# Mechanical Thrombectomy Outcomes With or Without Intravenous Thrombolysis

## Insight From the ASTER Randomized Trial

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***Background and Purpose***—Intravenous thrombolysis (IVT) within 4.5 hours of symptom onset is currently recommended before mechanical thrombectomy (MT). We compared functional outcome, neurological recovery, reperfusion, and adverse events according to the use or not of IVT before MT.

***Methods***—This is a post hoc analysis of the ASTER trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization). The primary outcome was favorable 90-day functional outcome defined as a modified Rankin Scale of ≤2. Secondary outcomes were successful reperfusion following all procedures and after the first-line procedure, number of device passes, and change in National Institutes of Health Stroke Scale score at 24 hours. Safety outcomes included 90-day mortality and any symptomatic intracerebral hemorrhage.

***Results***—Three hundred eighty-one patients were included, 250 of whom received IVT before MT (IVT+MT group). There were no significant differences between IVT+MT and MT-alone groups in 90-day favorable functional outcome, in successful reperfusion rate (modified Thrombolysis In Cerebral Infarction 2b or 3), in National Institutes of Health Stroke Scale score improvement at 24 hours, or in hemorrhagic complication rate. The 90-day mortality rate in the IVT+MT group was lower than after MT alone (fully-adjusted risk ratio, 0.59; 95% CI, 0.39–0.88). In a subgroup of patients without anticoagulant medication before stroke onset, we observed in the IVT+MT group a better functional outcome (fully-adjusted risk ratio, 1.38; 95% CI, 1.02–1.89), a higher successful recanalization rate after first-line strategy (fully-adjusted risk ratio, 1.26; 95% CI, 1.05–1.50), and a lower mortality rate (fully-adjusted risk ratio, 0.58; 95% CI, 0.36–0.93).

***Conclusions***—Our results show that IVT+MT patients in the ASTER trial have lower 90-day mortality compared with those receiving MT alone. In a selected population of patients without prestroke anticoagulation, we demonstrated that IVT associated with MT might improve functional outcome and recanalization while reducing mortality rates. **(*Stroke*. 2018;49:2383-2390. DOI: 10.1161/STROKEAHA.118.021500.)**

**Key Words:** anticoagulants ■ cerebral hemorrhage ■ National Institutes of Health (U.S.) ■ stroke ■ thrombectomy



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Six randomized controlled trials and an aggregate level analysis of their data have proven the superiority of mechanical thrombectomy (MT) over standard medical management alone after acute ischemic stroke because of large vessel occlusion.[1,2] Intravenous thrombolysis (IVT) within 4.5 hours is currently recommended before MT. Several studies suggested that IVT may influence recanalization rate and clinical outcome after MT.[3] However, its precise benefit remains under debate. IVT might be helpful, in particular, for cases

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of distal emboli after MT, but it may also increase the hemorrhagic complication rate. In addition, IVT could delay MT particularly in a drip-and-ship approach. To date, there is no randomized trial comparing MT after IVT versus MT alone.

The ASTER (Contact Aspiration vs Stent Retriever for Successful Revascularization) study[4] was a randomized clinical trial aiming to compare efficacy and safety of the contact aspiration (CA) technique versus the standard stent retriever (SR) technique. We performed a post hoc analysis to investigate the role and the safety of IVT, in cases of acute ischemic stroke caused by vessel occlusion, subsequently treated with MT within our ASTER trial population.

## Methods

### Patient Selection

We performed here a post hoc analysis from the ASTER trial.[4,5] ASTER was a randomized, multicenter, open-label, blinded end point clinical trial of first-line CA versus first-line SR to determine the best recanalization strategy in patients with a proximal arterial occlusion in the anterior circulation demonstrated on vessel imaging and treatable within 6 hours after symptom onset. IVT was delivered according to recommendations of the American Stroke Association and European Stroke Organization[6,7] within 4.5 hours after onset of symptoms in the absence of contraindications. Contraindications for IVT were as follows: late treatment (between 4.5 and 6 hours after onset) and treatment in patients with a possible high bleeding risk after thrombolytic therapy, including elevated increased international normalized ratio (1.7–3.0), thrombocyte count $<90\times10^9$/L, history of intracerebral hemorrhage, severe head injury in the preceding 4 weeks, previous acute ischemic stroke in the preceding 6 weeks and major surgery, gastrointestinal bleeding, or urinary tract bleeding within the previous 2 weeks.

The study protocol and the consent form were approved by the Comité de Protection des Personnes Ile de France VI (ID 2015-A00830-49). According to French laws, oral informed consent was sought from patients if their level of consciousness was sufficient or else from a relative. This study operated an emergency inclusion protocol because of the nature of the condition.

This study enrolled adults admitted with ischemic stroke secondary to occlusion of the anterior circulation (carotid terminus or M1 or M2 segments) within 6 hours of symptom onset. Immediately after baseline brain imaging and before the endovascular procedure, patients were randomly allocated in a 1:1 fashion to undergo either CA (intervention) or SR (control) thrombectomy as the first-line intervention. The data that support the findings of this study are available from B.L. on reasonable request.

### Outcomes

The primary outcome for this post hoc study was functional independence as defined by a 90-day modified Rankin Scale of ≤2. The secondary technical outcomes were the percentage of patients with successful revascularization defined as a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b or 3 at the end of angiography after all endovascular treatments, the percentage of patients with successful revascularization (mTICI 2b or 3) at the end of the first-line strategy, and the rate of MT requiring >2 device passes. The secondary clinical outcomes were the change in National Institutes of Health Stroke Scale (NIHSS) score at 24 hours, excellent outcome as defined by a 90-day modified Rankin Scale score of 0 or 1, and death because of any cause at 90 days. Intracranial hemorrhage rate was also reported as appreciated on imaging at 24 hours according to the European Cooperative Acute Stroke Study 3 classification,[8] and symptomatic intracranial hemorrhage at 24 hours, defined as any intracranial hemorrhage visualized on follow-up imaging and associated with a 4-point or greater worsening on the NIHSS score or that resulted in death. Adverse events also included procedure-related serious adverse events (arterial perforation, arterial dissection, embolization in a new vascular territory, subarachnoid hemorrhage, and vasospasm).

### Statistical Analysis

Quantitative variables are expressed as means (SD) in the case of normal distribution or medians (interquartile range) otherwise. Categorical variables are expressed as numbers (percentage). Normality of distributions was assessed using histograms and the Shapiro-Wilk test. Baseline characteristics were described according to the study groups (combined IVT and MT [IVT+MT] versus MT alone [MT]), and absolute standardized differences were calculated to evaluate baseline imbalance; an absolute standardized difference >20% was interpreted as meaningful imbalance. Comparisons in binary outcomes between the 2 study groups were performed using generalized estimating equations models (Poisson distribution, log-link function) to take into account the center effect and including as covariate the allocated first-line MT strategy (CA versus SR); adjusted risk ratios (RRs) were derived from generalized estimating equations models as effect size using MT group as reference. Comparison in change in NIHSS score at 24 hours from admission was performed using a linear mixed model included admission NIHSS score and first-line MT strategy as fixed effects and center as random effect; adjusted between-group mean difference was derived from this model as effect size. Normality of model residuals was checked and satisfied. Comparisons in outcomes were further adjusted for prespecified confounding factors (age, hypertension, diabetes mellitus, admission NIHSS, and Alberta Stroke Program Early CT Scores, site of occlusion, onset to puncture time). Between-group comparisons in outcomes were further stratified according to the first-line MT strategy. Heterogeneity across first-line strategy subgroups was tested by introducing the multiplicative term between study groups and first-line MT strategy into the generalized estimating equations and linear mixed models. Our first analyses covered the whole study group; all analyses were repeated after excluding patients with anticoagulant medication before stroke onset to acknowledge the large between-group difference because effective anticoagulation is a contraindication for IVT.

Statistical testing was conducted at the 2-tailed $\alpha$-level of 0.05. Data were analyzed using the SAS software version 9.4 (SAS Institute, Cary, NC).

## Results

From October 2015 to October 2016, 381 patients were randomized in the ASTER trial, and all were included in the present study. Of these, 250 (65.6%) were randomized after IVT treatment and constituted the IVT+MT group. Table 1 shows the baseline characteristics according to the 2 study groups. Several meaningful differences (absolute standardized difference >20%) were found; as expected, the strongest difference was observed for patients on anticoagulant therapy at stroke onset (40.9% in MT vs 8.2% IVT+MT). Of the 131 patients with in the MT alone group, 50 patients (38.2%) had possible elevated bleeding risk (international normalized ratio >1.7 or heparin or direct oral anticoagulant), 32 patients were admitted outside the window for IVT (24.4%), 16 patients (12.2%) had a non-neurological high bleeding risk, 10 patients (7.6%) had extensive ischemic lesion, and 23 patients (17.5%) were ineligible to IVT because of other causes.

As shown in Table 2, favorable outcome (our primary outcome) was achieved more frequently in the IVT+MT group, with an adjusted RR for center and first-line strategy of 1.43 (95% CI, 1.05–1.93). However, this difference remained nonsignificant after additional adjustment on prespecified confounding factors (adjusted RR, 1.27; 95% CI, 0.95–1.72).

**Table 1. Baseline Characteristics According to Use of Intravenous Thrombolysis Before Mechanical Treatment in the ASTER Trial**

| Characteristics | MT (n=131) | IVT+MT (n=250) | ASD, % |
|---|---|---|---|
| Age, y mean (SD) | 72.2 (13.0) | 68.7 (14.8) | 25.0 |
| Men | 65/131 (49.6) | 142/250 (56.8) | 14.4 |
| Direct admission | 51/131 (38.9) | 87/250 (34.8) | 8.6 |
| Medical history | | | |
| Hypertension | 90/128 (70.3) | 139/245 (56.7) | 28.5 |
| Diabetes mellitus | 27/130 (20.8) | 49/243 (20.2) | 1.5 |
| Hypercholesterolemia | 46/130 (35.4) | 85/241 (35.3) | 0.2 |
| Current smoking | 14/103 (13.6) | 48/218 (22.0) | 22.2 |
| Previous antithrombotic medications | 78/125 (61.4) | 104/245 (42.4) | 38.7 |
| Antiplatelet use | 32/127 (25.2) | 86/245 (35.1) | 21.7 |
| Anticoagulants | 52/127 (40.9) | 20/245 (8.2) | 82.4 |
| Coronary artery disease | 24/126 (19.0) | 39/243 (16.0) | 7.9 |
| Previous stroke or TIA | 28/130 (21.5) | 37/244 (15.2) | 16.5 |
| Current stroke event | | | |
| NIHSS score, median (IQR)* | 18.0 (11.0–21.0) | 17.0 (12.5–20.0) | 4.7 |
| ASPECTS, median (IQR)† | 7.0 (5.0–9.0) | 7.0 (6.0–9.0) | 4.7 |
| Prestroke Rankin ≥1 | 33/131 (25.2) | 29/248 (11.7) | 35.3 |
| Site of occlusion | | | 15.2 |
| M1-MCA | 96/131 (73.3) | 174/250 (69.6) | |
| M2-MCA | 14/131 (10.7) | 39/250 (15.6) | |
| Intracranial ICA | 18/131 (13.7) | 33/250 (13.2) | |
| Other‡ | 3/131 (2.3) | 4/250 (1.6) | |
| Favorable collaterals | 25/93 (26.9) | 49/191 (25.7) | 2.8 |
| Clot burden score§ | 7.0 (4.0–8.0) | 7.0 (5.0–8.0) | 2.8 |
| Clot length‖ | 12.0 (8.0–19.0) | 12.0 (8.0–18.0) | 4.0 |
| Suspected stroke cause | | | |
| Large artery atherosclerosis | 11/131 (8.4) | 19/250 (7.6) | 4.3 |
| Cardioembolic | 57/131 (43.5) | 106/250 (42.4) | |
| Others | 63/131 (48.1) | 125/250 (50.0) | |
| Endovascular treatment | | | |
| Onset-to-groin puncture min, median (IQR; 90th percentile)¶ | 230 (170–282; 390) | 225 (183–280;330) | 1.7 |
| Onset to imaging | 120 (80–167; 219) | 110 (85–143; 183) | 12.8 |
| Imaging to groin puncture | 103 (63–141; 180) | 115 (65–150; 178) | 13.0 |
| General anesthesia | 15/130 (11.5) | 31/249 (12.4) | 2.8 |
| First-line CA strategy | 66/131 (50.4) | 126/250 (50.4) | 0.04 |

Values expressed as no./total no. (%) unless otherwise indicated. ASD indicates absolute standardized difference; ASPECTS, Alberta Stroke Program Early CT Score; ASTER, Contact Aspiration Versus Stent Retriever for Successful Revascularization; CA, contact aspiration; ICA, intracranial carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; MCA, middle cerebral artery; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; and TIA, transient ischemic attack.

*Three missing values (2 in MT+IVT group).

†Five missing values (5 in MT+IVT group).

‡Tandem extracranial ICA stenosis/occlusion and intracranial proximal occlusion.

§One hundred twenty-seven missing values (79 in MT+IVT group).

‖Eighty-eight missing values (51 in MT+IVT group).

¶Four missing values (3 in MT+IVT group).

**Table 2. Outcomes in the ASTER Trial According to Use of Intravenous Thrombolysis Before Mechanical Treatment**

| Outcomes | MT (n=131) | IVT+MT (n=250) | RR (95% CI)* | *P* Value | RR (95% CI)*† | *P* Value |
|---|---|---|---|---|---|---|
| Angiographic outcomes | | | | | | |
| Reperfusion after first-line strategy | | | | | | |
| mTICI 3 | 45/131 (34.4) | 77/250 (30.8) | 0.90 (0.60 to 1.34) | 0.59 | 0.90 (0.62 to 1.31) | 0.58 |
| mTICI 2c/3 | 59/131 (45.0) | 118/250 (47.2) | 1.05 (0.78 to 1.41) | 0.75 | 1.04 (0.79 to 1.38) | 0.77 |
| mTICI 2b/3 | 79/131 (60.3) | 170/250 (68.0) | 1.13 (0.94 to 1.35) | 0.18 | 1.11 (0.94 to 1.32) | 0.21 |
| No. of passes >2 | 50/131 (38.2) | 94/250 (37.6) | 0.99 (0.76 to 1.25) | 0.90 | 0.97 (0.80 to 1.18) | 0.77 |
| Use of rescue therapy | 40/131 (30.5) | 68/250 (27.2) | 0.89 (0.59 to 1.35) | 0.59 | 0.90 (0.61 to 1.32) | 0.58 |
| Reperfusion at end of procedure | | | | | | |
| mTICI 3 | 56/131 (42.7) | 89/250 (35.6) | 0.83 (0.59 to 1.18) | 0.30 | 0.82 (0.59 to 1.13) | 0.23 |
| mTICI 2c/3 | 75/131 (57.3) | 140/250 (56.0) | 0.98 (0.76 to 1.25) | 0.86 | 0.94 (0.74 to 1.23) | 0.71 |
| mTICI 2b/3 | 106/131 (80.9) | 215/250 (86.0) | 1.06 (0.99 to 1.14) | 0.078 | 1.05 (0.98 to 1.13) | 0.16 |
| Procedural complications | 20/131 (15.3) | 41/250 (16.4) | 1.07 (0.68 to 1.70) | 0.76 | 0.99 (0.64 to 1.54) | 0.96 |
| Emboli | 29/131 (22.1) | 56/250 (22.4) | 1.01 (0.70 to 1.46) | 0.95 | 1.02 (0.75 to 1.39) | 0.91 |
| Clinical outcomes | | | | | | |
| Δ NIHSS at 24 h, mean (95% CI)‡ | −3.9 (−5.5 to -2.4)§ | −5.4 (−6.5 to −4.3)§ | −1.5 (−3.4 to 0.4)‖ | 0.13 | −0.8 (−2.7 to 1.1)‖ | 0.40 |
| Favorable outcome | 47/126 (37.3) | 126/237 (53.2) | 1.43 (1.05 to 1.93) | 0.022 | 1.27 (0.95 to 1.72) | 0.11 |
| Excellent outcome | 40/126 (31.7) | 97/237 (40.9) | 1.29 (0.87 to 1.90) | 0.20 | 1.11 (0.78 to 1.60) | 0.55 |
| 90-d mortality | 35/126 (27.8) | 35/237 (14.8) | 0.53 (0.34 to 0.84) | 0.006 | 0.59 (0.39 to 0.88) | 0.009 |
| Hemorrhagic complications | | | | | | |
| Any ICH | 58/130 (44.6) | 114/242 (47.1) | 1.06 (0.89 to 1.26) | 0.54 | 1.10 (0.96 to 1.26) | 0.18 |
| Parenchymal hematoma | 18/130 (13.8) | 38/242 (15.7) | 1.13 (0.87 to 1.47) | 0.35 | 1.19 (0.82 to 1.73) | 0.37 |
| sICH | 6/130 (4.6) | 16/242 (6.6) | 1.43 (0.82 to 2.51) | 0.21 | … | … |

Values expressed as no./total no. (%), unless otherwise stated. ASPECTS indicates Alberta Stroke Program Early CT Score; ASTER, Contact Aspiration Versus Stent Retriever for Successful Revascularization; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; mTICI, modified Treatment in Cerebral Infarction score; NIHSS, National Institutes of Health Stroke Scale; RR, risk ratio; and sICH, symptomatic intracranial hemorrhage.

*Calculated using MT group as reference after adjustment for center and first-line strategy.

†Additional adjustment on prespecified confounding factors (age, hypertension, diabetes mellitus, admission NIHSS and ASPECTS scores, site of occlusion, onset to puncture time).

‡Twenty-six missing values (15 in IVT+MT group).

§Mean change (95% CI) adjusted on baseline NIHSS score, center and first-line strategy.

‖Adjusted mean difference (IVT+MT vs MT).

There was no significant difference in angiographic outcomes in models adjusted for center and first-line strategy only or in models with additional adjustment on prespecified confounding factors. Regarding other clinical efficacy outcomes, there were no between-group differences in excellent outcome or the change in NIHSS score at 24 hours in either of the adjusted models. Regarding safety clinical outcomes, 90-day all-cause mortality rate was lower in IVT+MT patients compared with MT alone (14.8% vs 27.8%; center, first-line MT strategy-adjusted RR, 0.53; 95% CI, 0.34–0.84). This difference remained unchanged after additional adjustment on prespecified confounding factors (adjusted RR, 0.59; 95% CI, 0.39–0.88). Hemorrhagic complication rates (any, parenchymal hematoma, or symptomatic intracranial hemorrhage) were similar between the 2 study groups.

In sensitivity analysis restricted to patients without anticoagulant medication before stroke onset (see baseline characteristics available in Table in the online-only Data Supplement), a positive effect of the IVT+MT approach on favorable outcome (fully-adjusted, 1.38; 95% CI, 1.02–1.89), on successful reperfusion after first-line strategy (fully-adjusted RR, 1.26; 95% CI, 1.05–1.50), but not for near to complete (mTICI 2c/3) and complete (mTICI 3) reperfusion. In addition, we found a positive effect of IVT+MT approach on NIHSS change at 24 hours (fully-adjusted mean difference, 2.5 points; 95% CI, 0.2–4.8) and on 90-day all-cause mortality (fully-adjusted RR, 0.58; 95% CI, 0.36–0.93) was found. There was also a significantly lower rate of number of passes >2 in the IVT+MT group (fully-adjusted RR, 0.83; 95% CI, 0.70–0.97) compared with the MT alone group (Table 3).

When the analyses were stratified according to the first-line therapy (CA vs SR), there was no significant heterogeneity in effect sizes of combined IVT+MT for each study outcome (Figure). We only observed that patients treated by IVT+MT require more MT attempts and more often have intracranial hemorrhage than patients treated with MT in the CA first-line subgroup only (adjusted RR, 1.25; 95% CI, 1.01–1.54 and adjusted RR, 1.33; 95% CI, 1.03–1.72, respectively)

**Table 3. Outcomes in the ASTER Trial According to Use of Intravenous Thrombolysis Before Mechanical Treatment Among Patients Without Anticoagulant Medication Before Stroke Onset**

| Outcomes | MT (n=75) | IVT+MT (n=225) | RR (95% CI)* | *P* Value | RR (95% CI)*† | *P* Value |
|---|---|---|---|---|---|---|
| Angiographic outcomes | | | | | | |
| Reperfusion after first-line strategy | | | | | | |
| mTICI 3 | 27/75 (36.0) | 71/225 (31.6) | 0.88 (0.60 to 1.30) | 0.52 | 0.90 (0.61 to 1.33) | 0.60 |
| mTICI 2c/3 | 33/75 (44.0) | 109/225 (48.4) | 1.10 (0.81 to 1.50) | 0.53 | 1.17 (0.84 to 1.63) | 0.34 |
| mTICI 2b/3 | 42/75 (56.0) | 154/225 (68.4) | 1.22 (1.02 to 1.46) | 0.029 | 1.26 (1.05 to 1.50) | 0.013 |
| No. of passes >2 | 34/75 (45.3) | 85/225 (37.8) | 0.83 (0.65 to 1.07) | 0.15 | 0.83 (0.70 to 0.97) | 0.020 |
| Use of rescue therapy | 28/75 (37.3) | 59/225 (26.2) | 0.70 (0.43 to 1.15) | 0.16 | 0.70 (0.44 to 1.14) | 0.13 |
| Reperfusion at end of procedure | | | | | | |
| mTICI 3 | 37/75 (49.3) | 81/225 (36.0) | 0.73 (0.48 to 1.11) | 0.14 | 0.72 (0.43 to 1.13) | 0.15 |
| mTICI 2c/3 | 45/75 (60.0) | 128/225 (56.9) | 0.95 (0.69 to 1.30) | 0.74 | 0.96 (0.66 to 1.40) | 0.84 |
| mTICI 2b/3 | 63/75 (84.0) | 195/225 (86.7) | 1.03 (0.94 to 1.13) | 0.50 | 1.04 (0.93 to 1.16) | 0.45 |
| Procedural complications | 11/75 (14.7) | 35/225 (15.6) | 1.06 (0.57 to 1.97) | 0.83 | 1.01 (0.54 to 1.90) | 0.96 |
| Emboli | 17/75 (22.7) | 52/225 (23.1) | 1.01 (0.57 to 1.80) | 0.96 | 1.04 (0.60 to 1.81) | 0.89 |
| Clinical outcomes | | | | | | |
| Δ NIHSS at 24 h‡ | −2.5 (−4.5 to −0.6)‖ | −5.7 (−6.9 to −4.6)§ | −3.2 (−5.5 to −0.9)‖ | 0.006 | −2.5 (−4.8 to −0.2)‖ | 0.034 |
| Favorable outcome | 27/73 (37.0) | 117/214 (54.7) | 1.48 (1.07 to 2.03) | 0.020 | 1.38 (1.02 to 1.89) | 0.040 |
| Excellent outcome | 24/73 (32.9) | 90/214 (42.1) | 1.26 (0.84 to 1.96) | 0.25 | 1.16 (0.79 to 1.70) | 0.46 |
| 90-d mortality | 19/73 (26.0) | 29/214 (13.6) | 0.52 (0.31 to 0.88) | 0.014 | 0.58 (0.36 to 0.93) | 0.023 |
| Hemorrhagic complications | | | | | | |
| Any ICH | 36/75 (48.0) | 104/219 (47.5) | 0.99 (0.83 to 1.17) | 0.89 | 1.01 (0.85 to 1.20) | 0.90 |
| Parenchyma hematoma | 12/75 (16.0) | 32/219 (14.6) | 0.92 (0.74 to 1.14) | 0.45 | 0.97 (0.59 to 1.62) | 0.92 |
| sICH | 4/75 (5.3) | 13/219 (5.9) | 1.11 (0.42 to 2.90) | 0.82 | … | … |

Values expressed as no./total no. (%), unless otherwise stated. ASPECTS indicates Alberta Stroke Program Early CT Score; ASTER, Contact Aspiration Versus Stent Retriever for Successful Revascularization; ICH, intracranial hemorrhage; IVT, intravenous thrombolysis; MT, mechanical thrombectomy; mTICI, modified Treatment in Cerebral Infarction score; NIHSS, National Institutes of Health Stroke Scale; RR, risk ratio; and sICH, symptomatic intracranial hemorrhage.

*Calculated using MT group as reference after adjustment for center and first-line MT strategy.

†Additional adjustment on prespecified confounding factors (age, hypertension, diabetes mellitus, baseline NIHSS and ASPECTS scores, site of occlusion, onset to puncture time).

‡Twenty missing values (14 in IVT+MT).

§Mean change (95% CI) adjusted on baseline NIHSS score, center and first-line strategy.

‖Adjusted mean difference (IVT+MT vs MT).

while they more often have successful reperfusion at the end of procedure in the SR first-line subgroup only (adjusted RR, 1.12; 95% CI, 1.02–1.22). In addition, there were fewer deaths in the IVT+MT group compared with MT in SR first-line subgroups (adjusted RR, 0.44; 95% CI, 0.25–0.77). In sensitivity analysis restricted to patients without prestroke anticoagulation, several differences in effect sizes of combined IVT+MT were observed (Figure in the online-only Data Supplement). In the SR first-line subgroup, reperfusion after first-line strategy (2c/3 or 2b/2c/3) occurred more often in IVT+MT patients than after MT alone (adjusted RRs [95% CI]: 1.36 [1.05–1.76] and 1.63 [1.15–2.30], respectively), whereas no such differences were observed in CA first-line subgroup. In addition in the SR first-line subgroup only, patients treated by IVT+MT require fewer MT attempts (adjusted RR, 0.57; 95% CI, 0.36–0.90), had a lower death rate (adjusted RR, 0.35; 95% CI, 0.18–0.71), and a greater NIHSS change (adjusted mean difference, 4.0; 95% CI, 0.8–7.3) than patients treated by MT alone.

## Discussion

In this study of patients among the ASTER trial population, we compared clinical and angiographic outcomes and safety between those having received or not IVT before MT.

We observed no significant difference in favorable outcome and angiographic recanalization between the 2 groups. However, we found a higher mortality rate in the MT alone group. The effect of IVT before MT remains a matter of debate in the literature, which includes meta-analysis, retrospective analysis, and post hoc analysis of randomized studies.[3,9–12]

The reason for not using IVT constitutes a major bias in the interpretation of the present data. Contraindication to

| Outcomes | First-line strategy | MT (n=131) | MT+IVT (n=250) | RR (95%CI)* | P | P het | RR (95%CI)*,† | P | P het |
|---|---|---|---|---|---|---|---|---|---|
| **Angiographic outcomes** | | | | | | | | | |
| Reperfusion after first-line strategy | | | | | | | | | |
| mTICI 3 | CA | 22/66 (33.3) | 33/126 (33.1) | 0.79 (0.44 to 1.41) | 0.42 | 0.39 | 0.77 (0.47 to 1.24) | 0.28 | 0.28 |
| | SR | 23/65 (35.4) | 44/124 (35.5) | 1.00 (0.72 to 1.39) | 0.99 | | 1.04 (0.71 to 1.52) | 0.83 | |
| mTICI 2c/3 | CA | 28/66 (42.4) | 55/126 (43.7) | 1.03 (0.70 to 1.52) | 0.89 | 0.79 | 0.98 (0.69 to 1.38) | 0.89 | 0.39 |
| | SR | 31/65 (46.7) | 63/124 (50.8) | 1.07 (0.84 to 1.35) | 0.60 | | 1.11 (0.85 to 1.44) | 0.45 | |
| mTICI 2b/3 | CA | 40/66 (60.6) | 81/126 (64.3) | 1.06 (0.84 to 1.34) | 0.62 | 0.31 | 1.03 (0.85 to 1.26) | 0.75 | 0.23 |
| | SR | 39/65 (60.0) | 89/124 (71.8) | 1.20 (0.99 to 1.45) | 0.069 | | 1.20 (0.97 to 1.49) | 0.094 | |
| Number of passes>2 | CA | 23/66 (34.9) | 52/126 (41.3) | 1.18 (0.95 to 1.47) | 0.13 | 0.12 | 1.25 (1.01 to 1.54) | **0.038** | 0.089 |
| | SR | 27/65 (41.5) | 42/124 (33.9) | 0.82 (0.54 to 1.22) | 0.32 | | 0.76 (0.49 to 1.16) | 0.20 | |
| Use of rescue therapy | CA | 21/66 (31.8) | 42/126 (33.3) | 1.05 (0.71 to 1.55) | 0.82 | 0.39 | 1.08 (0.74 to 1.58) | 0.68 | 0.37 |
| | SR | 19/65 (29.2) | 26/124 (21.0) | 0.72 (0.32 to 1.62) | 0.43 | | 0.70 (0.30 to 1.64) | 0.42 | |
| Reperfusion at end of procedure | | | | | | | | | |
| mTICI 3 | CA | 28/66 (42.4) | 44/126 (34.9) | 0.82 (0.52 to 1.30) | 0.40 | 0.92 | 0.79 (0.55 to 1.14) | 0.21 | 0.79 |
| | SR | 28/65 (43.1) | 45/124 (36.3) | 0.84 (0.58 to 1.21) | 0.36 | | 0.85 (0.54 to 1.32) | 0.46 | |
| mTICI 2c/3 | CA | 37/66 (56.1) | 71/126 (56.4) | 1.01 (0.73 to 1.39) | 0.98 | 0.61 | 0.95 (0.71 to 1.28) | 0.75 | 0.99 |
| | SR | 38/65 (58.5) | 69/124 (55.7) | 0.95 (0.78 to 1.16) | 0.63 | | 0.95 (0.75 to 1.22) | 0.70 | |
| mTICI 2b/3 | CA | 56/66 (84.9) | 108/126 (85.7) | 1.01 (0.91 to 1.12) | 0.84 | 0.20 | 0.99 (0.91 to 1.09) | 0.92 | 0.20 |
| | SR | 50/65 (76.9) | 107/124 (86.3) | 1.12 (1.03 to 1.22) | **0.007** | | 1.12 (1.02 to 1.22) | **0.018** | |
| Procedural complications | CA | 10/66 (15.2) | 21/126 (16.7) | 1.10 (0.62 to 1.96) | 0.75 | 0.84 | 1.04 (0.56 to 1.91) | 0.91 | 0.74 |
| | SR | 10/65 (15.4) | 20/124 (16.1) | 1.05 (0.69 to 1.60) | 0.83 | | 0.95 (0.63 to 1.42) | 0.79 | |
| Embol | CA | 19/66 (28.8) | 33/126 (26.2) | 0.91 (0.74 to 1.12) | 0.38 | 0.47 | 0.95 (0.75 to 1.21) | 0.70 | 0.68 |
| | SR | 10/65 (15.4) | 23/124 (18.6) | 1.21 (0.51 to 2.83) | 0.67 | | 1.14 (0.50 to 2.56) | 0.76 | |
| **Clinical outcomes** | | | | | | | | | |
| Favorable outcome | CA | 23/63 (36.5) | 59/118 (50.0) | 1.37 (1.01 (1.86) | **0.046** | 0.68 | 1.15 (0.89 to 1.50) | 0.28 | 0.26 |
| | SR | 24/63 (38.1) | 67/119 (56.3) | 1.48 (0.99 to 2.21) | 0.057 | | 1.40 (0.92 to 2.14) | 0.12 | |
| Excellent outcome | CA | 18/63 (28.6) | 41/118 (34.8) | 1.22 (0.72 to 2.07) | 0.47 | 0.70 | 0.97 (0.66 to 1.42) | 0.86 | 0.24 |
| | SR | 22/63 (34.9) | 56/119 (47.1) | 1.35 (0.88 to 2.07) | 0.17 | | 1.25 (0.79 to 1.99) | 0.34 | |
| 90-day mortality | CA | 15/63 (23.8) | 20/118 (17.0) | 0.71 (0.52 to 0.98) | **0.036** | 0.12 | 0.78 (0.47 to 1.27) | 0.31 | 0.13 |
| | SR | 20/63 (31.8) | 15/119 (12.6) | 0.40 (0.21 to 0.77) | **0.006** | | 0.44 (0.25 to 0.77) | **0.004** | |
| **Hemorrhagic complications** | | | | | | | | | |
| Any ICH | CA | 26/66 (39.4) | 61/122 (50.0) | 1.27 (0.94 to 1.72) | 0.12 | 0.11 | 1.33 (1.03 to 1.72) | **0.027** | 0.11 |
| | SR | 32/64 (50.0) | 53/120 (44.2) | 0.88 (0.76 to 1.02) | 0.095 | | 0.91 (0.74 to 1.13) | 0.39 | |
| Parenchyma hematoma | CA | 6/66 (9.1) | 18/122 (14.8) | 1.62 (0.83 to 3.16) | 0.15 | 0.25 | 1.57 (0.84 to 2.94) | 0.16 | 0.18 |
| | SR | 12/64 (18.8) | 20/120 (16.7) | 0.89 (0.67 to 1.18) | 0.42 | | 0.97 (0.71 to 1.32) | 0.84 | |

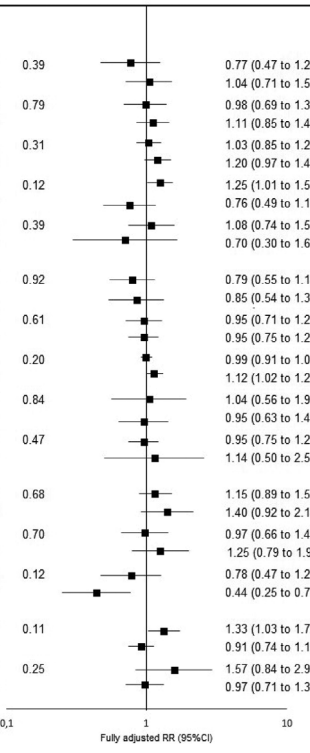


**Figure.** Outcomes in the ASTER (Contact Aspiration Versus Stent Retriever for Successful Revascularization) trial according to use of intravenous thrombolysis and first-line strategy (contact aspiration [CA] vs stent retriever [SR]). *Calculated using mechanical treatment (MT) group as reference after adjustment for center. †Additional adjustment on prespecified confounding factors (age, hypertension, diabetes mellitus, baseline National Institutes of Health Stroke Scale [NIHSS] and Alberta Stroke Program Early CT Scores, site of occlusion, onset to puncture time). P het indicates *P* values for heterogeneity in treatment effect sizes across first-line strategy subgroups. There no evidence of heterogeneity in intravenous thrombolysis (IVT) effect size on 24-h NIHSS change according to first-line strategy in 24 h; fully-adjusted mean between-group difference (95% CI): −1.0 (−4.2 to 2.2) in CA vs −4.0 (−7.3 to −0.8) in SR. ICH indicates intracranial hemorrhage; mTICI, modified Treatment in Cerebral Infarction score; RR, risk ratio; and sICH, symptomatic intracranial hemorrhage.



IVT inevitably selects a particular population with higher comorbidity rates, such as intercurrent pathology and medication or a recent history of surgery. This may explain a higher morbi-mortality in the MT-alone group. Several studies have already reported a decrease in mortality in patients who received IVT before MT, but the explanation for lower mortality remains unclear.[3]

In our study, as expected, baseline characteristics of our 2 groups are not comparable. Patients in the MT-alone group were older, with a higher prestroke modified Rankin Scale and more often had previous antithrombotic medication. Prestroke anticoagulant medication was one of the most relevant differences between groups. Therefore, we performed a subgroup analysis, comparing patients with and without prestroke anticoagulant medication. These 2 subgroup populations were comparable (Table in the online-only Data Supplement). Among patients without anticoagulants, we found a higher mTICI2b/3 reperfusion rate after first-line strategy in the IVT+MT group. This effect was not found on final recanalization rate, but interestingly, the number of MT passes was significantly lower in the IVT+MT group. As some authors previously suggested,[3,13] thrombolysis can, therefore, be thought to facilitate recanalization by reducing the number of passes required to obtain favorable recanalization. Among patients not on anticoagulants, our results demonstrate that functional outcome was significantly better in the IVT+MT group compared with MT alone, both in the short and long terms. We hypothesize that IVT may be beneficial in cases of incomplete recanalization with MT thanks to its action on distal clots inaccessible to endovascular treatment. This may contribute to achieve better final reperfusion. However, preclinical data suggest that the role of IVT is more complex than a simple proximal clot lysis. In an animal transient middle cerebral artery occlusion model, IVT acts on the downstream microvascular thrombosis that starts immediately after the occlusion, limiting the infarct extension and allowing better functional results.[14] Such elements may potentially explain better functional outcome and lower 90-day mortality for patients in the IVT+MT group not on anticoagulants before stroke onset.

Our stratified analysis according to first-line therapy in patients without oral anticoagulation suggests that thrombolysis facilitates thrombectomy by SR but not by CA. Indeed, reperfusion after the first-line strategy was significantly better in the IVT+MT group with a lower number of passes only in SR first-line subgroup patients. This may be explained by a potential lower sensitivity of SR compared with CA to thrombolysis-induced

thrombus fragmentation. This hypothesis is also sustained by the greater number of passes after thrombolysis in the CA first-line subgroup. These elements could thus justify the use of SR rather than CA in patients receiving IVT before MT.

The relationship between IVT and emboli in a new territory remains unclear. On the one hand, IVT could induce thrombus fragmentation and thus facilitate emboli during thrombectomy. But, conversely, in a post hoc analysis of the ESCAPE trial (The Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), Ganesh et al[15] concluded that IVT before thrombectomy reduced by approximately two-thirds the likelihood of an infarct in a new, previously unaffected territory, complicating MT. Their findings have not been reported in the other randomized clinical trials to date. In our study, we found no effect of thrombolysis on the occurrence of distal emboli.

Despite thrombolysis-induced coagulopathy, we found no difference in hemorrhagic complication rate in IVT+MT versus MT alone groups. Likewise, there was no difference in terms of procedural complications. These findings are consistent with the majority of previous publications[3,9–11] although one showed the possibility of an increased risk of asymptomatic intracranial hemorrhage.[16]

In our study, almost two-thirds of patients followed a drip-and-ship paradigm. Drip-and-ship patients in the MT+IVT group received IVT before transfer and therefore potentially benefited from the action of IVT on distal microthrombosis during transfer to the comprehensive stroke center. This would potentially be a further argument for thrombolysis in the drip-and-ship strategy. On the other hand, Gerschenfeld et al[17] recently reported that patients treated with the drip-and-ship approach had significantly longer process times (onset to IVT, onset to puncture, IVT to puncture, and onset to recanalization) compared with those benefiting from a mothership approach, without any effect on clinical outcome. In the meta-analysis of Mistry et al,[3] there was no clear argument in favor of extending the treatment times (onset-to-groin) associated with the use of IVT. In the present study, IVT was not responsible for any significant management delays as the different treatment times (onset-to-groin puncture, onset to imaging, and imaging to recanalization) were similar between the 2 groups.

The present study experiences several limitations. First, measured or unmeasured variables may represent potential confounding factors that cannot be ruled out despite our prespecified adjustment. Furthermore, we cannot exclude false positive results because of the multiple testing issues. In addition, the results of subgroups analysis should be taken with caution as we lack statistical power. Finally, despite the intention-to-treat study design, some patients were not included in the ASTER trial because of spontaneous intracranial recanalization after IVT alone, thereby underestimating the effect of thrombolysis. Tsivgoulis et al[18] recently showed that spontaneous recanalization after IVT and before thrombectomy occurred in 11% of cases and in 17% of cases if tandem occlusions are excluded.

Another potential limitation is the relatively small number of patients in the subgroup without prestroke anticoagulation among the MT alone population. Otherwise, in the MT-alone group, ≈25% of patients were ineligible to IVT because of an arrival outside the IVT window. Even if here door-to-groin times are similar, this is a potential bias. Indeed, patients with onset-imaging >4.5 hours could be overrepresented among MT alone group.

Despite our results, a randomized comparative study in patients eligible for IVT remains necessary to determine the exact impact of IVT in patients undergoing MT. This study should include patients in centers with comparable door-to-needle and door-to-groin times.

Finally, this is a post hoc analysis of patients randomized for MT first-line strategy and not for prethrombectomy IVT.

## Conclusions

Our results demonstrated that IVT+MT patients in the ASTER trial have lower 90-day mortality compared with those receiving MT alone potentially associated with a selection bias (age and comorbidities). In a subgroup analysis of patients not on anticoagulant medication before stroke onset, we demonstrate for IVT+MT patients a better functional outcome and a higher recanalization rate after the first-line strategy requiring a lower number of device passes, a lower mortality rate, and a comparable risk of hemorrhagic complications.

Our findings highlight the need for randomized trials to accurately determine the additional contribution of IVT in patients treated with MT.

## Appendix

*ASTER Trial (Contact Aspiration Versus Stent Retriever for Successful Revascularization) Investigators: Rothschild Foundation: Michel Piotin, Raphael Blanc, Hocine Redjem, Gabriele Ciccio, Stanislas Smajda, Mikael Mazighi, Robert Fahed, Jean Philippe Desilles; Foch Hospital: Bertrand Lapergue, Georges Rodesch, Arturo Consoli, Oguzhan Coskun, Federico Di Maria, Frédéric Bourdain, Jean Pierre Decroix, Adrien Wang, Maya Tchikviladze, Serge Evrard; Hospices Civils de Lyon: Francis Turjman, Benjamin Gory, Paul Emile Labeyrie, Roberto Riva; Limoges University Hospital: Charbel Mounayer, Suzanna Saleme; Montpellier University Hospital: Vincent Costalat, Alain Bonafé, Omer Eker, Grégory Gascou, Cyril Dargazanli; Nancy University Hospital: Serge Bracard, Romain Tonnelet, Anne Laure Derelle, René Anxionnat; Nantes University Hospital: Hubert Desal, Romain Bourcier, Benjamin Daumas-Duport; Bordeaux University Hospital: Jérôme Berge, Xavier Barreau, Gaultier Marnat; University Hospital Lille: Lynda Djemmane, Malek Ben Maacha, Julien Labreuche, Alain Duhamel.

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