and MT. Interestingly, the odds of any ICH was significantly higher among patients treated with IV rt-PA and MT in randomized clinical trials[2-5] and study by Hassan et al.[31] which may negatively affect quality of life among survivors,[32] an important outcome for patients and families.[33] There is a risk of ICH associated with IV rt-PA[34] which adds to the existing risk associated with MT.

Although, there are previous and on-going randomized trials that are addressing the question regarding the therapeutic benefit of IV rt-PA in patients undergoing MT, additional trials like ESTO provide valuable data regarding MT alone in patients who are eligible for IV rt-PA in various settings. Certain parameters in the setting can result in modifying the results the afore mentioned comparison. The proportion of patients that are transferred from another hospital[35-37] and the delay incurred during transfer[38,39] can vary between settings. A higher proportion of inter facility transfers and longer time interval between transfers may put patients who receive IV rt-PA may be at advantage in transferred patients because part of the treatment can be started during the transfer process. Post procedural care practices such as utilization of withdrawal of care and post hospitalization care in each patient population maybe different resulting in differences in survival. In our study, mortality within 90 days was relatively low but severe disability (mRS of 5) was relatively high (Figure 1) highlighting the unique attributes of the study population.

Therefore, current guidelines[1,7,8,9,10,11,12] have continued to recommend IV rt-PA prior to MT until reproducibility of results seen in initial trials can be documented in other settings.[40] Another aspect to consider is the increasing use of tenecteplase (TNK) instead of rt-PA in acute ischemic stroke patients. Existing data supports that provides strong evidence that TNK is noninferior to rt-PA in the treatment of acute ischemic stroke.[40] Due to non-inferiority, trials such as the Multi-arm Optimization of Stroke Thrombolysis (MOST)[41] have permitted use of either IV TNK or IV rt-PA as standard of care thrombolysis within the protocol. It is possible that if additional data may demonstrate superiority of IV TNK over IV rt-PA similar to the TNK versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial[42] than IV TNK maybe the IV thrombolysis used in a future comparative trial.

Based on these pre-specified comparisons with historical controls, a randomized trial of MT alone as compared with IV rt-PA followed by MT in patients presenting within 4.5 hours of symptom onset is being planned. The patient and procedural characteristics associated with functional independence and estimates of endpoints in ESTO will be used for developing enrichment strategies and sample size calculations for primary and secondary endpoints.

CONFLICT OF INTEREST STATEMENT

The grading scheme to categorize the initial site of occlusion and presence of collaterals was initially proposed by one of the authors Dr. Qureshi.

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