RESEARCH ARTICLE

Thrombolysis Alone vs With Argatroban or Eptifibatide

A Prespecified Subgroup Analysis of the MOST Trial

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Abstract

Background and Objectives

IV thrombolysis only (IVT-O) is the primary reperfusion therapy for most stroke patients. At least 50% of IVT-O patients remain disabled. We assessed 2 therapies added to IVT-O aimed at increasing clot lysis or preventing arterial reocclusion.

Methods

This 3-arm, adaptive, single-blinded, randomized controlled phase III clinical trial was conducted at 57 US sites. Patients with acute ischemic stroke (AIS) within 3 hours of onset receiving IV tissue plasminogen activator or tenecteplase were randomized to argatroban (100 μg/kg bolus and 12-hour infusion at 3 μg/kg/min), eptifibatide (135 μg/kg bolus and 2-hour infusion at 0.75 μg/kg/min), or placebo (bolus and 12-hour infusion). The primary end point was utility-weighted 90-day modified Rankin Scale score (uwmRS score; worst = 0, best = 10). This prespecified secondary analysis was conducted on the intent-to-treat population in the IVT-O cohort using a Bayesian normal dynamic linear model.

Results

Of 514 patients enrolled into Multi-arm Optimization of Stroke Thrombolysis (MOST) before the study was stopped for futility, 260 were in the IVT-O cohort (118 treated with placebo, 114 with eptifibatide, and 28 with argatroban; mean age 66 years, 46.9% female). Baseline variables were similar across groups (median NIH Stroke Scale score 8, mean time from symptom onset to IVT 105 minutes, mean time from IVT bolus to study drug start 62 minutes). A clot was visible in 30.8% of patients. There was only a 1% or 2.5% chance that argatroban or eptifibatide, respectively, was superior to placebo for the primary outcome (mean uwmRS scores [SD] of 5.5 [3.6], 6.6 [3.2], and 7.4 [2.6] for argatroban, eptifibatide, and placebo, respectively). No secondary outcomes favored either treatment group. The risk difference for symptomatic hemorrhage between the argatroban and eptifibatide arms vs placebo was −0.8% ($p = 0.82$) and 1.8% ($p = 0.36$). Mortality was 3.4% with placebo, 14.3% for argatroban ($p = 0.03$), and 11.4% for eptifibatide ($p = 0.02$). There was no benefit in any subgroup.

Discussion

Outcomes in patients treated with IVT-O were not improved by adding either argatroban or eptifibatide. Increased bleeding was not observed, but mortality was higher in both investigational arms. Limitations included small sample size in the argatroban subgroup.

Trial Registration Information

This study was registered on ClinicalTrials.gov (registration number: NCT03735979) on November 8, 2018. The first patient was enrolled on October 15, 2019.

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Class of Evidence
Criteria for rating therapeutic and diagnostic studies
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Supplementary Material

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Glossary

AIS = acute ischemic stroke; **EVT** = endovascular thrombectomy; **ICH** = intracranial hemorrhage; **ITT** = intent-to-treat; **IVT** = IV thrombolysis; **IVT-O** = IVT only; **LVO** = large vessel occlusion; **MOST** = Multi-arm Optimization of Stroke Thrombolysis; **mRS** = modified Rankin Scale; **NIHSS** = NIH Stroke Scale; **PH2** = type 2 parenchymal hemorrhage; **PTT** = partial thromboplastin time; **TNK** = tenecteplase; **tPA** = alteplase; **uwmRS** = utility-weighted mRS.

Classification of Evidence

This study provides Class II evidence that in patients with AIS treated with IVT within 3 hours of onset, argatroban or eptifibatide does not improve outcomes vs thrombolysis alone but does increase mortality.

Introduction

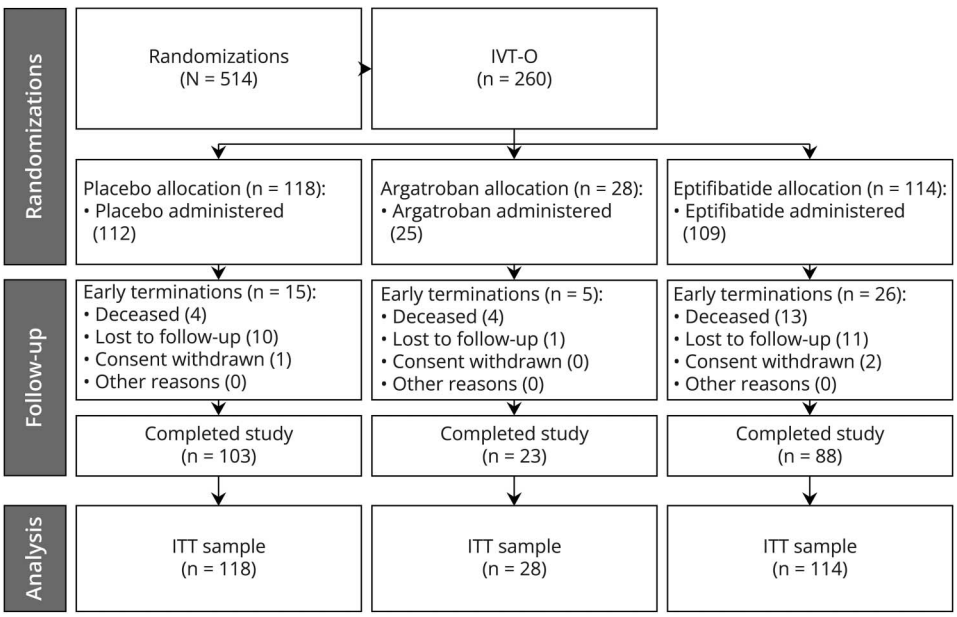
IV thrombolysis (IVT) is a highly effective treatment for patients experiencing acute ischemic stroke (AIS), by dissolving the clot causing the stroke and restoring blood flow through recanalization of the affected artery. In cases where clots are located in large cerebral arteries, endovascular thrombectomy (EVT) can also be used. However, for clots located in small or medium-sized cerebral arteries, IVT only (IVT-O) remains the sole reperfusion therapy available.

Patients receiving IVT-O represent a crucial group for exploring treatments that may augment the benefits of IVT. Clots in small and medium-sized arteries are easier to dissolve with IVT compared with clots in large vessel occlusions (LVOs). Nevertheless, at least 50% of IVT-O patients do not fully recover without some form of disability.[1] In addition, the IVT-O patient population represents the largest cohort of patients with AIS who are eligible for IVT, approximately 3 times larger than those who qualify for both IVT and EVT.[2]

Treatments that may augment clot lysis and prevent reocclusion are logical approaches to improve outcomes in IVT-O patients. The extent of complete clot lysis achieved with IVT-O is uncertain but is probably no higher than 50%.[3] This outcome depends on a number of factors including clot size, patient age, and clot composition. Arterial reocclusion occurs in 14%–34%[4] of IVT-treated patients within 2 hours and is associated with worse outcomes.

The Multi-arm Optimization of Stroke Thrombolysis (MOST) trial evaluated 2 medications that aimed to augment IVT by increasing clot lysis and preventing arterial reocclusion.[5] The MOST trial included patients who qualified for IVT-O or IVT + EVT and showed that both direct thrombin inhibition with argatroban and inhibition of the GP2b/3a receptor with eptifibatide were safe. However, neither treatment improved

Figure 1 Consort Diagram of the IVT-O Cohort



ITT = intent-to-treat; IVT-O = IV thrombolysis only.

Table 1 Demographics and Clinical Characteristics at Baseline

Characteristic	IVT-O participants by treatment group			
	Placebo (N = 118)	Argatroban (N = 28)	Eptifibatide (N = 114)	Overall (N = 260)
Age, y, median (IQR)	66 (16)	70 (14)	66 (24)	66 (18)
Sex, n (%)				
Male	64 (54.2)	14 (50)	60 (52.6)	138 (53.1)
Female	54 (45.8)	14 (50)	54 (47.4)	122 (46.9)
Race, n (%)[a]				
Asian	1 (0.8)	1 (3.6)	5 (4.4)	7 (2.7)
Black/African American	31 (26.3)	11 (39.3)	35 (30.7)	77 (29.6)
White	86 (72.9)	16 (57.1)	72 (63.2)	174 (66.9)
Baseline NIHSS score, median (IQR)	8 (5)	9 (5.5)	9 (5)	8 (5)
History of atrial fibrillation, n (%)	9 (7.6)	7 (25)	13 (11.4)	29 (11.1)
Received tPA	83 (70.3)	26 (92.9)	83 (72.8)	192 (73.8)
Received TNK	35 (29.7)	2 (7.1)	31 (27.2)	68 (26.2)
Stroke onset to thrombolysis initiation, min, mean (SD)	105 (38.9)	101 (45.6)	107 (38)	105 (39.1)
Stroke onset to study drug bolus, min, mean (SD)	164 (39.6)	164 (43.7)	170 (41.2)	167 (40.7)
Thrombolysis initiation to study drug bolus, min, mean (SD)	60 (17.9)	63 (14.4)	64 (21.8)	62 (19.5)
Historic, prestroke mRS score, n (%)				
0	79 (66.9)	22 (78.6)	75 (65.8)	176 (67.7)
1	19 (16.1)	1 (3.6)	15 (13.2)	35 (13.5)
2	9 (7.6)	3 (10.7)	7 (6.1)	19 (7.3)
3+	10 (8.5)	2 (7.1)	17 (14.9)	29 (11.2)
NA	1 (0.8)	0 (0)	0 (0)	1 (0.4)
Received EVT, n (%)	3 (2.5)	1 (3.6)	3 (2.6)	7 (2.7)
Visible clot in baseline neuroimaging				
Unknown	8 (6.8)	3 (10.7)	7 (6.1)	18 (6.9)
No	75 (63.6)	15 (53.6)	72 (63.2)	162 (62.3)
Yes	35 (29.7)	10 (35.7)	35 (30.7)	80 (30.8)
LVO or near-occlusion (M1, terminal ICA, vertebral, basilar)	4/35 (11.4)	3/10 (30)	3/35 (8.6)	10/80 (12.5)
Medium-distal branch occlusion or near-occlusion (M2–4, A1–2, P1–3, cerebellar)	18/35 (51.4)	5/10 (50)	21/35 (60)	44/80 (55)
Both	4/35 (11.4)	2/10 (20)	6/35 (17.1)	12/80 (15)
Neither/unknown[b]	9/35 (25.7)	0/10 (0)	5/35 (14.3)	14/80 (17.5)
Stroke circulation location				
Posterior	3 (2.5)	3 (10.7)	2 (1.8)	8 (3.1)
Anterior	56 (47.5)	17 (60.7)	58 (50.9)	131 (50.3)
Both anterior and posterior	15 (12.7)	3 (10.7)	12 (10.5)	30 (11.5)
Unknown	44 (37.2)	5 (17.9)	42 (37)	91 (35)
Anterior stroke hemisphere[c]				

Continued

Table 1 Demographics and Clinical Characteristics at Baseline *(continued)*

Characteristic	IVT-O participants by treatment group			
	Placebo (N = 118)	Argatroban (N = 28)	Eptifibatide (N = 114)	Overall (N = 260)
Right	34/71 (47.9)	12/20 (60)	25/70 (35.7)	72/161 (44.7)
Left	30/71 (42.3)	7/20 (35)	41/70 (58.6)	78/161 (48.4)
Both hemispheres	7/71 (9.9)	1/20 (5)	4/70 (5.7)	12/161 (7.5)

Abbreviations: EVT = endovascular thrombectomy; ICA = internal carotid artery; IQR = interquartile range; IVT-O = IV thrombolysis only; LVO = large vessel occlusion; TNK = tenecteplase; tPA = alteplase.
[a] Two participants were of other/unknown races.
[b] This includes participants who either did not meet the criteria for large or medium/distal branch occlusion or lacked data for determination.
[c] Anterior hemisphere stroke data include N = 131 with anterior strokes and N = 30 involving both anterior and posterior circulation.

outcomes in the overall population of patients treated with IVT, for example, IVT-O and IVT + EVT patients.[6]

The primary aim of this subanalysis of MOST was to evaluate the effect of these treatments in IVT-O patients. We hypothesized that adding either argatroban or eptifibatide would lead to improved outcomes. In a prespecified exploratory analysis, we hypothesized that certain baseline variables, in particular, the visualization of arterial clot, would be associated with IVT-O treatment response.

Methods

Trial Design and Oversight

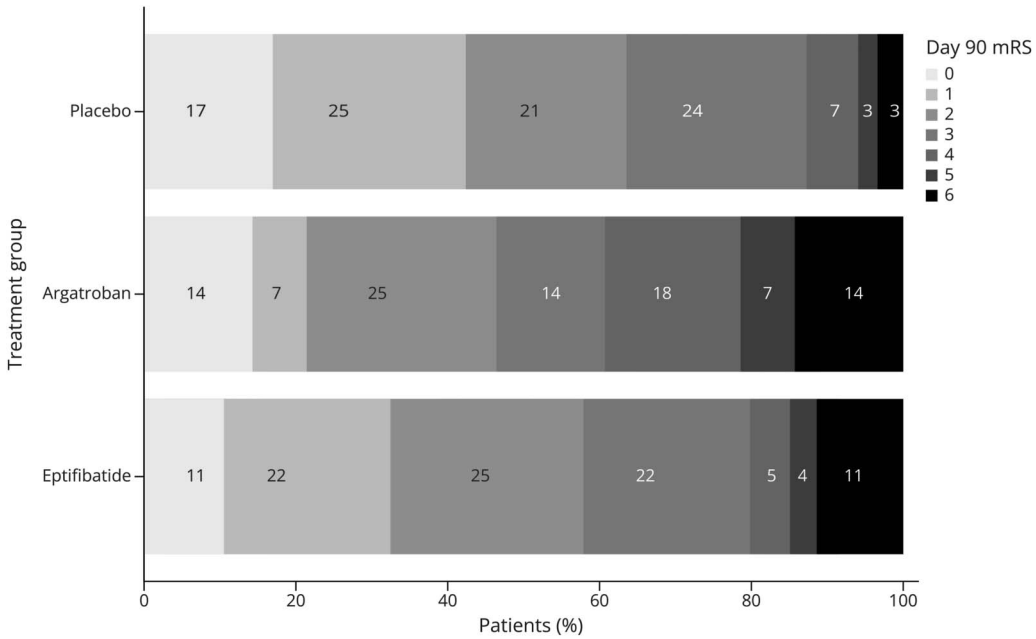
MOST was a three-arm, adaptive, single-blinded (participants), randomized controlled phase III clinical trial conducted at 57 sites in the United States, comparing argatroban and/or eptifibatide with placebo in patients with AIS treated with standard-of-care IVT. The trial protocol and primary results have been published.[6]

Standard Protocol Approvals, Registrations, and Patient Consents

The protocol was approved by the University of Cincinnati Central Institutional Review Board and the Food and Drug Administration (IND 63550). All patients or their legally authorized representative provided written informed consent. Enrollment into the trial was open from October 10, 2019, to July 5, 2023.

This study was registered on ClinicalTrials.gov (registration number: NCT03735979) on November 8, 2018.

Figure 2 Primary End Point Day 90 mRS Score by Treatment Group



mRS = modified Rankin Scale.

Table 2 Efficacy and Safety Outcomes

Primary outcome	All groups (N = 260) Mean (SD)	Placebo (N = 118) Mean (SD)	Argatroban (N = 28) Mean (SD)	Posterior mean difference (SD)	Posterior probability	Eptifibatide (N = 114) Mean (SD)	Posterior mean difference (SD)	Posterior probability
Day 90 utility-weighted mRS score	6.8 (3.0)	7.4 (2.6)	5.5 (3.6)	−1.7 (0.7)	0.01	6.6 (3.2)	−0.8 (0.4)	0.02

Primary safety outcome	N (%)	N (%)	N (%)	Risk difference, %	*p* Value[a]	N (%)	Risk difference, %	*p* Value[a]
Symptomatic ICH within 36 h after randomization	4 (1.5)	1 (0.8)	0 (0)	−0.8	0.82	3 (2.6)	1.8	0.36
All-cause mortality within 90 d	21 (8.1)	4 (3.3)	4 (14.3)	11	0.04	13 (11.4)	8.1	0.02

Secondary outcomes	N (%)	N (%)	N (%)	Odds ratio (95% CI)	*p* Value[b]	N (%)	Odds ratio (95% CI)	*p* Value[b]
90-d mRS score 0–1 or return to prestroke mRS score	108 (41.5)	54 (45.8)	7 (25)	0.4 (0.2–1)	0.05	47 (41.2)	0.8 (0.5–1.4)	0.49
NIHSS score change over 24 h, mean (SD)	−4.5 (6.4)	−4.7 (5.1)	−2.8 (7.4)	—	0.41	−4.8 (7.3)	—	0.16

Secondary safety outcomes	N (%)	N (%)	N (%)	Risk difference, %	*p* Value[c]	N (%)	Risk difference, %	*p* Value[c]
Any ICH within 36 h after randomization	40 (15.4)	17 (14.4)	7 (25)	11	0.25	16 (14)	−0.4	1
Major hemorrhage other than ICH within 7 d after randomization	4 (1.5)	3 (2.5)	0 (0)	−2.5	0.50	1 (0.9)	−1.7	0.53

Abbreviations: ICH = intracranial hemorrhage; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale.
[a] *p* Values were calculated using the Barnard test.
[b] For binary outcomes, the *p* value of a Wald χ^2 test. For ordinal/continuous outcome, the *p* value of a Wilcoxon rank-sum test.
[c] For secondary safety outcomes, the Fisher exact test or Barnard test was used.

Patients

All patients met the usual inclusion and exclusion criteria for IVT (alteplase [tPA] 0.9 mg/kg or tenecteplase [TNK] 0.25 mg/kg) within 3 hours of stroke symptom onset. Patients had to have a NIH Stroke Scale (NIHSS) score of at least 6 at the time of IVT, and the study drug had to be started within 75 minutes of IVT bolus. A baseline partial thromboplastin time (PTT) was also required to be within normal limits for the laboratory. During the process of patient screening and before randomization, investigators determined whether patients were intended to be treated with IVT-O or IVT + EVT based on presenting clinical data including NIHSS score, noncontrast CT, and vascular imaging. The primary analysis of MOST included both IVT-O and IVT + EVT cohorts. Prespecified secondary analyses of MOST included an exploration of the trial results for the intent-to-treat (ITT) population in the IVT-O and IVT + EVT cohorts separately. For this IVT-O ITT analysis, we included all patients who were intended to receive IVT-O and not EVT. Those IVT-O patients in whom LVO was found and EVT was performed were included in the ITT analysis. For this analysis, LVO was defined as occlusion or near-occlusion of the distal internal carotid artery, first segment of the middle cerebral (M1) artery, vertebral artery, or basilar artery. Occlusion or near-occlusion of more distal branches of the middle cerebral (M2–4), anterior cerebral (A1–2), posterior cerebral (P1–3), or cerebellar arteries was labeled as medium or distal branch arterial occlusion.

Group Allocation

The study enrollment was designed as follows. The first 150 patients were randomly allocated equally (1:1:1) to the 3 treatment groups (argatroban, eptifibatide, or placebo). After that, patients were allocated to treatment groups according to a response-adaptive randomization favoring the active arm showing the greater benefit compared with placebo based on accrued data after every 30 participants enrolled. Owing to a higher proportion of deaths observed among the first 50 patients randomized to argatroban, very few patients received argatroban thereafter. Once 500 patients were enrolled, one (or both) arm(s) could be stopped for futility if there was less than 20% probability of demonstrating benefit in either argatroban or eptifibatide group if the trial were to continue.

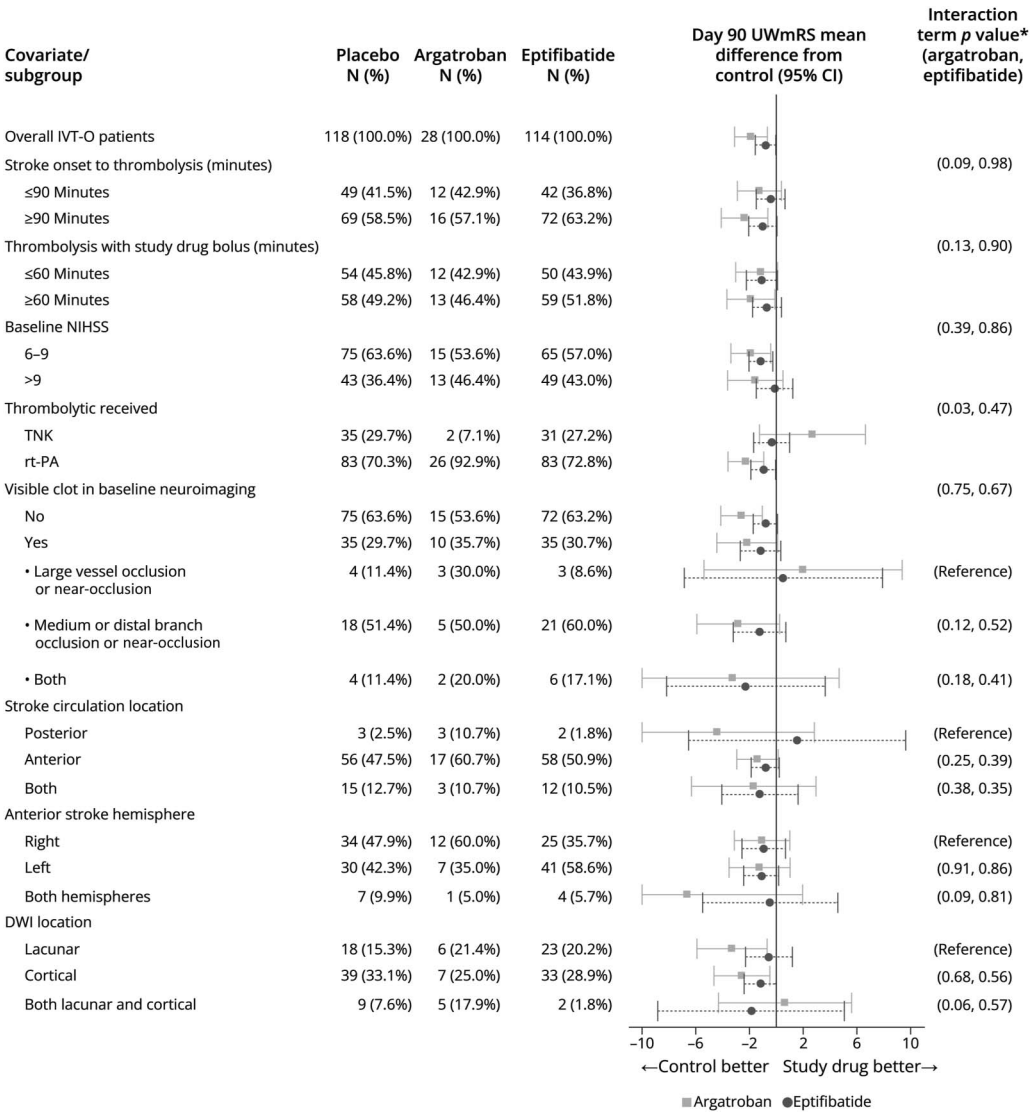
Interventions and Blinding

The study arms were as follows:

1. Argatroban (100 μg/kg bolus and a 12-hour infusion at 3 μg/kg/min titrated to achieve a PTT 2.5 × control)
2. Eptifibatide (135 μg/kg bolus and a 2-hour infusion at 0.75 μg/kg/min)
3. Placebo (bolus and a 12-hour infusion)

Argatroban and placebo participants received a bolus, followed by a 12-hour infusion. Eptifibatide participants received a bolus, followed by a 2-hour infusion. A 10-hour saline infusion was administered after the 2-hour eptifibatide infusion

Figure 3 Forest Plot of Subgroups by uwmRS Scores



DWI = diffusion-weighted imaging; IVT-O = IV thrombolysis only; mRS = modified Rankin Scale; TNK = tenecteplase; tPA = alteplase; uwmRS = utility-weighted mRS.

to maintain the single-blind design. Investigators were unblinded to treatment, but participants and legally authorized representatives remained blinded. The modified Rankin Scale (mRS) at day 90 was assessed through video-recorded face-to-face interviews. If this was not possible, a recorded remote assessment by video or telephone was used. A blinded central assessor assigned day 90 mRS scores from video recordings performed by local personnel (also blinded). This central mRS assignment was used for the primary outcome assessment. All serious adverse events and deaths were adjudicated by a central reviewer for relatedness to the study drug.

Outcomes

Baseline characteristics were tabulated for the overall IVT-O population and the 3 treatment groups including data on clot location. The primary outcome to be tested across all 3 treatment groups was the mean utility-weighted modified Rankin Scale (uwmRS) score at 90 days after stroke onset. The mRS score ranges from 0 (no deficit) to 6 (death), depending on the patients' value of that level of function. The uwmRS assigns values to each of the standard 7 functional levels of the mRS, and these values are reversed, with higher scores indicating better outcomes according to a patient's value system as a continuous measure (range from 0 [death] to 10 [no symptoms or disability]).[5,7] A difference of 0.3 or more on this scale has been stated to reflect a clinically important effect.[8] Secondary outcomes were 90-day mRS score 0–1 or return to prestroke mRS scores and NIHSS change over 24 hours. The primary safety outcomes were the rate of symptomatic intracranial hemorrhage (ICH), defined as a type 2 parenchymal hemorrhage (PH2) or a remote parenchymal hemorrhage with neurologic deterioration (≥4-

Table 3 Multivariable Logistic Regression Odds Ratios for Subgroups (Control Treatment Only) Achieving Day 90 mRS Score ≤1 With Baseline NIHSS Score as a Binary Variable

Subgroup	Adjusted odds ratio (95% CI)	Wald test *p* value
Stroke to thrombolysis (≤90 min vs >90 min)	1.47 (0.42–5.19)	0.55
Thrombolysis to study drug bolus (≤60 min vs >60 min)	2.36 (0.69–8.04)	0.17
Baseline NIHSS score (6–9 vs >9)	4.42 (1.15–16.91)	0.03
Thrombolytic received (tPA vs TNK)	1.01 (0.29–3.52)	0.99
Visible clot in baseline neuroimaging (no vs yes)	0.61 (0.18–2.11)	0.43
Stroke circulation location		
Posterior vs anterior	0.15 (0.01–3.91)	0.26
Anterior vs both	0.61 (0.15–2.53)	0.5
DWI sequence		
Lacunar vs cortical	1.07 (0.25–4.59)	0.93
Lacunar vs both	3.37 (0.38–29.51)	0.27

Abbreviations: DWI = diffusion-weighted imaging; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; TNK = tenecteplase; tPA = alteplase.

point worsening in the NIHSS) within 36 hours of randomization, and all-cause mortality within 90 days. Secondary safety outcomes included any ICH on brain imaging within 36 hours of randomization and major hemorrhage (defined as requiring >2 units of packed red blood cells) other than ICH within 7 days.

The following prespecified subgroups were tested for differences in outcomes between the 3 treatment groups and for association with outcomes in the placebo arm:

1. Those treated with IVT-O within 90 minutes from onset or 91–180 minutes
2. Time from IVT to study drug (≤60 minutes or >60 minutes)
3. Those with baseline NIHSS scores 6–9 or >9
4. Those treated with TNK or tPA
5. Those with visualized clot or without, and those with large, medium, or small vessel occlusion or near-occlusion
6. Anterior or posterior circulation stroke location

Statistical Analysis

The statistical analysis was conducted with the ITT population defined as those randomized and intended to receive IVT-O, as outlined in Sections 6 and 7 of the Statistical Analysis Plan. The primary assessment involved a comparative analysis between each active treatment arm and the placebo group on 90-day mRS utility scores (uwmRS), using a Bayesian normal dynamic linear model. For each active treatment arm, denoted as d, θ_d represented the difference in the expected uwmRS values between the active treatment and control group. The associated hypothesis test is H_0:$\theta_d \leq 0$ vs H_A:$\theta_d > 0$. The treatment effect θ_d was assigned a noninformative prior, with $\theta \sim N(0,2.5^2)$ ensuring an equal prior probability for a drug being beneficial or harmful.[9,10] Missing data on the primary outcome were imputed using a Bayesian multiple imputation method that considers baseline NIHSS score and the 30-day mRS score. When the 30-day mRS score was missing, it was first imputed using a hot deck imputation method. This involved randomly selecting the observed outcome from a pool of patients with observed mRS scores matched by treatment group, age, baseline NIHSS score, time to symptom onset, EVT received, and enrollment before the participant whose outcome was being imputed. The imputed 30-day mRS score was not carried forward to 90 days; rather, whether observed or imputed, the 30-day mRS score was used as an auxiliary variable in the Bayesian model to improve the precision and plausibility of imputations for the missing 90-day outcomes.

The secondary and safety outcomes were exploratory and not adjusted for multiple comparisons (2-sided $p < 0.05$). Binary efficacy outcomes were assessed using logistic regression with a Wald χ^2 test for comparison of treatment vs control. Subsequently, the primary safety outcome, symptomatic ICH, was evaluated using the Barnard test, necessitated by its extremely low frequency. For ordinal outcomes, each treatment arm was compared with the placebo arm using the Wilcoxon rank-sum test. Missing secondary outcomes were imputed through the hot deck imputation method matched by age, baseline NIHSS score, time to symptom onset, treatment group, EVT received, and enrollment before the participant whose outcome was being imputed.

Subgroup analyses were performed on prespecified covariates to examine the benefit of the MOST study treatments. The primary outcome uwmRS score was reanalyzed in a multiple

linear regression model that included treatment groups, the main effect of the covariate, and interaction terms between treatment groups and covariate.

To avoid any potential confounding by treatment, we restricted the exploratory analysis to the placebo group only. A multivariable logistic regression model of "good outcome" defined as 90-day mRS score 0–1 included the prespecified subgroups based on time from stroke to thrombolysis (>90 minutes vs ≤90 minutes), time from thrombolysis to study drug bolus (>60 minutes vs ≤60 minutes), baseline NIHSS score, type of thrombolytic received, presence of a visible clot on baseline neuroimaging, and location of stroke circulation. As a sensitivity analysis, baseline NIHSS score was also treated as a continuous variable.

Data Availability

The study protocol and statistical analysis plan were published and are freely available as open access.[6]

Complete deidentified patient data from this study are currently available through ClinicalTrials.gov (NCT03735979). Data are accessible to qualified researchers for scientific analysis. No end date for data availability has been specified.

Results

Patients

The study was terminated by the Data and Safety Monitoring Board at the first interim analysis because of futility in both active treatment arms. Five hundred fourteen patients were randomized to the MOST trial, of whom 260 intended to receive IVT-O (IVT-O cohort analyzed here) (Figure 1). Owing to the response-adaptive randomization, only 28 IVT-O patients were assigned to the argatroban group. Among all the IVT-O patients in the ITT sample, 53.1% were male and 29.6% were Black, with a median age of 66 years.

Baseline characteristics of the entire IVT-O cohort and the 3 treatment groups are summarized in Table 1. Patients were typical IVT-O candidates, with a median NIHSS score of 8 and time from symptom onset to IVT of 105 minutes. During the study period, 73.8% of patients received IVT with tPA while 26.2% received TNK. The study drug was started on average 62 minutes after the IVT bolus. A clot was visible in the relevant artery in 80 of 260 patients (30.8%) . Of these, 44 (55%) had complete or near-occlusion in medium or distal arterial branches that were not approachable by EVT. Seven IVT-O patients received EVT for LVO accessible to EVT. The 3 treatment groups were well balanced although there were nonsignificant differences favoring the placebo group. The argatroban group was slightly older, was more often Black, received tPA more than TNK, harbored more LVOs, had more atrial fibrillation at baseline, had more right hemisphere strokes, and had more posterior circulation stroke location. The eptifibatide group had more patients with baseline mRS score >2.

Efficacy and Safety Analysis

Day 90 mRS outcomes by treatment group are shown in Figure 2. There was no benefit of either intervention compared with placebo (Table 2). There was only a 1% or 2.5% chance that argatroban or eptifibatide, respectively, was superior to placebo for the primary outcome (mean uwmRS [SD] scores of 5.5 [3.6], 6.6 [3.2], and 7.4 [2.6], for argatroban, eptifibatide, and placebo, respectively). None of the secondary outcomes favored either treatment group. The percentage of placebo patients achieving a 90-day mRS score 0–1 or returning to prestroke mRS score was 45.8% compared with 25% for argatroban and 41.2% for eptifibatide (Table 2). The risk difference for symptomatic hemorrhage between the argatroban and eptifibatide arms compared with the placebo group was −0.8% ($p = 0.82$) and 1.8% ($p = 0.36$), respectively. For all-cause mortality within 90 days, the risk difference was 11% ($p = 0.04$) for argatroban and 8.1% ($p = 0.02$) for eptifibatide, compared with placebo. The risk differences for any ICH within 36 hours and major hemorrhage other than ICH within 7 days after randomization between the argatroban and eptifibatide arms compared with the placebo group were also not significant. Mortality was 3.4% with placebo, compared with 14.3% for argatroban (log-rank test $p = 0.03$) and 11.4% for eptifibatide (log-rank test $p = 0.02$). The excess deaths in the argatroban and eptifibatide groups were adjudicated as not related to the study drug.

Figure 3 illustrates the day 90 uwmRS mean difference scores for both treatment groups in comparison with the control group for the prespecified subgroups. The interaction p value of 0.03 for the argatroban treatment arm suggests that the effect of argatroban differs for the TNK group, but there were only 2 patients in this subgroup. There were no subgroups that benefited from either investigational treatment.

Exploratory Analysis

eFigure 1 shows the distribution of mRS scores for the prespecified subgroups among the placebo patients in the IVT-O cohort. Patients with a baseline NIHSS score of 6–9 achieved a good outcome of 90-day mRS score of 0 or 1 in 49.3% of cases, compared with 30.3% of those with a baseline NIHSS score >9 (Fisher exact test, $p = 0.05$). Although outcome differences were observed across variables such as large vs medium/small vessel occlusions, posterior vs anterior circulation, and right vs left hemisphere stroke location, none of these differences reached statistical significance.

Multivariable analysis revealed that only baseline NIHSS score of 6–9 in contrast to >9 stands out as an independent predictor of a good outcome at day 90 (mRS score ≤1), when adjusting for the potential influences of all other variables ($p = 0.03$) (Table 3). Patients with NIHSS score 6–9 (vs >9) had 4.42 times higher odds of a good outcome, indicating that a lower NIHSS score is associated with better results at day 90. However, when treating the baseline NIHSS score as a continuous variable, it did not attain significance ($p = 0.36$) as a predictor.

This study provides Class II evidence that in patients with AIS treated with IVT within 3 hours of onset, argatroban or eptifibatide does not improve outcomes vs thrombolysis alone but does increase mortality.

Discussion

This prespecified secondary analysis of the MOST trial showed that patients receiving IV thrombolytics only, without thrombectomy, did not benefit from the concomitant administration of either argatroban or eptifibatide. In fact, both treatment groups had worse mean uwmRS score at 90 days and higher mortality, although excess deaths were not due to increased symptomatic ICH or major systemic hemorrhage and were not adjudicated to be related to study medication. Worse outcomes in the treatment groups may have been influenced by nonsignificant imbalances in baseline features associated with worse outcomes such as increased age, more LVOs, and more posterior circulation strokes in the argatroban group; more baseline disability in the eptifibatide group; and the small number of patients assigned to argatroban treatment.

Other studies have demonstrated mixed results with argatroban given either after or without thrombolysis,[11,12] and a recent study of the GP2b3a antagonist tirofiban suggested benefit in patients given the drug at a median of 12.5 hours after onset.[13] While the incidence of clot lysis or reocclusion was not directly measured in this study, our results do not support the hypothesis on which this study was based that either strategy might augment clot lysis over that achieved by IVT alone or might prevent reocclusion after IVT. A companion analysis evaluating argatroban and eptifibatide in the cohort of patients who were candidates for thrombectomy showed similar results. While our data do not exclude the possibility that IVT outcomes can be improved by adding other therapeutic strategies, results suggest that approaches other than anticoagulation or GP2b3a platelet inhibition should be considered.

Consistent with our pilot data,[14-19] we observed no increased risk of symptomatic ICH or major systemic hemorrhage despite therapeutic levels of anticoagulation or therapeutic doses of a powerful antiplatelet agent for the 12 hours starting toward the end of the administration of thrombolysis. This finding is contrary to results from the ARTIS study that showed increased symptomatic hemorrhage when 300 mg of aspirin was given intravenously 90 minutes after tPA. Similar risk was seen when either aspirin or heparin was added to EVT.[20,21] Taken together, accumulated experience suggests that combining IVT with therapies that might theoretically result in increased bleeding risk may still be reasonable to pursue but requires careful scrutiny of pilot data to confirm safety.

One objective of this substudy was to perform an exploratory analysis to identify a subset of patients who do not respond to IVT-O and might be the best participants for future studies to enhance IVT. In particular, we were interested in whether the presence of arterial occlusion modified the treatment effect of IVT-O. Many studies have documented reduced benefit of IVT-O in patients with LVO, but there is much less information on patients with medium or distal branch occlusions. Using data from the IVT-O placebo patients, we found that the presence of visible clots occluding medium/distal arterial branches showed a numerical trend toward more favorable outcomes in this small group of patients, which was not statistically significant. This is consistent with a recent subanalysis of patients receiving IVT-O in the WAKE-UP study showing no heterogeneity in outcomes based on the presence of any vs no arterial occlusion.[22] Multivariable analysis identified baseline NIHSS score >9 as the sole independent predictor of a less favorable outcome at day 90, but it lacked significance when treated as a continuous variable, necessitating a cautious interpretation. Previous data from as far back as the original National Institute of Neurological Disorders and Stroke study showed that response to IVT-O was consistent across clinical variables[23] but did not include information on the presence or absence of arterial occlusion. Taken together with the previous literature, our data provide strong evidence that response to IVT-O does not differ based on the presence or absence of baseline clinical features, including whether medium or distal arterial clot is visualized.

Limitations of our study include the small sample size in the argatroban group, potential confounding factors, and the exploratory nature of subgroup analyses. In most cases, the study drug was not administered until an hour after the lytic bolus, by which time clot stabilization may have already occurred. We did not confirm the existence of ischemic penumbra before randomization. While we cannot exclude an interaction between the imaging identification of penumbra and benefit of our specific intervention, advanced imaging is not routinely needed to select patients for reperfusion therapy within 3 hours of onset. Although we failed to detect any clinical benefit from our interventions, we did not study recanalization or reperfusion, which may have been improved.

This study did not provide evidence of a beneficial effect of adding argatroban or eptifibatide to IVT alone in patients with ischemic stroke. Baseline characteristics including medium/distal arterial occlusion or NIHSS score could not confidently identify a treatment-responsive subgroup. The lack of benefit could not be explained by increased bleeding, but death occurred more often after study treatment.

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Author Contributions

A. Roy: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. J. Elm: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. J.R. Ingles: drafting/revision of the manuscript for content, including medical writing for content; analysis or interpretation of data. N. Sabagha: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. J.F. Huang: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. O. Bentho: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. T. Ranasinghe: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C. Streib: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Concha: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. P. Khatri: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. A. Vagal: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. M. Wintermark: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data. C.P. Derdeyn: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. J.P. Broderick: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. A.D. Barreto: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. O. Adeoye: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design. J.C. Grotta: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design.

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