Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

List of Sites, Investigators, and Administrative Staff

Enrolling Clinical Centers (number recruited)

Hospital Clinic of Barcelona (57): A. Chamorro (study chair), A. Renú (P.I), S. Amaro, X. Urra, L. Llull, C. Laredo, M. Vargas, V. Obach, S. Rudilosso, A. Rodríguez-Vázquez, D. Santana, J. Blasco, L. San Román, J. Macho, A. López-Rueda, N. Macías, E. Serrano, J. Moreno,

Hospital Germans Trias i Pujol (22): A. Ramos (P.I), M. Millán, A. Dávalos, N. Pérez de la Ossa, L. Dorado, M. Hernández-Pérez, M. Gomis, L. Muñoz, P. Rodríguez-Molinos, M. Boix, E. Palomeras, F. Núñez, C. Castaño, S. Remollo, M. Werner.

Hospital Dr. Josep Trueta Girona (13): M. Terceño (P.I), J. Serena, V. Vera, L. Paul, L. Pardo, M. Reina, S. Bashir, U. Bojaryn, Y. Silva, M. Guasch, A.D. Murillo, J. Rodríguez Álvarez-Cienfuegos, M. Comas, B. Martínez, E. Nogué,

Hospital de Bellvitge (11) : P. Cardona (P.I), O. Chirife, H. Quesada, R. Barranco, B. Lara, A. Paipa, L. Aja, P. Mora. M.A. de Miquel, S. Aixut, A.M. Ferrer.

Hospital Santa Creu i Sant Pau (8): J.Martí-Fàbregas (P.I), R. Marin, L. Prats-Sánchez, R. Delgado-Mederos, A. Martínez-Domeño, J. Branera, R. Guerrero, J. Villalba, A. Rodríguez, N. Berga, E. Jiménez-Xarrié.

Hospital del Mar (6): E. Cuadrado (P.I), J. Roquer, G. Romeral, A. Ois, J. Jiménez, C. Avellaneda, N. Cayuela, A. Rodríguez, E. Giralt, M. Espona, L. Guimaraens, E. Vivas, J. Saldaña.

Hospital Vall d'Hebrón (4): M. Muchada (P.I), A. Tomasello, D. Hernández, M. Ribó, C. Piñana, N. Rodríguez, S. Boned, C.A. Molina, M. Rubiera, J. Juega, D. Rodríguez-Luna, J. Pagola, A. García-Tonel, M. Deck, V. Sala, E. Sanjuan, K. Santana, C. Losada, P. Suñé.

Steering Committee: Á. Chamorro (chair), S. Amaro, P. Cardona, A. Dávalos, J. Macho, J. Martí-Fábregas, L. Oleaga, J. Roquer, F. Torres (Biostatistician), X. Urra.

Data Safety Monitoring Board (DSMB): T. Jovin (chair), E. Leira, J. Rios (independent biostatistician)

Neuroimaging Corelab: L. San Román (chair), A. López-Rueda, C. Laredo

Critical Events Committee: J. Martí-Fàbregas

Neurointerventionalism Harmonization: J. Blasco (chair), A. Tomasello, L.Guimaraens, R. Barranco, C. Castaño.

Patient's recruitment Board: M. Millán (chair), M. Muchada, E. Cuadrado.

Clinical Study Management: ANAGRAM-ESIC.

Data Management -eCRF – Statistics: IDIBAPS - Hospital Clínic Barcelona

Sponsor: Fundació Clínic per la Recerca Biomèdica.

CHOICE Trial Data Safety Monitoring Board (DSMB) Charter

I. Membership

The Data Safety Monitoring Board (DSMB) is an independent board of 3 individuals who are not otherwise participating in any other role in the study: Dr. Tudor Jovin – chair of committee, Dr. Enrique Leira, Dr. Jose Rios (statistician).

All members will sign a consulting agreement with the study Principal Investigator that provides for indemnification.

II. Responsibilities

The roles of the DSMB are to assist trial investigators; to ensure that the rights and welfare of trial subjects are protected; and to decide about study continuation on interim analyses:

1. Active participation in decisions made by the steering committee.

2. Regular partially masked monitoring of the study safety by review of occurrence rates of Significant Adverse Events (SAEs) as defined in the study protocol and provided by the CRO (Anagram) after adjudication by the Clinical Events Committee.

Recommendations to halt the study prematurely will be based on a clinically unacceptable occurrence of Procedure and/or Device related SAEs or clinically important difference in the patient outcomes between the 2 arms that are sufficient to raise ethical concerns. Formal rules triggering additional, in depth and unblinded data review base on safety concerns are outlined in the attached file.

All recommendations will be made directly to the chairman of the CHOICE trial (Dr. Angel Chamorro)

The CRO (Anagram) and chairman of CHOICE will review significant adverse events that are collected during ongoing monitoring of the Study, and will ensure that any significant safety concerns are provided to the participating DSMB members in a timely manner.

The CHOICE statistical office will directly send interim safety statistical analyses to all members of the DSMB.

III. Meeting Frequency and Format

DSMB pre-scheduled teleconferences will occur at regular intervals without participation from the Sponsor, co-chairmen nor Steering Committee.

Safety monitoring will occur after every 50 enrolled subjects reach the first week of follow up. The data provided to the DSMB will be blinded (Group A and B). The meetings will routinely include review of data output tables from the trial for enrolled patients. If the DSMB determines that not enough information is available to make a fully informed determination about the safety profile of either arm of the study they may request additional information or analyses.

The DSMB members will make reasonable efforts to meet by phone conference within 2 weeks after each new data set or interim analyses report is received. If a request for an urgent meeting is made, the DSMB will make every effort to convene within 24-48 hours.

IV. Methods of Organizing the Data for Review

Any event which is, or could potentially be, categorized as a Procedure or Device related SAE including all of the following will be identified and will be adjudicated by the Clinical Events Committee:

- Vessel perforation
- Intramural Arterial dissection
- ICH or death occurring within 24 (-6/+12) hours post-procedure

- Embolization to a previously uninvolved territory
- Access site complication requiring surgical repair or blood transfusion
- In vivo device failure (in vivo breakage)

These events will be reported to the DSMB independently by group A vs. B data to allow blinding between groups. All SAEs that do not increase the likelihood of unmasking will be included with the Group A vs. B demographic and outcome data.

The DSMB may, at any time, request additional information or statistical analyses to be provided in order to conduct a thorough review of the data. The DSMB also reserves the right to request unblinding of the data (Group A vs. B treatment groups) if sufficient safety concerns arise regarding Procedure or Device related SAEs or clinically important differences in the patient outcomes between the 2 arms that raise ethical concerns

V. Documentation of Meeting Minutes

The DSMB Chair or administrative assistant will be responsible for communication with the DSMB members regarding scheduling of meetings. Meetings will be scheduled and facilitated by the DSMB Chair using e-mail. Every effort will be made to schedule meetings at a time that is mutually convenient for all 3 members of the committee.

Input from all 3 members is required for DSMB decisions to be finalized. The DSMB Chair or delegate member will document the results of the DSMB meeting discussions and determination, as well as any requests for follow up information and all action items and send this information by email to the Principal Investigators with 24 hours after each meeting.

VI. Confidentiality Statement

By signing this charter, the DSMB members hereby certify that they are willing and able to maintain strict confidentiality of all analyses, DSMB meeting discussions, determinations, and minutes.

VII. Post-study Roles and Responsibilities

At the conclusion of the study the results of the final statistical analyses will be shared with the DSMB members. The DSMB members will be included in the primary publication.

VIII. Statement of agreement with this Charter

By signing and dating below I indicate my agreement with the content of this charter and willingness to serve on the DSMB.

_____ **26/07/2019**

DSMB Chair – Tudor Jovin

[1] European Stroke Organization (ESO) Executive Committee; ESO Writing Committee. Guidelines for management of ischemic stroke and transient ischemic attack 2008; Cerebrovasc Dis 2008;25:457-507.

eAppendix. Supplementary Methods

Specified intervention requirements and medical therapy arm.

Stroke Unit admission & General treatment

One independent contract research organization was responsible for monitoring sites for accuracy and completeness of the data, and data management. Patients were admitted at acute stroke units providing semi-intensive care and continuous cardiovascular monitoring (or ICU if needed). Patients were treated following the European Stroke Organization ESO guidelines.[1] Most important aspects of the medical management included antiplatelet therapy (aspirin) after exclusion of intracerebral hemorrhage except in patients who had received iv t-PA in whom antithrombotic therapy was only instituted after 24 hours. Blood pressure management generally was not recommended in the first 24 hours until extremely high (220 mmHg systolic /120 mm Hg diastolic). In patients receiving iv t-PA these values were lower (185 mmHg and 110 mmHg respectively). Hemicraniectomy as a life preserving measure could be performed early in the course of brain swelling and in younger patients. Stroke unit care included early mobilization, DVT prophylaxis, aspiration prevention, and secondary stroke prevention according to stroke etiology. Individual Centers defined prior to initiation of the study common additional criteria and protocols to treat patients outside the trial. Concomitant medications and non-pharmacological therapies were recorded during the trial.

Systemic Thrombolysis and Endovascular thrombectomy

Intravenous alteplase was used in a dose of 0.9 mg/kg body weight as a bolus (10% of total dose) followed by the remaining dose as an infusion over 1 hour in eligible patients. Endovascular treatment was performed according to the usual practice of each center. Once intracranial occlusion was confirmed, the thrombectomy was performed using any of the techniques currently available, provided that the device used had a CE mark. The use of a balloon catheter was at the discretion of the neurointerventionalist, as well as the thrombectomy system, which could be aspiration, stent retriever type devices or combination of both techniques. In contrast, patients were not treated with investigational devices. Systemic anticoagulation was not allowed other than in the heparinized saline infusion as per local interventional procedure standards. Balloon angioplasty and/or stenting of extracranial ICA in cases with ICA/M1 tandem occlusions was allowed as per site specific protocols but patients were not eligible into the study if dual antiplatelet therapy was required. A maximum of three passes or three aspirations were accepted for the patient to meet the inclusion criteria in CHOICE. This criterion was extended up to 6 passes on November 28, 2019. Likewise, the type of was decided by the team that performed the procedure, not being grounds for exclusion any of the options, local anesthesia, sedation or general anesthesia.

Administration of the study medication

The endovascular procedure was considered completed once the neurointerventionalist considered that the angiographic result was consistent with CHOICE's angiographic criteria and it did not seem reasonable to continue the procedure using endovascular techniques for better revascularization. Once the thrombectomy procedure was completed, patients that met the angiographic and clinical criteria for inclusion in CHOICE were randomized. The neurointerventionalist received the medication of the study to be injected according to protocol, proceeding to inject it through a distal access catheter or microcatheter located at the proximal level of the residual thrombus and distally to the origin of the lenticulostriates branches. Administration of placebo/alteplase was performed as an intra-arterial infusion for 30'. The duration of administration of the study medication was reduced to 15' on November 28, 2019. The super-selective catheterization of the occluded branch(s) to perform the administration of the medication vs the injection of said medication from more proximal positions was done at the discretion of the neurointerventionalist depending on the difficulty of access, risk of distal catheterization, patient agitation, occluded branches, etc. The CRF of the study recorded whether the placebo/alteplase infusion was performed either from M1, ACA1, PCA1, or from one of the branches of bifurcation. The recommendation was not to inject immediately proximal into an occluded, dead-end artery at the risk of directly accumulating a higher concentration of the drug there. The infusion was stopped at 20´to assess if the mTICI had improved (qualitative assessment) and if so, the infusion was finalized. Further, 10´after the end of the infusion of the study medication an angiographic series was performed in front and profile projections to establish the degree of final reperfusion. The angiographic control at 20´of the start of the study was suspended when the amendment proposing the administration of the study medication was introduced to be 15´.

Imaging assessment

Patients had a non-contrast CT scan (NCCT) -or brain MRI- at hospital admission to rule out the presence of blood and estimate the Alberta stroke program early CT score (ASPECTS). A whole brain CT-Perfusion (CTP) -or DWI-MRI- was performed before transfer of the patient to the angio-suite. At 24 +12 hours of randomization, a second NCCT (or MRI) was performed to assess the presence of early bleeding complications. At 48+24 hours of randomization, a brain MRI was performed to measure the volume of the infarction, estimate the growth of the infarction and assess the presence of late bleeding complications.

Angiographic assessment

All cerebral angiography studies were evaluated by two senior readers at a core imaging laboratory blinded to clinical data. Diagnostic anterior-posterior and lateral runs or contrast injection of the occlusion were available at the end of the standard thrombectomy to determine the pretreatment eTICI score. Similar runs determined the final eTICI score after 10′of completion of the experimental treatment. Any angiography score disagreement was resolved by consensus. The mTICI and eTICI scores agreement rates (weighted κ) between two readers was previously assessed in 30 patients with mTICI 2b or superior, to define the inter-rater reliability of the distinction between eTICI 2b50 (50–66% reperfusion, mTICI 2B) and eTICI 2b67 (67–89% reperfusion, TICI 2B). In the eTICI metrics, eTICI grade 0 is equivalent to 0% filling of the target downstream territory; eTICI 1 reflects thrombus reduction without any reperfusion of distal arteries; eTICI 2a is reperfusion in 1–49% of the territory; eTICI 2b50 is 50–66% reperfusion; eTICI 2b67 is 67–89% reperfusion; eTICI 2c is 90–99% reperfusion; and eTICI 3 is complete or 100% reperfusion. The final angiographic score was further defined as improved, worsened or unchanged with regard to the baseline angiography.

eTable 1. Inclusion and Exclusion Criteria and Summary of Protocol Amendments

Inclusion Criteria

1. Patients with symptomatic large vessel occlusion (LVO) in the anterior, middle or posterior cerebral artery treated with MT resulting in an mTICI score 2b/3 at end of the conventional procedure. Patients with large vessel occlusion on CTA or MRA but an mTICI score 2b/3 on the diagnostic cerebral angiography before the onset of MT are also eligible for the study.

2. Estimated delay to onset of rescue intraarterial rt-PA administration <24 hours from symptom onset, defined as the point in time the patient was last seen well

3. No significant pre-stroke functional disability (modified Rankin scale 0-1), or mRS >1 that according to the investigator is not related to neurological disease (i.e. amputation, blindness)

4. Age ≥18

5. ASPECTS ≥6 on non-contrast CT (NCCT) scan or MRI if symptoms lasting <4.5 hours or ASPECTS >6 on CT-Perfusion (CTP) or DWI-MRI if symptoms >4.5 <24 hours.

6. Informed consent obtained from patient or acceptable patient surrogate

Exclusion Criteria

1. NIHSS score on admission >25

2. Contraindication to IV t-PA as per local national guidelines (except time to therapy)

3. Use of carotid artery stents during the endovascular procedure requiring dual antiplatelet therapy during the first 24h

4. Female who is pregnant or lactating or has a positive pregnancy test at time of admission

5. Current participation in another investigation drug or device treatment study (except observational study i.e.: RACECAT or clinical trials not testing new medical devices or new drugs i.e. IMAGECAT)

6. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency

7. Known coagulopathy, INR > 1.7 or use of novel anticoagulants < 48h from symptom onset

8. Platelets < 50,000

9. Renal Failure as defined by a serum creatinine > 3.0 mg/dl (or 265.2 μmol/l) or glomerular Filtration Rate [GFR] < 30

10. Subject who requires hemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram for whatever reason

11. Any hemorrhage on CT/MRI

12. Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT or MRI scan is normal

13. Suspicion of aortic dissection

14. Subject currently uses or has a recent history of illicit drug(s) or abuses alcohol

15. History of life-threatening allergy (more than rash) to contrast medium

16. SBP >185 mmHg or DBP >110 mmHg refractory to treatment

17. Serious, advanced, terminal illness with anticipated life expectancy < 6 months

18. Pre-existing neurological or psychiatric disease that would confound evaluation

19. Presumed vasculitis or septic embolization

20. Unlikely to be available for 90-day follow-up (e.g. no fixed home address, visitor from overseas)

Summary of protocol amendments

Protocol version number (date)	Notes regarding the new version
V1 (March 07, 2018)	Initial version
V2 (March 08, 2019)	**<u>Changes in the inclusion criteria:</u>** 1. Patients with symptomatic large vessel occlusion (LVO) in the anterior, middle or posterior cerebral arteries treated with MT resulting in a mTICI score 2b at end of the procedure. **This corresponds to ≥50% and <100% brain reperfusion.** **Patients with a mTICI score 2b on the diagnostic cerebral angiography MT are also eligible for the study**. 3. No significant pre-stroke functional disability (modified Rankin scale 0-1), **or mRS >1 that according to the investigator is not related to neurological disease (i.e. amputation, blindness)** 5. ASPECTS ≥6 on non-contrast CT (NCCT) scan or MRI if symptoms lasting <4.5 hours or ASPECTS > 6 on CT-Perfusion (CTP) or DWI-MRI if symptoms >4.5 <24 hours. **<u>Changes in the exclusion criteria</u>:** 3. Use of carotid artery stents during the endovascular procedure requiring dual antiplatelet therapy **during the first 24h** 5. Current participation in another investigation drug or device treatment study (except observational study i.e.: RACECAT **or clinical trials not testing new medical devices or new drugs i.e. IMAGECAT**) **<u>Interventions</u>** Patients with confirmed large vessel occlusion (LVO) of the anterior, middle or posterior cerebral artery and treated with MT will receive alteplase (Actylise®) or placebo if the mTICI score **on cerebral angiography** is 2b. **Patients displaying an mTICI score 2b on cerebral angiography before a first pass with an endovascular device could still be eligible for randomization into the study because we define the onset of mechanical thrombectomy as the time of groin puncture.** **<u>Subgroup analysis added</u>** **Baseline angiographic score >90<100% brain reperfusion (rTICI2c) versus baseline angiographic score ≥50<91% brain reperfusion**
V3.1 (November 28, 2019)	**Hospital U. de Girona Doctor Josep Trueta added as a participant site** **<u>Inclusion criteria:</u>** 1. Patients with symptomatic large vessel occlusion (LVO) in the anterior, middle or posterior cerebral arteries treated with MT resulting in a mTICI score 2b **or 3** at end of the procedure. Patients with an mTICI score 2b/**3** on the diagnostic cerebral angiography before the onset of MT are also eligible for the study. **The maximum will be six passes or six aspirations for the patient to meet the criteria for inclusion in CHOICE.** **<u>Primary Outcome modified</u>**

	Proportion of patients with a mRS 0 to 1 at 90 days. **<u>Secondary Outcome added</u>** ● **Proportion of patients with angiographic changes on the eTICI score. To that aim, all the baseline angiographies will be scored at the core lab by central and blinded reviewers using the eTICI and classified as eTICI2b50, eTICI2b67, eTICI2c, and eTICI3. The post treatment angiographies will be scored using the eTICI and classified as "improved", "worsened" or "unchanged" with regard to the baseline eTICI score.** **<u>Changes in the Study objectives:</u>** The study objective is to evaluate whether rt-PA is safe and efficient as an add-on to mechanical thrombectomy in patients with acute ischemic stroke and complete or near-complete recanalization of a proximal vessel occlusion **and successful** brain reperfusion on cerebral angiogram (corresponding to mTICI score 2b/**3**). **Reduction of the IA infusion time to 15 minutes** to increase the drug concentration to increase its potential efficacy and to reduce the patients' time in the angiography room.

eTable 2. Timing of Study Procedures

Assessments	Baseline information	Procedure/ Allocation	F up 24h (-/+12h)	F up 48h (-/+ 24h)	F up 5 days (±2 d)	F up 90 days (± 14 d)
Admission Details	X					
Demographics	X					
Medical History	X					
Eligibility Criteria		X				
Informed Consent	X					
Randomization		X				
Blood test *Including INR*	X					
mRS	X[1]				₡	₡
NIHSS assessment	X		₡	₡	₡	₡
NCCT / MRI	X		X			
CT-P/ DWI-MRI	X					
Angiogram		X				
Blinded Study medication administration		X				
Post-MT angiography		X (if applicable)				
MRI (DWI/T2 sequences) *Or NCCT if MRI not possible*				X		
Stroke etiology						X
Procedure Details		X				
Barthel Scale						X
EuroQol EQ-5D						X
(S) AEs	…..on an ongoing basis…..					
Relevant Meds	X	X	X	X	X	

[1] This mRS score should be based on subject's score prior to the stroke symptom onset.
₡ To be done by an accredited local evaluator

eTable 3. Additional Baseline Characteristics of the 121 Patients

	Alteplase N=61	Placebo N=52
Weight (Kg), mean (SD)	74.3 (12%)	74.6 (13%)
Current/former smokers— no. (%)	26 (43%)	18 (35%)
Dyslipidemia— no. (%)	29 (56%)	24 (50%)
Ischemic heart disease— no. (%)	9 (17%)	9 (19%)
Peripheral vascular disease— no. (%)	3 (6%)	4 (8%)
Renal insufficiency— no. (%)	5 (10%)	8 (17%)
Hyperuricemia / Gout— no. (%)	8 (15%)	1 (2%)
Previous medication— no. (%)		
Antihypertensive	79 (65%)	71 (68%)
Antidiabetic	39 (32%)	31 (30%)
Lipid-lowering drugs	83 (67%)	57 (55%)
Antiplatelets	62 (75%)	37 (60%)
Stroke etiology— no. (%)		
Cardioembolism	29 (48%)	29 (56%)
Large artery atherothrombosis	7 (12%)	3 (6%)
Undetermined cause	23 (38%)	19 (37%)
Unusual cause	2 (3%)	1 (2%)
Workflow times		
Median time from stroke onset to imaging at referral center (IQR) — min	209 (78-528)	246 (123-525)
Median time from stroke onset to intravenous alteplase (IQR) — min	90 (70-145)	132 (91-265)
Median time from stroke onset to groin puncture (IQR) — min	261 (125-630)	292 (190-596)

eTable 4. First Post-Hoc Sensitivity Analysis for the Primary Outcome (Score of 0 to 1 in the Modified Rankin Scale at 90 Days): Analyses Using Other Populations and Statistical Strategies, Including Center as a Random Effect and Unadjusted Models

Population	Intraarterial Alteplase n/N (%)	Intraarterial Placebo n/N (%)	Analysis adjusted by	Rate Difference [95% CI]	p-value
Treated as allocated	36/61 (59.0%)	21/52 (40.4%)	Previous alteplase use	18.4% [0.3% to 36.4%]	0.04
			Previous alteplase use and centre as a random effect	18.8% [0.8% to 36.8%]	0.04
			Raw (no adjustment)	18.6% [0.5% to 36.8%]	0.04
Randomised	36/65 (55.4%)	23/56 (41.1%)	Previous alteplase use	14.5% [-3.0% to 32.0%]	0.10
			Previous alteplase use and centre as a random effect	14.9% [-2.5% to 32.3%]	0.09
			Raw (no adjustment)	14.3% [-3.4% to 32.0%]	0.11
Treated as allocated with protocol adherence	35/59 (59.3%)	21/50 (42.0%)	Previous alteplase use	16.9% [-1.6% to 35.4%]	0.07
			Previous alteplase use and centre as a random effect	17.1% [-1.3% to 35.5%]	0.06
			Raw (no adjustment)	17.3% [-1.2% to 35.9%]	0.06

n/N: number of patients with the primary outcome / number of total patients per group.
The treated as allocated population (all treated patients as randomised) was predefined for the primary analysis. The randomised population included all patients randomised regardless of treatment exposure. The treated as allocated with protocol adherence population consisted of all as treated patients without major protocol deviations (see flow diagram).
The primary analysis was predefined to be conducted on the treated as allocated population and adjusted by the fixed effect of previous alteplase use. The rest of analyses with the other populations and adjustment strategies are secondary. The unadjusted analyses were predefined in the protocol. The analysis including centre as a random effect in the statistical model was conducted post-hoc as requested by reviewers.

eTable 5. Second Post-Hoc Sensitivity Analysis for the Primary Outcome (Score of 0 to 1 in the Modified Rankin Scale at 90 Days): Series of Models Considered Imbalances in Baseline Variables

Model	Analysis						P	Absolute risk difference (95%CI)
1	**Primary**						**0.047**	**18.3% [0.3% to 36.4%]**
2-14	**Post-hoc sensitivity adjusted analyses**							
#	**Covariates**						**P**	**Absolute risk difference (95%CI)**
	Diabetes mellitus[a]	**SBP[b]**	**DBP[c]**	**Glucose[d]**	**Time to rand.[e]**	**Time to med.[f]**		
2	X						0.035	19.4% [1.4% to 37.4%]
3		X					0.043	18.7% [0.6% to 36.7%]
4			X				0.033	19.7% [1.6% to 37.8%]
5				X			0.049	18.4% [0.0% to 36.7%]
6					X		0.055	17.6% [-0.3% to 35.5%]
7						X	0.035	19.1% [1.4% to 36.8%]
8	X	X	X	X	X	X	0.034	19.7% [1.5% to 38.0%]
9	X	X	X	X	X		0.042	18.6% [0.6% to 36.6%]
10	X	X		X	X		0.050	18.0% [0.0% to 35.9%]
11	X		X	X	X		0.042	18.6% [0.6% to 36.6%]
12	X	X	X	X		X	0.028	20.0% [2.2% to 37.7%]
13	X	X		X		X	0.034	19.2% [1.5% to 37.0%]
14	X		X	X		X	0.028	20.0% [2.2% to 37.7%]

Between treatment observed differences at baseline were: [a]diabetes mellitus 10%, [b]median systolic blood pressure (SBP) at hospital arrival (3 mm Hg), [c]median diastolic blood pressure (DBP) at hospital arrival (3 mm Hg), [d]median glucose level at hospital arrival (15 mmol/liter), [e]median time from stroke onset to randomization (39 min), [f]median time from stroke onset to start the study medication (41 min).

Model 1 was the primary analysis including only adjustment by the pre-defined stratification variable "prior alteplase use". The rest of models were constructed post-hoc as per the reviewers' request.

Models 2 to 7 include a new covariate for each model at a time. Model 8 is a full model which includes all variables from the above list. Models 9 to 14 are combinations derived from the full model by removing one variable at a time from the two pairs of highly correlated variables: SBD - DBP, and time to randomization - time to medication.

eTable 6. Other Adjudicated Serious Adverse Events by Treatment Groups

Serious Adverse Events, n	Placebo (N=52)	Alteplase (N=61)
Atrioventricular block second degree	0	1
Cardiac arrest	0	1
Cardiac failure	0	1
Myocardial infarction	0	1
COVID-19	0	2
Pneumonia	1	1
Respiratory tract infection	2	3
Cerebral thrombosis	1	2
Cerebrovascular accident	2	2
Hemorrhage intracranial	2	0
Nervous system disorder	0	1
Neurological symptom	0	1
Stroke in evolution	1	0
Acute kidney injury	0	1
Bronchospasm	1	0
Pneumonia aspiration	2	0
Thoracic hemorrhage	0	1
Deep vein thrombosis	0	1
Hypotension	0	1
TOTAL	**12**	**20**

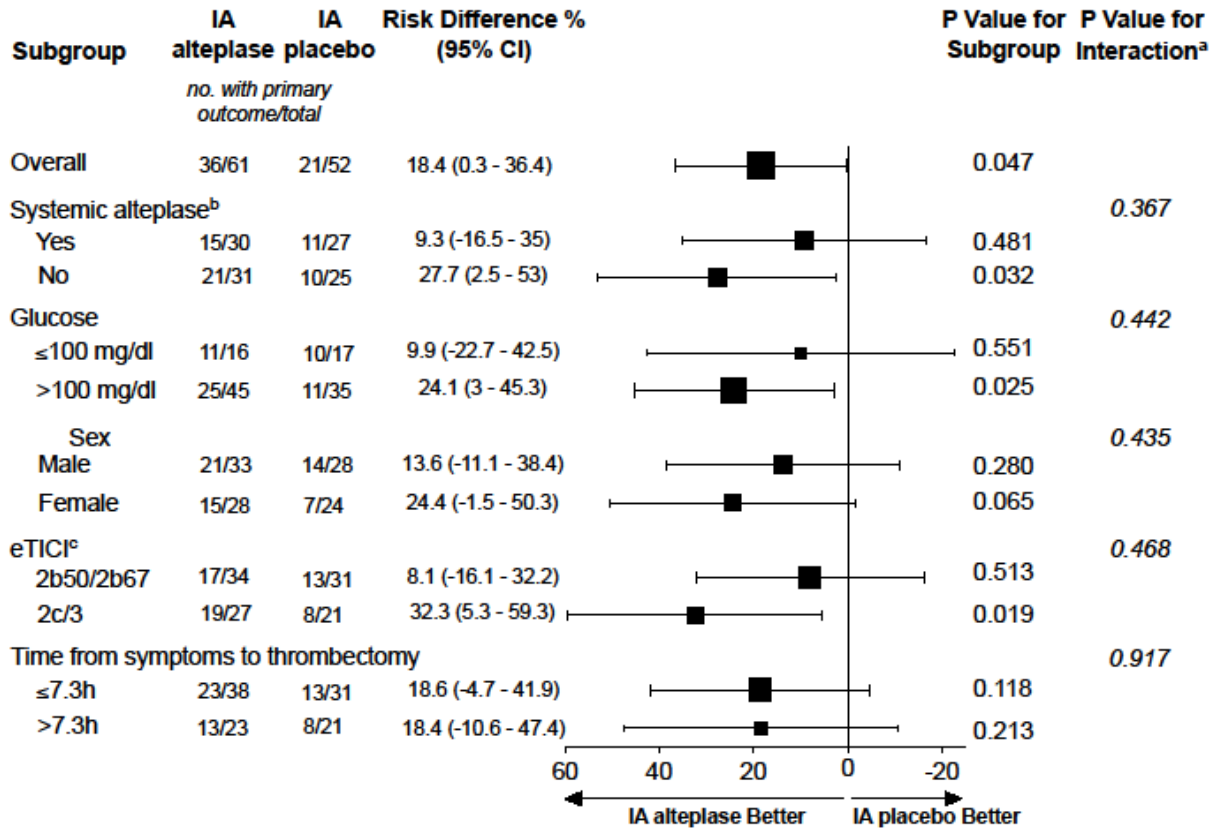
eTable 7. Other Adverse Events Reported by Local Investigators by Treatment Groups*

* Adverse events are classified following the MedDRA medical terminology dictionary

Adverse Events, n	Placebo (N=52)	Alteplase (N=61)	Total (N=113)
Nervous system disorders	**20**	**22**	**42**
Cerebral reperfusion injury	0	1	1
Cerebral thrombosis	2	1	3
Epilepsy	1	1	2
Headache	12	12	24
Stroke in evolution	0	1	1
Syncope	0	3	3
Transient ischemic attack	1	0	1
Blood and lymphatic system disorders	**2**	**7**	**9**
Anemia	2	6	8
Thrombocytopenia	0	1	1
Cardiac disorders	**15**	**14**	**29**
Atrial fibrillation	9	8	17
Atrial flutter	0	2	2
Cardiac failure	2	1	3
Presyncope	0	2	2
Sinus bradycardia	1	0	1
Tachycardia	3	1	4
Ear and labyrinth disorders	**1**	**0**	**1**
Vertigo	1	0	1
Endocrine disorders	**0**	**1**	**1**
Hypothyroidism	0	1	1
Eye disorders	**1**	**2**	**3**
Eyelid oedema	1	0	1
Ocular hyperemia	0	1	1
Vitreous floaters	0	1	1
Gastrointestinal disorders	**11**	**14**	**25**
Constipation	4	8	12
Diarrhea	4	0	4
Dyspepsia	0	1	1
Dysphagia	0	1	1
Gastrointestinal hemorrhage	1	0	1
Nausea	0	1	1
Odynophagia	0	1	1
Rectal hemorrhage	1	0	1
Vomiting	1	2	3
General disorders and administration site conditions	**6**	**6**	**12**
Chest pain	0	2	2
Device embolization	0	2	2
Face oedema	1	0	1
Pyrexia	3	2	5
Vessel puncture site hematoma	2	0	2
Infections and infestations	**13**	**22**	**35**
Bacteremia	0	1	1
COVID-19	1	1	2
Cellulitis	0	1	1
Conjunctivitis	1	1	2
Fungal infection	1	0	1
Gastroenteritis	0	1	1
Oral infection	1	0	1
Pneumonia	2	1	3
Respiratory tract infection	1	2	3
Staphylococcal infection	0	1	1
Urinary tract infection	6	12	18

Adverse Events, n	Placebo (N=52)	Alteplase (N=61)	Total (N=113)
Vulvovaginitis	0	1	1
Injury; poisoning and procedural complications	**2**	**2**	**4**
Craniocerebral injury	0	1	1
Fracture	1	0	1
Joint injury	0	1	1
Spinal fracture	1	0	1
Investigations	**1**	**0**	**1**
Vitamin B12 decreased	1	0	1
Metabolism and nutrition disorders	**16**	**19**	**35**
Diabetes mellitus	0	1	1
Dyslipidemia	4	7	11
Electrolyte imbalance	1	0	1
Hyperglycemia	9	10	19
Hyperkalemia	0	1	1
Hypoglycemia	1	0	1
Hypokalemia	1	0	1
Musculoskeletal and connective tissue disorders	**2**	**3**	**5**
Arthralgia	1	0	1
Back pain	1	0	1
Pain in extremity	0	3	3
Psychiatric Disorders	**10**	**10**	**20**
Agitation	9	10	19
Confusional state	1	0	1
Renal and urinary disorders	**8**	**8**	**16**
Acute kidney injury	2	1	3
Hematuria	2	2	4
Urinary retention	4	5	9
Reproductive system and breast disorders	**2**	**1**	**3**
Acquired phimosis	1	0	1
Prostatitis	1	0	1
Pruritus genital	0	1	1
Respiratory; thoracic and mediastinal disorders	**4**	**4**	**8**
Hypoxia	1	1	2
Pharyngitis	1	0	1
Pleural effusion	1	0	1
Pneumonia aspiration	0	3	3
Tachypnea	1	0	1
Skin and subcutaneous tissue disorders	**0**	**3**	**3**
Dermatitis	0	1	1
Rash	0	1	1
Urticaria	0	1	1
Surgical and medical procedures	**0**	**2**	**2**
Cardiac ablation	0	1	1
Cardioversion	0	1	1
Vascular disorders	**21**	**25**	**46**
Deep vein thrombosis	1	0	1
Device embolization	1	0	1
Hematoma	4	5	9
Hypertension	4	9	13
Hypotension	7	2	9
Phlebitis	4	7	11
Pulmonary embolism	0	1	1
Vasospasm	0	1	1
TOTAL	**135**	**165**	**300**

eFigure. Subgroup Analyses



a. The subgroup-by-treatment interaction significance was calculated by including that term in an additional model.
b. Intravenous alteplase before the endovascular procedure.
c. eTICI: 2b50: 50–66% reperfusion, 2b67: 67–89% reperfusion, 2c: 90–99% reperfusion, 3: 100% reperfusion.