Functional Outcome, Recanalization, and Hemorrhage Rates After Large Vessel Occlusion Stroke Treated With Tenecteplase Before Thrombectomy

Gaspard Gerschenfeld, Didier Smadja, Guillaume Turc, Stephane Olindo, François-Xavier Laborne, Marion Yger, Jildaz Caroff, Bruno Gonçalves, Pierre Seners, Marie Cantier, et al.

Intravenous Thrombolysis with Tenecteplase Before Thrombectomy for Acute Ischemic Stroke

Gaspard Gerschenfeld, Didier Smadja, Guillaume Turc, Stephane Olindo, François-Xavier Laborne, Marion Yger, Jildaz Caroff, Bruno Gonçalves, Pierre Seners, Marie Cantier, et al.

Functional Outcome, Recanalization, and Hemorrhage Rates After Large Vessel Occlusion Stroke Treated With Tenecteplase Before Thrombectomy

Author(s):

Gaspard Gerschenfeld, MD, PhD[1,2]; Didier Smadja, MD[3]; Guillaume Turc, MD, PhD[4]; Stephane Olindo, MD[5]; François-Xavier Laborne, MD[6]; Marion Yger, MD[1]; Jildaz Caroff, MD, PhD[7]; Bruno Gonçalves, MD[4]; Pierre Seners, MD, PhD[4]; Marie Cantier, MD[1]; Yann L'Hermitte, MD[3]; Manvel Aghasaryan, MD[3]; Cosmin Alecu, MD, PhD[3]; Gaultier Marnat, MD[8]; Wagih Ben Hassen, MD[9]; Erwah Kalsoum, MD[10]; Frédéric Clarençon, MD, PhD[11]; Michel Piotin, MD, PhD[12]; Laurent Spelle, MD, PhD[7]; Christian Denier, MD, PhD[13]; Igor Sibon, MD, PhD[5]; Sonia Alamowitch, MD[1, 14]; Nicolas Chausson, MD, PhD[3] on behalf of the TETRIS study group

Equal Author Contributions:

Dr Gerschenfeld and Dr Smadja contributed equally as co-first authors. Dr Chausson and Dr Alamowitch contributed equally as co-senior authors.

Corresponding Author:

Nicolas Chausson

nicolas.chausson@chsf.fr

Affiliation Information for All Authors: 1. Service de Neurologie et Urgences Neuro-vasculaires, Hôpital Saint-Antoine, AP-HP, Paris, France; 2. Faculté de Médecine, Sorbonne Université, Paris, France; 3. Service de Neurologie, Unité Neuro-vasculaire, Hôpital Sud Francilien, Corbeil-Essonnes, France; 4. Service de Neurologie, GHU Paris Psychiatrie et Neurosciences, Université de Paris, INSERM U1266, FHU Neurovasc, Paris, France; 5. Service de Neurologie, Unité Neuro-vasculaire, CHU de Bordeaux, Bordeaux, France; 6. Unité de Recherche Clinique, Hôpital Sud Francilien, Corbeil-Essonnes, France; 7. Service de Neuroradiologie interventionnelle (NEURI), Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France; 8. Service de Neuroradiologie diagnostique et interventionnelle, CHU de Bordeaux, Bordeaux, France; 9. Service de Neuroradiologie, GHU Paris Psychiatrie et Neurosciences, Université de Paris, INSERM U1266, FHU Neurovasc, Paris, France; 10. Service de Neuroradiologie, Hôpital Henri-Mondor, AP-HP, Créteil, France; 11. Service de Neuroradiologie, Hôpital Pitié-Salpêtrière, AP-HP, Paris, France; 12. Service de Neuroradiologie interventionnelle, Hôpital Fondation Rothschild, Paris, France; 13. Service de Neurologie, Hôpital Bicêtre, AP-HP, Le Kremlin-Bicêtre, France; 14. CRSA, Sorbonne Université, INSERM, UMRS 938, Hôpital Saint-Antoine, Paris, France.

Contributions:

Gaspard Gerschenfeld: 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

Didier Smadja: 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

Guillaume Turc: 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

Stephane Olindo: 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

François-Xavier Laborne: Drafting/revision of the manuscript for content, including medical writing for content; Analysis or interpretation of data

Marion Yger: 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

Jildaz Caroff: Major role in the acquisition of data

Bruno Gonçalves: Major role in the acquisition of data

Pierre Seners: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Marie Cantier: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Yann L'Hermitte: Major role in the acquisition of data

Manvel Aghasaryan: Major role in the acquisition of data

Cosmin Alecu: Major role in the acquisition of data

Gaultier Marnat: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Wagih Ben Hassen: Major role in the acquisition of data

Erwah Kalsoum: Major role in the acquisition of data

Frédéric Clarençon: Drafting/revision of the manuscript for content, including medical writing for content; Major role in the acquisition of data

Michel Piotin: Drafting/revision of the manuscript for content, including medical writing for content

Laurent Spelle: Drafting/revision of the manuscript for content, including medical writing for content

Christian Denier: Drafting/revision of the manuscript for content, including medical writing for content

Igor Sibon: Drafting/revision of the manuscript for content, including medical writing for content

Sonia Alamowitch: Drafting/revision of the manuscript for content, including medical writing for content; Study concept or design; Analysis or interpretation of data

Nicolas Chausson: 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

Number of characters in title: 88

Abstract Word count: 283

Word count of main text: 3417

References: 50

Figures: 4

Tables: 3

Supplemental: STROBE checklist Appendix 1. List of authors Appendix 2. List of TETRIS co-investigators Figures 1 to 4 in vector format Revised manuscript with tracked changes

Statistical Analysis performed by: François-Xavier Laborne, Centre Hospitalier Sud-Francilien, Unité de Recherche Clinique, MD

Search Terms: [2] All Cerebrovascular disease/Stroke, [6] Infarction, [324] Class IV

Study Funding: The authors report no targeted funding

Disclosures: G. Gerschenfeld reports no disclosures relevant to the manuscript; D. Smadja received a grant and personal fees (consultancy and lectures) from Boehringer Ingelheim and Bristol Myers Squibb, outside the submitted work; G. Turc reports no disclosures relevant to the manuscript. S. Olindo reports no disclosures relevant to the manuscript; F.-X.Laborne received personal fees (lectures) from Boehringer Ingelheim, outside the submitted work; M. Yger received reimbursement for conference registration fees from Pfizer and Boehringer Ingelheim, outside the submitted work; J. Caroff reports no disclosures relevant to the manuscript; B. Gonçalves reports no disclosures relevant to the manuscript; P. Seners reports no disclosures relevant to the manuscript; M. Cantier reports no disclosures relevant to the manuscript; Y. LHermitte reports no disclosures relevant to the manuscript; M. Aghasaryan reports no disclosures relevant to the manuscript; C. Alecu reports no disclosures relevant to the manuscript; G. Marnat reports no disclosures relevant to the manuscript; W. Ben Hassen reports no disclosures relevant to the manuscript; E. Kalsoum reports no disclosures relevant to the manuscript; F. Clarençon received personal fees from Medtronic (lectures), Guerbet (lectures), Balt Extrusion (lectures), Penumbra (lectures), Codman Neurovascular and Microvention (Core lab) outside the submitted work; M. Piotin reports no disclosures relevant to the manuscript; -L. Spelle reports no disclosures relevant to the manuscript; C. Denier reports no disclosures relevant to the manuscript; I. Sibon reports no disclosures relevant to the manuscript; S. Alamowitch received personal fees from the Revue Neurologique (editorial board), AstraZeneca (consultancy and lectures), Bayer (lectures) and BMS-Pfizer (lectures), outside the submitted work; N. Chausson received a grant and personal fees (consultancy and lectures) from Boehringer Ingelheim and Bristol Myers Squibb, outside the submitted work.

Abstract

Objective To investigate in routine care the efficacy and safety of IV thrombolysis (IVT) with tenecteplase prior to mechanical thrombectomy (MT) in patients with large vessel occlusion acute ischemic strokes (LVO-AIS), either secondarily transferred after IVT or directly admitted to a comprehensive stroke center (CSC).

Methods We retrospectively analyzed clinical and procedural data of patients treated with 0.25 mg/kg tenecteplase within 270 minutes of LVO-AIS who underwent a brain angiography. The main outcome was 3-month functional independence (modified Rankin scale score ≤ 2). Recanalization (revised Treatment in Cerebral Ischemia score 2b-3), was evaluated before (pre-MT) and after MT (final).

Results We included 588 patients (median age 75 years [interquartile range (IQR) 61-84]; 315 women [54%]; median NIH Stroke Scale [NIHSS] score 16 [IQR 10-20]), of which 520 (88%) were secondarily transferred after IVT. Functional independence occurred in 47% (n = 269/570; 95%CI 43.0-51.4) of patients. Pre-MT recanalization occurred in 120 patients (20.4%; 95%CI 17.2-23.9), at a similar rate across treatment paradigms (direct admission, n = 14/68 [20.6%]; secondary transfer, n = 106/520 [20.4%]; $p > .99$) despite a shorter median IVT-to-puncture time in directly admitted patients (38 [IQR 23-55] vs 86 [IQR 70-110] minutes; $p < .001$). Final recanalization was achieved in 492 patients (83.7%; 95%CI 80.4-86.6). Symptomatic intracerebral hemorrhage occurred in 2.5% of patients (n = 14/567; 95%CI 1.4-4.1).

Conclusions Tenecteplase before MT is safe, effective and achieves a fast recanalization in everyday practice in patients secondarily transferred or directly admitted to a CSC, in line with published results. These findings should encourage its wider use in bridging therapy.

Classification of Evidence This study provides class IV evidence that tenecteplase within 270 minutes of LVO-AIS is increases the probability of functional independence.

Introduction

Management of acute ischemic stroke with large vessel occlusion (LVO-AIS) currently consists of intravenous thrombolysis (IVT), generally with alteplase administered as a 10% bolus followed by a one-hour infusion, combined with mechanical thrombectomy (MT).[1–7] The rationale for IVT in patients with LVO-AIS is to achieve timely recanalization, if possible prior to MT (pre-MT). This applies to patients directly admitted in a comprehensive stroke center (CSC; "direct admission") and those admitted in a primary stroke center (PSC) before being transferred to a CSC to receive MT ("secondary transfer"). Although pre-MT recanalization rates can reach 20%,[8] alteplase often yields lower rates, especially in patients directly admitted in a CSC with much shorter IVT-to-puncture times.[9–14]

Tenecteplase is a genetically modified more fibrin-specific variant of alteplase with a longer half-life, allowing a single bolus administration.[15] Recently, the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial demonstrated that 0.25 mg/kg (maximum 25 mg) tenecteplase led to a higher incidence of pre-MT recanalization and better functional outcome than alteplase.[16] Following these results, tenecteplase was added in stroke guidelines as an alternative to alteplase for IVT in bridging therapy,[17,18] and some stroke units have started using it routinely instead of alteplase.[19] However, there is little real-life data available on its use in bridging therapy. Our aim was to assess the neurological and safety outcomes and the pre-MT recanalization rate of patients admitted for a LVO-AIS who underwent bridging therapy with 0.25 mg/kg tenecteplase, either directly admitted or secondarily transferred to a CSC.

Methods

The primary research question is to evaluate the 3-month functional independence rate of patients treated with tenecteplase within 270 minutes of LVO-AIS (Class IV evidence).

Study population

The TEnecteplase TReatment in Ischemic Stroke (TETRIS) database is a multicenter retrospective registry based on the prospective AIS registries of 4 French stroke centers which opted for tenecteplase instead of alteplase for bridging therapy: two PSC, the Sud Francilien (SFH) and Saint Antoine (SAH) hospitals, and two CSC, the Bordeaux University Hospital (BUH) and GHU Paris Psychiatrie et Neurosciences (GHU). In each center, patients were included once the transition to tenecteplase occurred: the SFH started on May 1st 2015 to use it off-label based on two published clinical trials;[20,21] the other centers transitioned after the publication of EXTEND-IA TNK[16] on May 28th 2018 (SAH), July 15th 2018 (GHU) and April 16th 2019 (BUH). Inclusion ended in all center on December 31st 2019. Tenecteplase was standard of care in each center during the study period. Patients who fulfilled the following criteria were included: (i) 18 years or older, (ii) evidence of LVO-AIS, (iii) IVT with 0.25 mg/kg tenecteplase (maximum 25 mg) within 4h30 of symptoms onset, or in the presence of a magnetic resonance imaging (MRI) mismatch between diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) in case of unknown onset,[22] and (iv) a brain digital subtraction angiography (DSA) followed or not by MT. LVO was defined as an occlusion of either the intracranial internal carotid artery (ICA), the first or second segment of the middle cerebral artery (MCA), or the basilar artery. Patients admitted in SFH and SAH were secondarily transferred after IVT to the nearest CSC: Bicêtre, Rothschild Foundation and Henri-Mondor hospitals for SFH; Pitié-Salpêtrière hospital for SAH.

Data collection

The following data were extracted from the registry, reviewing medical records when data were missing or insufficiently detailed: age, sex, vascular risk factors (smoking, hypertension, diabetes mellitus, dyslipidemia, history of myocardial infarction and stroke), prestroke medication (statin, antiplatelet and anticoagulant), stroke onset (time, if known, or unknown), neurological severity measured with the National Institutes of Health Stroke Scale (NIHSS), time points (IVT, groin puncture and recanalization),[23] final determined cause of stroke at the 3-month consultation according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification (large-artery atherosclerosis, cardioembolism, small vessel occlusion, undetermined, or other cause).[23] Neurological outcome was assessed with the 24-hour NIHSS and 3-month modified Rankin Scale (mRS) scores. Three-month mRS scores were collected by neurologists during post-stroke consultations or phone interviews. Assessors for the clinical outcome data were unblinded to the pathway of care.

The main outcome was functional independence (mRS $\leq$ 2) 3 months after stroke. Secondary outcomes were substantial recanalization (revised Treatment in Cerebral Ischemia [rTICI] score 2b-3) before ("pre-MT") and after MT ("post-MT"),[24] and early neurological improvement (ENI) defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 after 24 hours. Safety outcomes were symptomatic intracranial hemorrhage (sICH) and major systemic bleeding (hemoglobin decline of at least 2 g/dl). We used the Safe Implementation of Thrombolysis in Stroke-Monitoring (SITS-MOST) study definition of sICH (local or remote type 2 parenchymal hemorrhage associated with an increase of at least 4 points in the NIHSS score within 36 hours of IVT).[25]

Brain imaging analysis

Patients underwent either brain MRI or computed tomography angiography (CTA) on admission and 24 hours after IVT. All imaging data were assessed retrospectively by experienced stroke neurologists (GG, DS, SO, MY, YH, MA, CA, NC). The following variables were collected from the first brain imaging: occlusion site on time-of-flight

magnetic resonance angiography (MRA) or CTA, presence and length of thrombus susceptibility vessel sign (SVS) on gradient echo-sequences for intracranial occlusions and diffusion-weighted imaging Alberta Stroke Program Early Computed Tomography Score (DWI-ASPECTS) for patients with an anterior circulation occlusion.[26] Occlusion sites were categorized as extracranial ICA (in the presence of an intracranial occlusion), intracranial ICA, M1 MCA, M2 MCA and basilar artery. The 24-hour brain imaging (MRI in BUH, SFH and GHU; CT in SAH), was used to assess ICH transformation according to the European Cooperative Acute Stroke Study (ECASS) radiological classification.[27] The use of brain MRI or CT was considered to be comparable as they have similar sensitivities to detect post-IVT type 2 parenchymal hemorrhages (PH).[28] When available, 24-hour recanalization was also retrieved. Brain DSAs were reevaluated for the initial and final rTICI score by a trained neuroradiologist or neurologist for SFH (JC, PS, EK or MP), SAH (FC) and BOR (GM) patients. In GHU, they were assessed by two trained neurologists (PS, GT) and discrepancies were resolved by consensus. Assessors for the radiological outcome data were unblinded to the pathway of care.[19]

Statistical analysis

Quantitative variables were described as median [interquartile ranges (IQR)] and qualitative parameters as counts and percentages. Categorical variables were compared with Chi-square or Fisher's exact test and continuous variables with Wilcoxon's row sum or Kruskal-Wallis test, as appropriate. To identify associations between baseline characteristics and the main outcome (3-month mRS ≤ 2), we used a univariable and multivariable logistic regression analysis across the whole cohort. All continuous variables were checked for log linearity. Non-log-linear variables were discretized according to their inflexion points or based on the literature. Non-collinear variables that yielded P values smaller than .25 in univariable analysis were included in the multivariable model, and no variable exclusion was performed afterwards. Under the hypothesis of randomly missing data, multiple imputations

were used to replace missing values when appropriate, using the Multivariate Imputation by Chained Equations (MICE) algorithm. Sixteen copies of the dataset were created with the missing values replaced by imputed values, based on observed data including outcomes and baseline characteristics of participants. The results of the analysis of each dataset were aggregated into a final result using Rubin's rules. The Hosmer-Lemeshow goodness-of-fit test and area under the receiver operating characteristic (ROC) curve were computed for the final model. Associations between variables and the main outcome are reported as odds ratios (ORs) with their 95% confidence intervals (CIs). The direct admission and secondary transfer subgroup analysis was carried out as a secondary analysis. All tests were two-sided and P values < .05 were considered significant. Analyses were performed using R statistical software version 4.0.5.

Standard Protocol Approvals, Registrations, and Patient Consents

As per current French law regarding retrospective studies of anonymized standard care data, patients were informed of their participation in this research and offered the possibility to withdraw. No written consent to participate in this research and no Internal Review Board approval were required.

Data Availability Statement

The anonymized data supporting these analyses is available from the corresponding author upon reasonable request.

Results

Patient characteristics

Over the study period, 2625 patients were hospitalized in the participating centers for an AIS eligible for reperfusion therapy (Figure 1): 217 were treated with MT alone because of contraindications to IVT, 1748 were treated with IVT alone and 660 were treated with IVT followed by MT. Of these 660 patients, 72 were excluded: 32 received 0.9 mg/kg alteplase; 2 were treated with 0.5 mg/kg tenecteplase; 27 received IVT after 270 minutes; 9 had only a P1 posterior cerebral artery occlusion; 2 had a cervical-only carotid artery occlusion. The resulting 588 patients were therefore included in the main analysis. Most of them (471 [80.1%]) were included at the SFH. Median age was 75 years (IQR, 61-84 years) and 315 (53.6%) patients were women (Table 1). The leading documented cause of stroke was cardioembolism (n=321 [54.6%]), followed by large-artery atherosclerosis (n=69 [11.7%]). Twenty-five (4.3%) patients had a cervical artery dissection. No stroke etiology was identified in 153 (26.0%) patients.

Stroke characteristics

A total of 528 (89.8%) patients underwent brain MRI as first-line imaging. Median baseline NIHSS score and DWI-ASPECTS were 16 (IQR, 10-20) and 7 (IQR, 6-8), respectively. The most frequent occlusion sites were M1 MCA (n=364 [61.9%]), ICA (n=128 [21.8%]) and M2 MCA (n=73 [12.4%]). Fifty-nine (10.1%) patients also had an extracranial (tandem) ICA occlusion. Basilar artery occlusions accounted for 23 (3.9%) patients. All patients underwent DSA. Median process times (IQR) in minutes were the following: onset-to-IVT 148 (121-180), IVT-to-puncture 82 (65-106) and onset-to-recanalization 290 (249-340; for those who still required MT after IVT). MT was started (groin puncture) after 360 minutes in 21 patients (3.6%).

Main and secondary outcomes

Three-month mRS scores were available for 570 (96.9%) patients, of whom 269 (47.2%; 95% CI 43.0-51.4) achieved functional independence (Table 2 and Figure 2). The association between collected variables and the main outcome was first assessed in a univariable analysis, followed by a multivariable analysis with replacement of missing data (Table 3). The variables independently associated with the main outcome were: age (odds ratio [OR] 0.95; 95%CI 0.94-0.97), baseline NIHSS score (OR 0.86; 95%CI 0.83-0.9), onset-to-IVT time ≥ 160 minutes (OR 0.58 ; 95%CI 0.35-0.95), unknown stroke onset (OR 0.53 ; 95%CI 0.29-0.95) and no recanalization (OR 0.42; 95%CI 0.21-0.82). In a sensitivity analysis, unknown onset was independently associated with a poor outcome (OR 0.48; 0.3-0.77; $P < .01$).

A total of 492 patients (83.7%; 80.4-86.6) had a substantial recanalization, and in 120 patients (20.4%; 17.2-23.9) it was identified on the first angiographic run (Table 2). Among them, 44 patients (36.7%) with a 2B and 4 patients (3.3%) with a 2C rTICI score still underwent MT, resulting in a near-complete recanalization (rTICI 2C-3) for 32 (66.7%) of them. Thrombectomy procedures in those patients did not differ with those of patients without pre-MT recanalization in terms of median procedure times (47 min [IQR 30-73] *vs* 50 min [30-79]; $P = .67$) and of median number of passages (2 [1-2] versus 1 [1-3]; $P = .14$). The pre-MT recanalization rate followed a proximo-distal gradient at 4.7% (n=6/128), 22.5% (n=82/364) and 32.9% (n=24/73) for ICA, M1 and M2 MCA, respectively. The global pre-MT recanalization rate did not increase with the IVT-to-puncture time, remaining stable around 20% (Figures 3 and 4A), with a similar trend for M1 and M2 occlusions (data not shown). Twenty-four hour-NIHSS score was available for 561 (95.4%) patients, with a median of 8 (IQR, 3-17). ENI occurred in 40.8% (n=232/568; 36.8-45.0) of patients (Table 2). On follow-up brain imaging, 43 (7.5%), 25 (4.4%) and 4 (0.7%) patients had a type-1, type-2 and remote PH, respectively (Table 2). Fourteen (2.5%; 1.4-4.1) patients had sICH.

Four (0.7%) patients had a major systemic bleeding: gastro-intestinal (n=2), hematuria (n=1) and groin puncture hematoma (n=1); none of which was fatal.

Subgroup analysis

We performed a subgroup analysis comparing patients secondarily transferred (n=520 [88.4%]) and directly admitted (n=68 [11.6%]) to a CSC (Tables 1 and 2). Directly admitted and secondarily transferred patient baseline characteristics were similar in both groups. Median process times were significantly longer in the secondary transfer group: onset-to-IVT time of 150 minutes (IQR, 124-180) vs 130 minutes (IQR, 106-153; $P < .01$), IVT-to-puncture time of 86 minutes (IQR, 70-110) vs 38 minutes (IQR, 23-55; $P < .001$), and onset-to-recanalization time of 300 minutes (IQR, 260-347) vs 210 minutes (IQR, 169-255; $P < .001$). Both groups had similar pre-MT recanalization (n=106 [20.4%] in the secondary transfer group and n=14 [20.6%] in the direct admission group; $P > .99$) and post-MT recanalization rates (n=432 [83.1%] in the secondary transfer group and n=60 [88.2%] in the direct admission group; $P = .38$). The proportion of patients who achieved functional independence was significantly higher in the direct admission group at 61.8% (n=42) versus 45.2% (n=227) in the secondary transfer group ($P = .01$). Rates of sICH were 2.4% (n=12/500) in the secondary transfer group and 3.0% (n=2/67) in the direct admission group ($P = .68$).

Discussion

In this study, we assessed in 'real-life' the use of 0.25 mg/kg tenecteplase for IVT before MT in a large population of LVO-AIS patients. The proportion of patients who achieved functional independence was 47.2% (43.0-51.5). We found that patients treated with tenecteplase had a pre-MT recanalization rate of 20.4% (17.2-23.9), even with short IVT-to-puncture times. Finally, with a sICH rate of 2.5% (1.4-4.1), there was no significant safety concern.

Pre-MT recanalization is the main expected benefit of IVT prior to MT, as it has been shown that shorter onset-to-reperfusion times are associated with lower degrees of 3-month disability.[29] Even when incomplete, pre-MT recanalization has been reported to be associated with a better functional outcome.[30,31] Although the pre-MT recanalization rate can reach up to 20% with alteplase, it is lower when the IVT-to-puncture time is shorter and in more proximal occlusions.[14,16,32] In our study, we found an average pre-MT recanalization rate of 20.5% (17.3-24.0), ranging from 5.4% for ICA to 29.8% for M2 MCA occlusions, similar to published data from the pooled analysis of the EXTEND-IA TNK trials (20.3%; 15.5-25.8).[16,33] Strikingly, the pre-MT recanalization rate remained stable for IVT-to-puncture times under one hour (Figure 2), indirectly supporting a faster recanalization compared to alteplase, which has been reported to be under 10% for similar times (Figure 3).[11,12,14,16,32] The faster recanalization with tenecteplase, which has been demonstrated in patients with myocardial infarction,[34] may be explained by its pharmacokinetic properties which allow a bolus administration of its full dose,[15,35] unlike alteplase which requires after its bolus a one-hour infusion. Moreover, it has been shown that a bolus to infusion delay or an infusion interruption may significantly impact its efficacy.[36] This finding may be of importance in the ongoing debate regarding relevance of IVT for LVO-AIS patients. Indeed, trials are comparing bridging therapy with alteplase and MT alone in patients directly admitted to a

CSC, and are therefore likely to minimize the benefit of IVT because of their short IVT-to-puncture times. For instance, in the DIRECT-MT and DEVT trials which found MT alone to be non-inferior to bridging therapy with alteplase, pre-MT recanalization occurred respectively at a 7% and 2.5% rate with IVT with a median IVT-to-puncture time around 30 minutes, and a 2.4% and 1.7% rate without it.[11,12] This significant efficacy gap between alteplase and tenecteplase in short IVT-to-puncture times warrants clinical trials comparing bridging therapy with tenecteplase and MT alone.

Our patients achieved a 3-month functional independence rate of 47.2% (43.0-51.4), similar to the reported rate in the HERMES meta-analysis of five trials with alteplase (46.0%; 42.0-49.9),[2] which is also in line with recently published meta-analyses of the five randomized clinical trials that have compared tenecteplase and alteplase in AIS.[16,20,21,37,38] Indeed, they reported no statistically significant difference in terms of 3-month neurological outcome.[39–42] However, our 3-month functional independence rate was lower than the one reported in the pooled analysis of the EXTEND-IA TNK trials (57.8%; 51.4-64.0; Figure 1).[16,33] This difference likely results from our 'real-life' setting, as it has been shown that in such studies patients tend to be outside of randomized clinical trials core inclusion criteria, with older ages and larger infarct cores, leading to worse clinical outcomes.[43] Indeed, our patients were older with a median age of 75 years compared to 68 in HERMES and an average age of 72 in the pooled EXTEND-IA TNK trials. Furthermore, 40.3% of our patients were at least 80 years old. They also had larger ischemic cores with a median DWI-ASPECTS of 7 (IQR, 6-8) compared to a median CT-ASPECTS of 9 (IQR, 7-10) in HERMES and an estimated median DWI-ASPECTS of 8 in EXTEND IA TNK.[44] Additionally, our cohort differed from the EXTEND-IA TNK trials in two significant ways. First, most of our patients were secondarily transferred (88.5% vs 30.7%), which resulted in a longer median onset-to-puncture time (237 versus 168 minutes). Second, contrary to the EXTEND IA TNK trials, 127 patients (21.7%) had a stroke with unknown onset, which was

independently associated with a poor outcome in our cohort. Indeed, while the benefit of IVT with alteplase and MT in strokes of unknown onset based on imaging selection has been clearly demonstrated when compared with standard care,[45,46] whether these patients have a similar outcome compared to those with a known onset is less clear.[47,48] Moreover, while several meta-analyses have reported an improved ENI rate with tenecteplase, our patients had a rate of 40.8% (36.8-45.0), lower than in HERMES (50.2%; 46.1-54.2) and the EXTEND-IA TNK trials (65.7%; 59.5-71.6). This result is likely due to the higher age, larger ischemic cores and longer treatment times in our cohort. Interestingly, in our direct admission subgroup we observed a 3-month functional independence rate of 61.8% (Table 2) similar to the pooled EXTEND-IA TNK trials (57.8%) and a higher ENI rate of 50.7%. Overall, these results are encouraging regarding the efficacy of tenecteplase in routine clinical care.

Finally, our study did not disclose any safety concern with tenecteplase, with a sICH rate of 2.5% (1.4-4.1) similar to those reported in the pooled EXTEND-IA TNK trials (1.2%; 0.2-3.5) and HERMES (4.4%; 3.0-6.3),[2,16,33] despite our population being older, with longer process times and larger ischemic cores. These results are consistent with several meta-analyses that did not find an increased risk with 0.25 mg/kg tenecteplase.[39–42] Parenchymal hematomas were more frequent in our study (11.2%) than in the pooled EXTEND-IA TNK trials (4.8%). While it cannot be excluded that MRI may overestimate type 1 PHs, these results are similar to previously published 'real-life' studies with alteplase.[32,49] In everyday practice, incorrect alteplase dosage occurs frequently given that it is often based on an estimated weight.[50] In our study, two patients who were excluded from the analysis were given an inappropriate dose of 0.50 mg/kg due to the graduated syringe for cardiological use, and none had any complication. Moreover, the EXTEND-IA TNK Part 2 trial did not show safety concern with a higher dose of 0.40 mg/kg tenecteplase, providing reassurance that there may be a window of safety if weight is inadvertently overestimated.[33]

Strengths and Limitations

Our study has several strengths. It is a multi-centric study of both PSC and CSC from metropolitan and rural areas with a significant number of consecutive patients. There were few missing data (≤ 5%) for baseline NIHSS score evaluation, recanalization status, 24-hour NIHSS and 3-month mRS scores, making major biases on efficacy and safety interpretation unlikely. All initial and follow-up brain images were reviewed by a trained neurologist and subsequently compared with their initial reports.

Our study also has limitations. Its design was retrospective and without a control group of patients treated with alteplase. While four stroke centers contributed to the registry, 80% of the inclusions were from one center (SFH) and patients secondarily transferred to a CSC represented 88% of the population, limiting the generalizability of our study. Therefore, the interpretation of our data deserves particular caution and further replication in a wider range of centers is needed. Finally, assessors for the clinical and radiological outcome data were unblinded to the pathway of care, which represents a potential bias.

Conclusions

Our study shows the feasibility, efficacy and safety of using 0.25 mg/kg tenecteplase before MT in a large population of LVO-AIS patients either directly admitted or secondarily transferred to a CSC. Our ability to replicate a fast pre-MT recanalization and functional independence rates similar to those published in clinical trials supports the use of tenecteplase in bridging therapy for all eligible patients.

Acknowledgments

Dr. Gerschenfeld and Prof. Smadja contributed equally as co-first authors. Prof. Alamowitch and Dr. Chausson contributed equally as co-last authors.

Sources of Funding

None.

Conflict-of-Interest/Disclosures

Prof. Smadja and Dr. Chausson reported receiving a grant and personal fees (consultancy and lectures) from Boehringer Ingelheim and Bristol Myers Squibb, outside the submitted work. Dr. Laborne reported receiving personal fees (lectures) from Boehringer Ingelheim, outside the submitted work. Dr. Yger reported reimbursement for conference registration fees from Pfizer and Boehringer Ingelheim, outside the submitted work. Prof. Alamowitch reported receiving personal fees from the Revue Neurologique (editorial board), AstraZeneca (consultancy and lectures), Bayer (lectures) and BMS-Pfizer (lectures), outside the submitted work. Prof. Clarençon reported receiving personal fees from Medtronic (lectures), Guerbet (lectures), Balt Extrusion (lectures) and Penumbra (lectures), outside the submitted work; and a conflict of interest with Codman Neurovascular and Microvention (core lab; outside the submitted work). No other disclosures were reported.

References

1. Berkhemer OA, Fransen PSS, Beumer D, et al. A Randomized Trial of Intraarterial Treatment for Acute Ischemic Stroke. New Engl J Medicine. 2015;372:11–20.

2. Goyal M, Menon BK, Zwam WH van, et al. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. Lancet. 2016;387:1723–1731.

3. Goyal M, Demchuk AM, Menon BK, et al. Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke. New Engl J Medicine. 2015;372:1019–1030.

4. Saver JL, Goyal M, Bonafe A, et al. Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke. New Engl J Medicine. 2015;372:2285–2295.

5. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 Hours after Symptom Onset in Ischemic Stroke. New Engl J Medicine. 2015;372:2296–2306.

6. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurology. 2016;15:1138–1147.

7. Campbell BCV, Mitchell PJ, Kleinig TJ, et al. Endovascular Therapy for Ischemic Stroke with Perfusion-Imaging Selection. New Engl J Medicine. 2015;372:1009–1018.

8. Seners P, Turc G, Maïer B, Mas J-L, Oppenheim C, Baron J-C. Incidence and Predictors of Early Recanalization After Intravenous Thrombolysis. Stroke. 2016;47:2409–2412.

9. Fjetland L, Kurz KD, Roy S, Kurz MW. Evaluation of the recombinant tissue plasminogen activator pretreatment in acute stroke patients with large vessel occlusions treated with the direct bridging approach. Is it worth the effort? Eur J Neurol. 2015;22:322–327.

10. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke. New Engl J Medicine. 2013;368:893–903.

11. Yang P, Zhang Y, Zhang L, et al. Endovascular Thrombectomy with or without Intravenous Alteplase in Acute Stroke. New Engl J Med. 2020;382:1981–1993.

12. Zi W, Qiu Z, Li F, et al. Effect of Endovascular Treatment Alone vs Intravenous Alteplase Plus Endovascular Treatment on Functional Independence in Patients With Acute Ischemic Stroke. Jama. 2021;325:234–243.

13. Suzuki K, Matsumaru Y, Takeuchi M, et al. Effect of Mechanical Thrombectomy Without vs With Intravenous Thrombolysis on Functional Outcome Among Patients With Acute Ischemic Stroke. Jama. 2021;325:244–253.

14. Seners P, Turc G, Naggara O, et al. Post-Thrombolysis Recanalization in Stroke Referrals for Thrombectomy. Stroke. 2018;49:2975–2982.

15. Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and Pharmacodynamics of Tenecteplase in Fibrinolytic Therapy of Acute Myocardial Infarction. Clin Pharmacokinet. 2002;41:1229–1245.

16. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke. New Engl J Medicine. 2018;378:1573–1582.

17. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50:e344–e418.

18. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. European Stroke J. Epub 2021.:239698732198986.

19. Seners P, Caroff J, Chausson N, et al. Recanalization before Thrombectomy in Tenecteplase vs. Alteplase-Treated Drip-and-Ship Patients. J Stroke. 2019;21:105–107.

20. Parsons M, Spratt N, Bivard A, et al. A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke. New Engl J Medicine. 2012;366:1099–1107.

21. Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurology. 2015;14:368–376.

22. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset. New Engl J Med. 2018;379:611–622.

23. Jr HPA, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41.

24. Goyal M, Fargen KM, Turk AS, et al. 2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials. J Neurointerv Surg. 2014;6:83.

25. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275–282.

26. Barber PA, Hill MD, Eliasziw M, et al. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. J Neurology Neurosurg Psychiatry. 2005;76:1528.

27. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke. New Engl J Medicine. 2008;359:1317–1329.

28. Arnould M-C, Grandin CB, Peeters A, Cosnard G, Duprez TP. Comparison of CT and three MR sequences for detecting and categorizing early (48 hours) hemorrhagic transformation in hyperacute ischemic stroke. Ajnr Am J Neuroradiol. 2004;25:939–944.

29. Saver JL, Goyal M, Lugt A van der, et al. Time to Treatment With Endovascular Thrombectomy and Outcomes From Ischemic Stroke: A Meta-analysis. Jama. 2016;316:1279–1288.

30. Alves HC, Treurniet KM, Jansen IGH, et al. Thrombus Migration Paradox in Patients With Acute Ischemic Stroke. Stroke. 2019;50:3156–3163.

31. Flint AC, Avins AL, Eaton A, et al. Risk of Distal Embolization From tPA (Tissue-Type Plasminogen Activator) Administration Prior to Endovascular Stroke Treatment. Stroke. 2020;51:2697–2704.

32. Gerschenfeld G, Muresan I-P, Blanc R, et al. Two Paradigms for Endovascular Thrombectomy After Intravenous Thrombolysis for Acute Ischemic Stroke. Jama Neurol. 2017;74:549.

33. Campbell BCV, Mitchell PJ, Churilov L, et al. Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke. Jama. 2020;323:1257–1265.

34. Binbrek AS, Rao NS, Neimane D, Hatou E, Abdulali S, Sobel BE. Comparison of rapidity of coronary recanalization in men with tenecteplase versus alteplase in acute myocardial infarction. Am J Cardiol. 2004;93:1465–1468.

35. Benedict CR, Refino CJ, Keyt BA, et al. New Variant of Human Tissue Plasminogen Activator (TPA) With Enhanced Efficacy and Lower Incidence of Bleeding Compared With Recombinant Human TPA. Circulation. 1995;92:3032–3040.

36. Smith C, Al‐Nuaimi Y, Wainwright J, et al. The influence of bolus to infusion delays on plasma Tissue Plasminogen Activator levels. Int J Stroke. 2014;9:939–942.

37. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurology. 2017;16:781–788.

38. Jr ECH, Thompson JLP, Grotta JC, et al. Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke. Stroke. 2010;41:707–711.

39. Kheiri B, Osman M, Abdalla A, et al. Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. J Thromb Thrombolys. 2018;46:440–450.

40. Burgos AM, Saver JL. Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke. Stroke. 2019;50:2156–2162.

41. Huang X, MacIsaac R, Thompson JL, et al. Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials. Int J Stroke. 2016;11:534–543.

42. Thelengana A, Radhakrishnan DM, Prasad M, Kumar A, Prasad K. Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. Acta Neurol Belg. 2019;119:359–367.

43. Deb-Chatterji M, Pinnschmidt H, Flottmann F, et al. Stroke patients treated by thrombectomy in real life differ from cohorts of the clinical trials: a prospective observational study. Bmc Neurol. 2020;20:81.

44. Siegler JE, Messé SR, Sucharew H, et al. Noncontrast CT versus Perfusion - Based Core Estimation in Large Vessel Occlusion: The Blood Pressure after Endovascular Stroke Therapy Study. J Neuroimaging. 2020;30:219–226.

45. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for Stroke at 6 to 16 Hours with Selection by Perfusion Imaging. New Engl J Medicine. 2018;378:708–718.

46. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 Hours after Stroke with a Mismatch between Deficit and Infarct. New Engl J Medicine. 2017;378:11–21.

47. Jadhav AP, Aghaebrahim A, Jankowitz BT, et al. Benefit of Endovascular Thrombectomy by Mode of Onset. Stroke. 2019;50:3141–3146.

48. Bücke P, Pérez MA, Hellstern V, AlMatter M, Bäzner H, Henkes H. Endovascular Thrombectomy in Wake-Up Stroke and Stroke with Unknown Symptom Onset. Am J Neuroradiol. 2018;39:494–499.

49. Weisenburger-Lile D, Blanc R, Kyheng M, et al. Direct Admission versus Secondary Transfer for Acute Stroke Patients Treated with Intravenous Thrombolysis and Thrombectomy: Insights from the Endovascular Treatment in Ischemic Stroke Registry. Cerebrovasc Dis. 2019;47:112–120.

50. Chung LS, Tkach A, Lingenfelter EM, et al. Tissue Plasminogen Activator Prescription and Administration Errors within a Regional Stroke System. J Stroke Cerebrovasc Dis. 2016;25:565–571.

Tables

Table 1. Baseline characteristics and process times.

Characteristic	TETRIS cohort			*P* Value
	All patients (n=588)	Secondary transfer (n=520)	Direct admission (n=68)	
Age, y	75 [61-84]	76 [61-84]	72 [62-83]	.48
Female sex	315/588 (53.6)	279/520 (53.7)	36/68 (52.9)	>.99
Vascular risk factors				
Hypertension	378/582 (64.9)	339/514 (66.0)	39/68 (57.4)	.18
Diabetes mellitus	104/583 (17.8)	96/515 (18.6)	8/68 (11.8)	.18
Smoking	119/553 (21.5)	106/485 (21.9)	13/68 (19.1)	.75
History of stroke	64/588 (10.9)	62/520 (11.9)	2/68 (2.9)	.02
History of myocardial infarction	67/588 (11.4)	60/520 (11.5)	7/68 (10.3)	>.99
Prestroke treatment				
Antiplatelet agent				.96
Monotherapy	152/574 (26.5)	135/506 (26.7)	17/68 (25.0)	
Bitherapy	12/574 (2.1)	11/506 (2.2)	1/68 (1.5)	
Anticoagulant	64/575 (11.1)	62/507 (12.2)	2/68 (2.9)	.02
Statin	171/581 (29.4)	160/513 (31.2)	11/68 (16.2)	.01
TOAST classification				.67
CE	321/588 (54.6)	288/520 (55.4)	33/68 (48.5)	
LAA	69/588 (11.7)	61/520 (11.7)	8/68 (11.8)	
ODE	45/588 (7.7)	39/520 (7.5)	6/68 (8.8)	
UDE	153/588 (26.0)	132/520 (25.4)	21/68 (30.9)	
Baseline NIHSS, n=586	16 [10-20]	16 [10-20]	15 [10-19]	.56
MRI imaging	528/588 (89.8)	465/520 (89.4)	63/68 (92.6)	.53
DWI-ASPECTS, n=504	7 [6-8]	7 [6-9]	7 [6-8]	.40
Intracranial occlusion				.06

ICA	128/588 (21.7)	118/520 (22.1)	13/68 (19.1)	
M1 MCA	364/588 (61.9)	323/520 (62.1)	41/68 (60.3)	
M2 MCA	73/588 (12.4)	59/520 (11.3)	14/68 (20.6)	
Basilar artery	23/588 (3.9)	23/520 (4.4)	0/68 (0.0)	
Extracranial ICA occlusion	59/585 (10.1)	47/517 (9.1)	12/68 (17.6)	.05
SVS	370/414 (89.4)	318/352 (90.3)	52/62 (83.9)	.18
SVS length, mm, n=353	10 [7.5-14.0]	10 [7.7-14.0]	11 [6.8-14.2]	.95
Known onset	461/588 (78.4)	414/520 (79.6)	47/68 (69.1)	.06
Process times, min				
Onset-to-IVT, n=461	148 [121-180]	150 [124-180]	130 [106-153]	<.01
IVT-to-puncture, n=582	82 [65-106]	86 [70-110]	38 [23-55]	<.001
Onset-to-recanalization, n=335*	290 [249-340]	300 [260-347]	210 [169-255]	<.001

Data is presented as No. (%) or median [IQR]. Percentages are expressed among the patients for which the data was available. * Patients with a Pre-MT recanalization who did not require MT (n=72) were excluded from the onset-to-recanalization time.

Abbreviations: CE, cardioembolism; DWI-ASPECTS, diffusion weighted imaging Alberta stroke program early computed tomography score; FLAIR, fluid attenuated inversion recovery; ICA, internal carotid artery; IQR, interquartile range; IVT, intravenous thrombolysis; LAA, large-artery atherosclerosis; MCA, middle cerebral artery; mRS, modified Rankin scale; NIHSS, National Institute of Health stroke score; ODE, other determined etiology; SVS, susceptibility vessel sign; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UDE, undetermined etiology.

Table 2. Clinical and safety outcomes.

Characteristic	TETRIS cohort			*P* Value
	All patients (n=588)	Secondary transfer (n=520)	Direct admission (n=68)	
Clinical outcomes				
Pre-MT recanalization	120/588 (20.4)	106/520 (20.4)	14/68 (20.6)	>.99
Post-MT recanalization	492/588 (83.7)	432/520 (83.1)	60/68 (88.2)	.38
24-hour recanalization	378/436 (86.7)	327/375 (87.2)	51/61 (83.6)	.42
24-hour NIHSS, n=561	8 [3-17]	8 [3-17]	7 [2-15]	.23
Early neurological improvement	232/568 (40.8)	198/501 (39.5)	34/67 (50.7)	.09
3-month mRS ≤ 2	269/570 (47.2)	227/502 (45.2)	42/68 (61.8)	.01
3-month mRS, n=570	3 [1-5]	3 [1-5]	2 [0-4]	<.01
Safety outcomes				
sICH	14/567 (2.5)	12/500 (2.4)	2/67 (3.0)	.68
Hemorrhagic transformation				.48
PH-1	43/570 (7.5)	40/503 (8.0)	3/67 (4.5)	
PH-2	25/570 (4.4)	23/503 (4.6)	2/67 (3.0)	
Remote PH	4/570 (0.7)	3/503 (0.6)	1/67 (1.5)	
Major systemic bleeding	4/572 (0.7)	3/505 (0.6)	1/67 (1.5)	.39

Data is presented as No. (%) or median [IQR]. Percentages are expressed among the patients for which the data was available. Recanalization is defined as a rTICI score ≥ 2B. Early neurological improvement is defined as a reduction of 8 points or more on the NIHSS or a score of 0 or 1 after 24 hours. sICH is defined as a local or remote type 2 PH associated with an increase of 4 points or more in the NIHSS score.

Abbreviations: HI, hemorrhagic infarction; IQR, interquartile range; mRS, modified Rankin scale; MT, mechanical thrombectomy; rTICI, modified treatment in cerebral infarction; NIHSS, National Institute of Health stroke score; PH, parenchymal hemorrhage; sICH, symptomatic intracranial hemorrhage.

Table 3. Factors associated with three-month functional independence (mRS ≤ 2).

Characteristic	Univariable			Multivariable		
	OR	**(95% CI)**	***p* Value**	**OR**	**(95% CI)**	***p* Value**
Age, y	0.95	(0.94-0.96)	<.001	0.95	(0.94-0.97)	<.001
Female sex	0.68	(0.49-0.95)	.02	0.9	(0.56-1.43)	.65
Vascular risk factors						
Hypertension	0.53	(0.37-0.74)	<.001	1.13	(0.68-1.86)	.64
Diabetes mellitus	0.53	(0.34-0.83)	<.01	0.75	(0.41-1.36)	.34
Smoking	1.97	(1.31-2.98)	<.01	1.24	(0.7-2.2)	.46
History of stroke	0.56	(0.33-0.97)	.04	1.20	(0.57-2.55)	.63
History of myocardial infarction	0.79	(0.47-1.34)	.38			
Prestroke treatment						
Antiplatelet	0.82	(0.57-1.18)	.29			
Anticoagulant	0.62	(0.36-1.07)	.09	0.86	(0.42-1.77)	.69
Statin	1.15	(0.8-1.64)	.46			
TOAST classification			<.001			.16
CE	1			1		
LAA	2.12	(1.25-3.61)		2.33	(1.11-4.91)	
ODE	4.05	(2-8.17)		1.16	(0.45-3.01)	
UDE	1.52	(1.03-2.26)		1.35	(0.79-2.33)	
Baseline NIHSS, n=604	0.89	(0.87-0.92)	<.001	0.86	(0.83-0.9)	<.001
Intracranial occlusion			.01			.02
M1 MCA	1			1		
M2 MCA	0.90	(0.54-1.5)		0.62	(0.31-1.25)	
ICA / Carotid terminus	0.50	(0.33-0.77)		0.53	(0.3-0.92)	
Basilar artery	0.65	(0.27-1.58)		0.26	(0.09-0.81)	
Extracranial ICA occlusion	1.16	(0.67-2)	.59			
Secondary transfer to a CSC	0.50	(0.3-0.85)	.01	0.73	(0.31-1.71)	.46
Onset-to-IVT time, n=606			<.001			.04
< 160 min	1			1		

≥ 160 min	0.67	(0.46-0.97)		0.58	(0.35-0.95)	
Unclear onset	0.42	(0.27-0.65)		0.53	(0.29-0.95)	
IVT-to-puncture time, n=578			<.01			.34
60 – 120 min	1			1		
< 60 min	1.82	(1.16-2.86)		1.48	(0.71-3.09)	
≥ 120 min	0.72	(0.45-1.15)		0.76	(0.41-1.41)	
Recanalization status			<.001			.02
Post-MT recanalization	1			1		
Pre-MT recanalization	1.21	(0.8-1.84)		1.28	(0.72-2.28)	
None	0.32	(0.19-0.54)		0.42	(0.21-0.82)	
Early neurological improvement	5.80	(4.01-8.37)	<.001	6.86	(4.13-11.41)	<.001
Parenchymal hemorrhage	0.28	(0.16-0.49)	<.001	0.55	(0.27-1.13)	.11
	Hosmer-Lemeshow test : p=.13 *Area under the ROC curve =.86* *Fraction of Missing Data : 16%*					

Logistic regression model after replacement of missing values using the multivariate imputation by chained equations algorithm.

Abbreviations: CE, cardioembolism; CI, confidence interval; ICA, internal carotid artery; LAA, large-artery atherosclerosis; MCA, middle cerebral artery; MT, mechanical thrombectomy; NIHSS, National Institute of Health stroke score; ODE, other determined etiology; OR, odds ratio; SVS, susceptibility vessel sign; TOAST, Trial of Org 10172 in Acute Stroke Treatment; UDE, undetermined etiology.

Figures

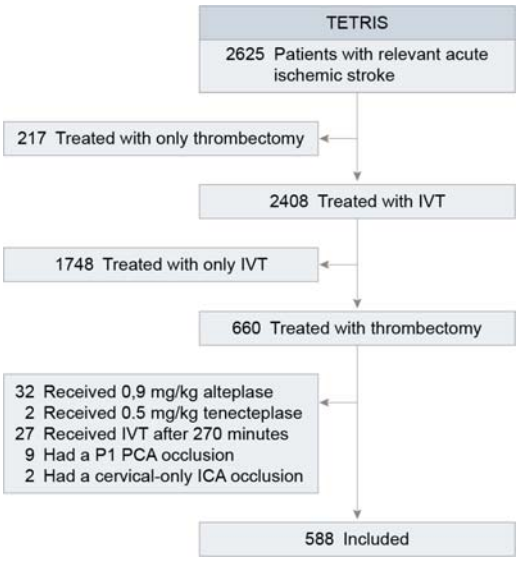

Figure 1. Flow diagram of the study inclusion and exclusion.

Abbreviation: ICA, internal carotid artery; IVT, intravenous thrombolysis; PCA, posterior cerebral artery.

Figure 2. Functional independence (mRS) at 3 months.

Data are proportion of patients. The first and third rows represent the result of the bridging therapy groups in the HERMES meta-analysis of five trials which used alteplase for IVT, and the pooled analysis of the EXTEND-IA TNK trials, which used tenecteplase for IVT.

Abbreviations: EXTEND-IA TNK, Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke; HERMES, Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke Trials; IVT, intravenous thrombolysis; mRS, modified Rankin score; TETRIS, Tenecteplase Treatment in Ischemic Stroke.

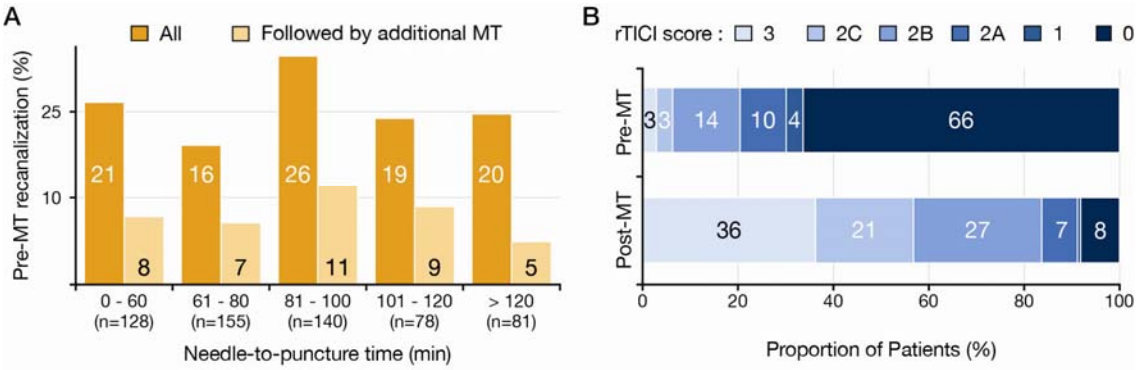

Figure 3. Pre-MT recanalization rate depending on the IVT-to-puncture time and pre- and post-MT rTICI scores.

Data are proportion of patients. A, Pre-MT recanalization rate depending on the IVT-to-puncture time. B, Each panel represents the repartition of the rTICI scores at the first angiographic run (pre-MT) and at the end of the procedure (post-MT).

Abbreviations: IVT, intravenous thrombolysis; MT, mechanical thrombectomy; rTICI, modified Treatment in Cerebral Ischemia.

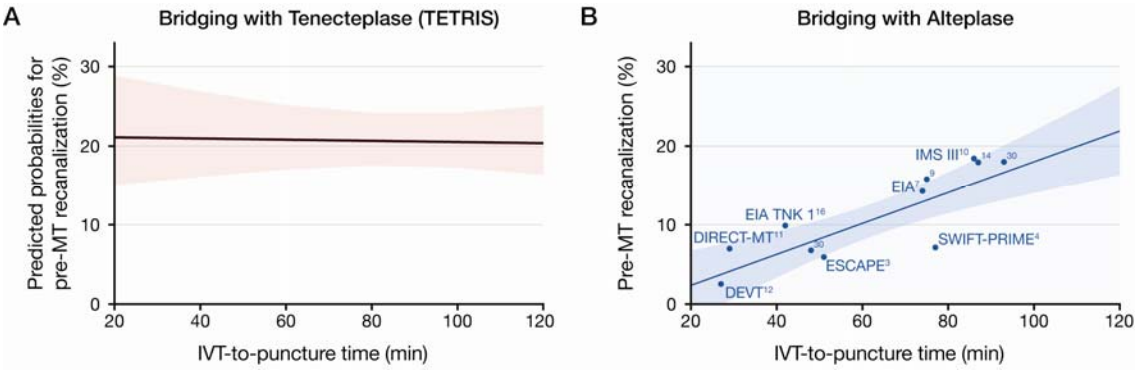

Figure 4. Comparison of pre-MT recanalization with Tenecteplase and Alteplase.

A, Predicted probabilities for pre-MT recanalization with tenecteplase depending on the IVT-to-puncture time based on the TETRIS cohort (logistic regression). B, Pre-MT recanalization rates with alteplase compared with the IVT-to-puncture time in recent clinical trials and registry studies. For better comparison we included those in which all patients received IVT with 0.9 mg/kg (maximum 90 mg) alteplase and underwent a brain DSA. Shaded area represents the 95% CIs.

Abbreviations: DEVT, Direct Endovascular Thrombectomy vs Combined IVT and Endovascular Thrombectomy for Patients With Acute Large Vessel Occlusion in the Anterior Circulation; DIRECT-MT, Direct Intraarterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial; EIA, Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-arterial; EIA TNK, Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke; ESCAPE, Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times; IMS III, Interventional Management of Stroke III; IVT, intravenous thrombolysis; SWIFT PRIME, Solitaire FR With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke; TETRIS, Tenecteplase Treatment in Ischemic Stroke.