Supplementary Appendix

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

Supplement to: Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med 2013;368:893-903. DOI: 10.1056/NEJMoa1214300

SUPPLEMENTAL APPENDIX

TABLE OF CONTENTS

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2) SUPPLEMENTAL METHODS:

Patients

Supplementary Table 1 lists the inclusions and exclusions which are similar to those used in the NINDS t-PA Stroke Trial[1] and current national guidelines[2] but with several notable differences. Most importantly, eligible subjects had to have an NIHSS of 10 or more, or after implementation of Amendment 3 in January 2009 at institutions where baseline CTA imaging is standard of care for acute stroke patients, an NIHSS of 8-9 with evidence by CT or MR angiography of an occlusion of the internal carotid artery (ICA), first division of middle cerebral artery (M1) or basilar artery.

Subjects older than 80 years old were initially excluded due to possibly increased ICH rates based on prior IV and IA studies.[3, 4] The age exclusion was expanded to age 83 and older with Amendment 3. Additional notable exclusions include seizure at stroke onset, which precludes knowledge of the baseline NIHSS score; ongoing hemodialysis, due to possibly increased ICH risk based on the IMS I Trial; and hyperglycemia greater than 400 mg/dL (22 mmol/L), based on increased ICH risk.

Imaging criteria for exclusion are consistent with the NINDS t-PA Stroke Trial and prior IMS Trials.[1, 5, 6] Specifically, patients with large regions of clear hypodensity (i.e., darker than white matter and brighter than CSF) on CT scan, such as greater than one-third of the middle cerebral artery vascular territory, are excluded. An ASPECTS score of < 4[7] could be used as a guideline when evaluating >1/3 region of territory involvement but was not considered a specific exclusion. However, sulcal effacement and/or loss of grey-white matter differentiation were not contraindications for treatment.

Process of Subject Enrollment and Randomization

One of the guiding principles of the IMS III Trial was rapid initiation of thrombolytic therapy to an eligible subject to provide maximal benefit. To minimize any delay in the administration of IV t-PA, a proven effective therapy, the standard dose of IV t-PA (0.9 mg/kg; 90 mg maximum) could be initiated prior to randomization. In addition, the IV t-PA could be initiated in a patient who could not provide informed consent for the study and for whom legally authorized representative was not yet available (as part of standard of care). Randomization was performed at any time prior to completion of 40 minutes of the IV t-PA infusion (approximately two-thirds of the 0.9 mg/kg dose). This allowed time to complete the determination of trial eligibility, confirm interventional staff availability, obtain consent from patient and/or legal representative, and obtain the randomization assignment. If the patient and/or legal representative could not provide informed consent for participation or the subject could not be successfully randomized into the trial prior to completion of 40 minutes of IV t-PA infusion, the remainder of the 0.9 mg/kg standard dose of t-PA was completed within the one hour as part of standard of care. This patient would not be included as a participant in the IMS III Trial. A subject was considered to be in the IMS III Trial only when the sealed randomization envelope was opened. If the patient was randomized to the IV t-PA alone group, he/she received the remaining full dose (0.9 mg/kg, 90 mg max) of IV t-PA over an hour, as per the FDA-approved standard of care. If the patient was randomized to the endovascular group, the IV t-PA infusion was stopped at 40 minutes, and the subject was taken to cerebral angiography at the hospital where the IV t-PA was initiated or transferred to a participating tertiary care hospital where the angiography was performed.

Subjects were randomized in a 2:1 ratio with more subjects assigned to the endovascular group. This randomization regimen was chosen based on pilot data suggesting a higher rate of favorable clinical outcome in the endovascular group in the IMS I and II trials as compared to comparable historical controls from the NINDS t-PA Stroke Trial. In addition, this randomization

scheme added to the ongoing interventional experience of neuro-interventionalists in the IMS III trial.

Design and implementation of the randomization scheme was conducted by the Data Coordination Unit (DCU) at the Medical University of South Carolina. The randomization scheme used a combination of minimization and biased coin methodology to ensure a 2:1 (endovascular: IV alone) treatment group distribution within each baseline NIHSS score stratum (≤19 or ≥20), each performance site, and throughout the overall study. The implementation of randomization used the "step-forward" method[8] as follows. First, randomization assignments were individually placed in a sealed envelope with a subject identification number (randomly selected), and appropriate number of envelopes were distributed to each clinical site, with one of the envelopes having a "USE NEXT" label on it. When the first eligible subject at a site was ready to be randomized, the "USE NEXT" envelope was opened and the patient treated according to the treatment assignment. Within 8 hours of this subject's randomization, the site entered the required subject data into the web-based study database. The computer algorithm imbedded into the study database then provided the site with the subject ID number to be assigned to the next future eligible subject at that site. The site personnel then placed another "USE NEXT" label on the corresponding envelope. When the next eligible patient was ready to be randomized, the study personnel simply retrieved that envelope and opened it to discover the treatment assignment for this subject. The data entry and placing of the "USE NEXT" label process was repeated for subsequent eligible patients at that site. This system was designed to allow for rapid randomization since it does not require a phone call, fax back system, or access to a website prior to treatment.

Treatments

<u>IV-only group</u>

Subjects randomized to the IV t-PA group received IV t-PA at a dose of 0.9 mg/kg over an hour with 10% as a bolus.

Endovascular group

In Amendment 1-4 of the IMS III Trial, subjects randomized to the endovascular group received the IV t-PA bolus and infusion as per the standard dose but had the IV t-PA infusion stopped at 40 minutes. After Amendment 5, subjects in the endovascular group received the entire standard t-PA dose over an hour. Subjects in the endovascular group were taken for angiography as quickly as possible after randomization.

It was expected that the artery puncture would occur shortly following completion of the IV t-PA administration, but it could be also initiated during the IV t-PA infusion. If no treatable occlusion was demonstrated on angiography, the procedure was terminated. If a major arterial occlusion was demonstrated and the decision was made to deliver intra-arterial therapy, 2000 units of IV heparin were administered. Concurrently, an IV heparin infusion was started and maintained at a rate of 450 units per hour during intra-arterial therapy. The heparin infusion was discontinued at the end of the procedure. The guide catheter used for introducing the microcatheter into the target vessel was connected to a continuous heparinized saline flush which was recommended to be maintained at approximately 30 cc/hour until removal at the end of the procedure, except for during the intra-arterial t-PA study drug infusion The recommended heparin concentration for all intra-arterial flush solutions was 1 unit/cc 0.9% normal saline. The total IV and intra-arterial heparin administered (minus the IV bolus) during the interventional procedure was approximately 540 units / hour.

After reviewing the location and extent of the thrombus, the tortuosity of the arterial system, and the presence of proximal arterial stenosis or occlusions, the study neurointerventionalist chose

the intervention to initiate (i.e., embolectomy therapy with the Merci® Retriever or Penumbra System™, the Solitaire™ FR Revascularization Device, t-PA infusion through the EKOS MicroSonic® SV Infusion System , or intra-arterial delivery of t-PA).

Intra-arterial t-PA Via Microcatheter

For subjects who were treated initiated with the standard microcatheter infusion of t-PA, the t-PA concentration for intra-arterial administration was 0.5 mg/1 ml solution (50 mg/100 cc - reconstitute with 50 cc of sterile water without preservatives and dilute to 100 cc total with 50 cc normal saline). A maximum intra-arterial dose of 22 mg was administered over two hours of infusion. Arterial occlusive lesions treated in this fashion will include distal internal carotid artery (ICA), middle cerebral artery segments (M1 and M2), anterior cerebral artery segments (A1 and A2), posterior cerebral artery (PCA), superior cerebellar artery (SCA), vertebral and basilar arterial occlusions, and more proximal occlusions that could not be treated with other devices available at that point in the trial. Following introduction of the microcatheter, 1 mg of t-PA was hand injected, at low pressure, over 2 minutes distal to the thrombus. The microcatheter was retracted just proximal into the proximal thrombus. An additional 1 mg t-PA was slowly hand injected at low pressure over 2 minutes immediately followed by infusion at the rate of 10 mg/hr via low pressure hand infusion or the preferred route using an infusion pump or syringe pump set at the rate of 20 cc/hr (no filter was required). Angiographic assessment and documentation of the occlusion was conducted every 15 minutes after the start of the IA drug infusion.

EKOS MicroSonic® SV Infusion System

Primary occlusions identified in the following vessels were not treated with the EKOS MicroSonic® SV Infusion System Catheter: 1) ACA; 2) SCA; 3) posterior inferior cerebellar artery (PICA); 4) anterior inferior cerebellar artery (AICA); or 5) occlusions due to other etiologies or suspected etiologies that prevent the safe passing of a micro-guidewire and

catheter through the occlusive lesion, such as, but not limited to, dissection, chronic atherosclerosis, vasculitis, arterial spasm, Moya-Moya, arteriopathy, fibromuscular dysplasia, will not be acceptable for treatment with the EKOS Micro-Infusion Catheter.

Following catheter preparation, under direct fluoroscopic guidance, with road-mapping technique if available, a micro-guidewire and the EKOS catheter was carefully navigated through the intracranial artery and into the occluded artery segment. The micro-guidewire must have been advanced through the occlusion. The tip of the EKOS catheter was placed into the proximal portion of the thrombus. If the micro-guidewire could not be successfully passed through the occlusive lesion or the EKOS catheter could not be safely placed into the thrombus, the EKOS catheter was removed and replaced with a standard infusion microcatheter. Alternatively in the interest of reducing time, the EKOS catheter could be placed as close as technically feasible to the thrombus (local infusion). A local infusion is an infusion in which the catheter is as close to the thrombus as physically possible, but not imbedded within the thrombus. Subjects received a maximum of 22 mg of t-PA administered as a 2 mg slow, hand injected, low pressure bolus over 4 minutes. Drug infusion was then immediately initiated at 10mg/hr preferably using an infusion pump or syringe pump via the EKOS catheter for up to 120 minutes. The infusion was at a rate of 20cc/hour (10mg/hour) in the presence of ultrasound, which was activated upon initiation of t-PA infusion through the EKOS catheter. During intra-arterial study drug infusion, the catheter tip was to remain positioned within the proximal portion of the thrombus. Every effort was made to ensure that the catheter tip is within the thrombus both at the initiation of infusion and at the 15 minute interval angiographic assessments. If at the time of angiogram assessment complete lysis had not occurred, the micro-guidewire could be passed to and fro through the thrombus for mechanical disruption at these intervals.

Merci® Retriever

The following vascular lesions were excluded from treatment with the Merci® Retriever per the MERCI Trial:[9] (1) the presence of dissection that precludes safe passage of the microcatheter; (2) significant (> 50%) atherosclerotic stenosis or occlusion of the proximal common, proximal ICA, or vertebral artery that will obstruct retrograde extraction of the thrombus; (3) prominent vessel tortuosity. If the Merci® Retriever was chosen, per the IMS III Trial protocol, the operator was limited to no more than six total retrieval attempts in the same vessel. The number of passes per individual device model must not have exceeded the Instructions For Use (IFU) specifications. Prior to initiation of device deployment, but after placement of the device microcatheter, a pre-treatment guide-catheter arteriogram must have been performed with the device catheter in place to confirm arterial occlusion and appropriate catheter placement. An angiogram assessment was to be obtained after each pass of the Merci® Retriever. Following completion of the final pass with the Merci® Retriever, if time permitted, standard microcatheter infusion of t-PA could be used in the following circumstances : (1) incomplete or no recanalization demonstrated following completion of attempted thrombus removal via the Merci® Retriever; or (2) angiographically demonstrated and clinically significant distal emboli. Intra-arterial t-PA could be administered in up to two 2 mg boluses delivered over 4 minutes prior to or during the use of the Merci ® Retriever. After the final Merci® pass the remaining IA dose could be administered according to the standard protocol for IA infusion outlined above, but the infusion must have been completed within two hours of the initiation of treatment with the Merci® Retriever.

Penumbra System™

Primary occlusions identified in the following vessels were suitable for treatment with the Penumbra System™: internal carotid artery, middle cerebral artery [M1 or M2], vertebral and basilar arteries, or other appropriately sized vessels at the neurointerventionalist's discretion. Prior to beginning thrombus aspiration, but after placement of the reperfusion catheter, a pre-

treatment guide-catheter arteriogram was performed with the reperfusion catheter in place to confirm arterial occlusion and appropriate catheter placement. An angiogram assessment was obtained at least every 15 minutes after beginning aspiration up to a total allowed time of 120 minutes of use of the Penumbra System™ (see IFU). Intra-arterial t-PA bolus(es) could be administered, at the discretion of the treating neurointerventionalist, prior to the initial aspiration attempt or between any subsequent thrombus aspiration attempt(s) as follows: a maximum of two 2 mg boluses could be administered for a total dose not to exceed 4 mg. Following completion of thrombus aspiration with the Penumbra System™, if time permitted, standard microcatheter infusion of t-PA could be used in the following circumstances: (1) incomplete or no recanalization demonstrated following completion of attempted thrombus aspiration via the Penumbra System™; or (2) angiographically demonstrated and clinically significant distal emboli. Intra-arterial t-PA could be administered according to the standard protocol for IA infusion outlined above but the infusion must be completed within two hours of the initiation of treatment with the Penumbra System as described above for the Merci® Retriever.™

Solitaire Stent Revascularization Device

The Solitaire™ FR Revascularization Device could be used for clot removal by operators familiar with device description, materials required for use, indications, contraindications, potential complications, and warnings included in device IFU. Use of the Solitaire™ Device was contraindicated under the following circumstances: 1) patients with hypersensitivity to nickel-titanium; 2) patients with stenosis proximal to the thrombus site that may preclude safe recovery of the Solitaire™ device; 3) patients with angiographic evidence of carotid or vertebral artery dissection. If the Solitaire™ device was used, the operator was limited to no more than three total recovery attempts in the same vessel. The operator was not to use a Solitaire™ device for more than two flow restoration recoveries. After placement of the device microcatheter, but prior to device deployment, a pre-treatment guide-catheter arteriogram was performed with the

device catheter in place to confirm arterial occlusion and appropriate catheter placement. An angiogram assessment was obtained after each pass of the Solitaire™ device(s). Intra-arterial t-PA could be administered in up to two 2mg boluses delivered over 4 minutes prior to or during the use of the Solitaire™ device. Following completion of the final pass with the Solitaire™ device, if time permitted, standard microcatheter infusion of t-PA could be used in the following circumstances: (1) incomplete or no recanalization demonstrated following completion of attempted thrombus removal via the Solitaire device; or (2) angiographically demonstrated and clinically significant distal emboli. If such circumstances existed, the remaining intra-arterial dose could be administered according to the standard protocol for intra-arterial infusion outlined above but the infusion must have been completed within two hours of the initiation of treatment with the Solitaire™ device.

Termination of the endovascular treatment procedure occurred for the following reasons: 1) angiographic demonstrated mass effect that may not be explained by early edema; 2) suspicion of extravasation of contrast suggesting vessel rupture; 3) CT demonstration of hemorrhage (i.e., for a subject who deteriorated and the procedure is interrupted for a CT, the procedure could be re-started if the CT showed no hemorrhage and if time permitted); 4) worsening of clinical deficit that was not explained by angiographic findings; 5) seizure; 6) achievement of TICI 2b or 3; 7) 120 minutes of intra-arterial infusion of t-PA or combined treatment had occurred or 8) time had reached 7 hours from symptom onset. In addition to these criteria for stopping the endovascular procedure, investigators were allowed to apply clinical judgment in determining when to stop IA therapy based upon the perceived risks and benefits.

General Medical Management in IMS III Subjects

Except for the heparin administered as part of the intra-arterial procedure to subjects randomized to the endovascular group, administration of heparin, oral anticoagulants, or

antiplatelet agents \was prohibited for the first 24 hours until after the safety CT scan had been performed. Subjects who had a likely cardioembolic source could be started on IV heparin 24 hours following onset of symptoms and after the safety CT, but in general, heparin use, except for prevention of deep vein thrombosis was discouraged. Prior to initiation of heparin, either a CT scan or MRI had to be performed. Other drug therapy was at the discretion of the treating physician.

As in the IMS I and II Pilot Studies, medical management of subjects enrolled into the study followed the current AHA guidelines for acute stroke therapy.[2] This includes monitoring of vital signs and neurologic functions, management of intracranial hemorrhage and bleeding complications, management of blood pressure, blood sugar, fever, and angioedema, prevention of deep venous thrombosis, swallowing evaluation, and institution of anti-thrombotic therapy and statins as appropriate. While the practice among clinical sites regarding the use of anesthesia, intubation, sedation, etc. was addressed with the IMS III Trial investigators, and conscious sedation during the interventional procedure was considered preferable, a standardized protocol addressing subject sedation management was not mandated. Anesthesia, intubation, and sedation were dictated by physician clinical judgment and standard institutional operating procedure at each clinical center.

Training of IMS III Investigators

Outcome Assessments

All IMS III investigators had to be trained and certified in the performance of the NIHSS and mRS by review of training videos and subsequent completion of a test to validate competence. Certification for the NIHSS and mRS was done prior to entry of subjects into the Trial at the respective sites and re-certification of the NIHSS was required at least every two years. Re-certification of the mRS was required within one year of the date stated on the certificate itself.

Once two exams have been provided the certification is considered completed with no additional certification required.

Requirement for Training and Experience for Study Interventionalists

All neuro-interventionalists listed on FDA 1572 must have met the following credentialing guidelines by training and experience.

1) Successful completion of an accredited residency (Board Eligible [BE] or Board Certified [BC]) in Diagnostic Radiology which includes four years of experience, training, and supervision in diagnostic neuro-imaging and completion of a one year post-graduate fellowship in Neuroradiology in an accredited program, or an equivalent.

OR

2) Successful completion of an accredited residency (BE or BC) in Neurosurgery which includes five years of experience, training, and supervision in diagnostic neuro-imaging.

OR

3) Successful completion of an accredited residency (BE or BC) in Neurology which includes three years of experience, training, and supervision in diagnostic neuro-imaging and completion of a one year post-graduate fellowship in Vascular Neurology.

AND

4) Experience and training in cerebral angiography performance and interpretation to serve as the prerequisite year for Advance Training. This experience should include performance and interpretation of 100 cerebral angiogram procedures as primary operator, with indications, success, and complications detailed according to published Quality Improvement Guidelines.

AND

5) Minimum one year fellowship in Endovascular Surgical Neuroradiology that meets and/or reflects the training requirements for performance and interpretation set forth by a national

multidisciplinary council and the ACGME. This experience should include at least ten intra-arterial intracranial thrombolysis procedures.

In the absence of formal advanced training as detailed above, qualifying training and experience would include all of the following:

1) Successful completion of an accredited residency (BE or BC) and completion of a one year post-graduate fellowship in an accredited program, or equivalent.

2) Experience and training in cerebral angiography performance and interpretation in an approved program. This experience should include performance and interpretation of 200 cerebral angiogram procedures, with indication, success, complications detailed, according to published Quality Improvement Guidelines.

3) Participation in 50 endovascular surgical neuroradiology procedures under the supervision of a director who otherwise qualifies as a Program Director under the Program Requirements for Residency Education in Endovascular Surgical Neuroradiology, and performance of 50 endovascular surgical neuroradiologic procedures as primary operator, with record of indications, success, complications, according to the published Standards of Practice of the American Society of Interventional and Therapeutic Neuroradiology (ASITN), including at least 10 intra-arterial thrombolysis procedures.

Interventionalist credentialing assumed capability to perform microcatheter thrombolysis. Interventionalists did not need to be credentialed for use of all devices; however, interventionalists could not use a device that he/she was not credentialed to use. Interventionalists were instructed to use devices as per training and instructions for use. To be eligible to use a given IMS III-approved device within the IMS III Trial, the interventionalist must have provided documented experience with the device; or if no documented prior experience, the Interventionalist must have attended and successfully completed a training Course in the

use of the device and then subsequently performed and documented 2 patient treatments outside of the IMS III Trial. The Clinical Principal Investigator (J. Broderick) and the Principle Neurointerventionalist (T. Tomsick) of the IMS III Trial reviewed the credentials and documented experience of all interventionalists in the Trial prior to acceptance as a treating trial investigator.

Outcome Assessment

Clinical Efficacy Outcomes

Clinical outcomes were assessed by the modified Rankin Score (mRS), the NIHSS, the Barthel Index,[10] Trail Making Test[11] Parts A and B, and the EuroQol EQ-5D. The primary outcome measure of the IMS III Trial was a mRS ≤ 2 (slight or no disability, i.e. functionally independent) at 90 days. The mRS score is a measure of disability and functional status after stroke that ranges from 0 = no symptoms to 5 = severe disability, bedridden.[12] For outcomes in clinical trials, death is assigned a score of 6. A mRS score ≤ 2 is more suited to studies of moderate to severe stroke as demonstrated by the PROACT II[13] and IMS I[6] and II[5] Pilot Studies. In addition, the modified Rankin Scale (mRS)[12] to ascertain the subject's functional status prior to the qualifying stroke (pre-event) was obtained at baseline.

The NIHSS, a serial measure of neurologic deficit, is a 42-point scale that quantifies neurologic deficits in 11 categories. For example, a mild facial paralysis is given a score of 1, and complete right hemiplegia with aphasia, gaze deviation, visual field deficit, dysarthria, and sensory loss is given a score of 25. Normal function without neurologic deficit is scored as zero. The National Institutes of Health Stroke Scale (NIHSS) assessment [14, 15] was performed in every subject immediately prior to initiation of IV t-PA, following 40 +/- 5 minutes of IV t-PA infusion, at 24 +/- 6 hours, at 5 +/- 1 day or discharge from hospital, 90 +/- 14 days after the stroke. The 24-hour NIHSS examiner was was to be blinded to the 24 hour CT scan results.

The Barthel index is a reliable and valid measure of the ability to perform activities of daily living such as eating, bathing, walking, and using the toilet. Patients able to perform all activities with complete independence are given a score of 100 and those unable to do any tasks are scored a 0. The Barthel Index was a secondary clinical outcome measure at 90 days. An excellent outcome on the Barthel was dichotomized as in prior stroke reperfusion trials as a score of 95-100.

The EuroQol EQ-5D[16] provides a simple descriptive profile of health in five dimensions (mobility, self-care, social, pain, and psychological), each with three levels and has been used in many stroke studies previously. The patient's health state can be classified into one of 243 (3^5) theoretically possible health states, each of which has been assigned a utility (i.e., value to the patient). The EuroQol EQ-5D also includes a visual analogue scale on which patients rate their own health between 0 and 100, thereby providing an overall numeric estimate of their health-related quality of life. Baseline Resource Utilization and EuroQol EQ-5D were obtained at day 5 or discharge to allow for maximum cognitive ability and participation by the stroke subject. The EuroQol EQ-5D was also a secondary outcome measure at 90 days.

Finally, the Trail Making Test[11] Parts A and B was also measured at 90 days. This test is a brief evaluation designed to assess executive function and attention. A mRS, a resource utilization survey and EuroQol EQ-5D was also obtained at 3, 6, 9, and 12 months (+/- 14 days) for the economic analysis.

All 90-day outcome assessments were to be performed by study investigators who were not directly involved with acute treatment of the subject and who were blinded to treatment assignment. Subjects were instructed not to discuss their initial hospitalization and treatment. All investigators were certified and maintained certification for the NIHSS and mRS during the

study and also received standardized training regarding the Barthel, Trail Making Test Parts A and B, and EuroQol EQ-5D assessments. Each blinded examiner, as the final act of blinded assessment, indicated whether they believe the subject was in the endovascular group or IV t-PA alone group to allow assessment of blinding.

Safety Outcomes

The primary measures of safety were mortality within 90 days and the presence of symptomatic intracerebral hemorrhage (ICH) within 24 (+/- 6) hours of randomization. Symptomatic ICH is defined as an intracranial hemorrhage temporally related to a decline in neurological status as well as new or worsening neurologic symptoms *in the judgment of the clinical investigator* and which may warrant medical intervention. A 4 or more point increase in the NIHSS score from baseline to subsequent CT scan at the time of potential worsening could be used as a guide by the clinical investigator for what represents a significant change in neurologic status. The final judgment by the clinical investigator could include any worsening deemed significant. The Internal Safety Monitor also reviewed every case of intracranial hemorrhage and could request a written clinical summary or clinical data to determine independently whether the hemorrhage is symptomatic or asymptomatic.

Other measures of safety included: the incidence of parenchymal Type II (PH2) hematomas and any asymptomatic ICH as determined by a standard head CT scan obtained within 24 (+/- 6) hours as determined by central review by the imaging center at the University of Calgary; incidence and severity of non-intracerebral bleeding complications; incidence and severity of non-bleeding serious adverse events; changes in laboratory parameters (i.e. hemoglobin and hematocrit) from baseline to 5 day or discharge; the incidence of blood and/or blood products transfusion of 3 or more units, changes in laboratory parameters (serum creatinine) from baseline to 5 days or discharge, and the incidence and severity of procedure- and device-

related complications. Device-related complications were defined as vascular perforation, dissection, or embolization of a previously uninvolved territory. Procedure-related complications were defined as device related complications in addition to any other complication judged by the interventionalist to be related to the procedure (e.g., clinically significant groin complications). An external Neurointerventionalist Medical Monitor was the final adjudicator for disagreements between the Internal Medical Monitor and site investigator regarding device and procedure related events.

CT and CT Angiography Assessment and Outcomes

CT scans were done at baseline, at 24 +/- 6 hours, and for change in subject condition (safety CTs). However at sites where MR imaging was the standard baseline imaging and the performance of a CT scan necessitated a delay in treatment, an MR was acceptable with prior approval. In addition, a CT angiogram of the intracranial vasculature was performed at baseline at those study sites that routinely used this as part of their baseline imaging. CT angiography was done on all subjects at the time of the safety CT at 24 hours to assess vascular patency. For those subjects who were allergic or unable to tolerate addition contrast dye, MR angiography could be substituted.

A consensus panel of 3 CT reading experts (one neuroradiologist was mandatory for each panel) at the University of Calgary IMS III Imaging Center reviewed all images (baseline CT, change in clinical condition CT, 24 hour follow-up CT) blinded as to treatment group. This panel was responsible for determination of the following: a description of the quality of the study, presence or absence of an infarct, the arterial distribution of the infarct, digital measurement of the cerebral infarct volume, the presence or absence of hemorrhage and type of hemorrhage, measurement of volume of any intracerebral hematoma, categorization of early CT findings (including ASPECTS scoring of early CT changes),[17] dense artery signs as per NINDS Study,[18]

and presence or absence of white matter disease (Van Swieten Scale).[19] The ASPECTS score assesses systematically each of ten regions on the CT scan and assigns a score of 1 for a normal, and 0 for a region showing signs of ischemia. Signs of ischemia are defined as x-ray hypoattenuation, loss of the grey-white boundary (which is due to x-ray hypoattenuation of the grey matter), and/or effacement of cortical sulci. The ASPECTS is only scored for early ischemic changes. The slices are subdivided into two levels: subcortical structures (lentiform nucleus, caudate nucleus and internal capsule – genu and posterior limb only) and cortical structures (insular cortex, M1 through M6 above the level of the head of caudate). In practice all slices of the CT scan are evaluated to rate the ASPECTS.

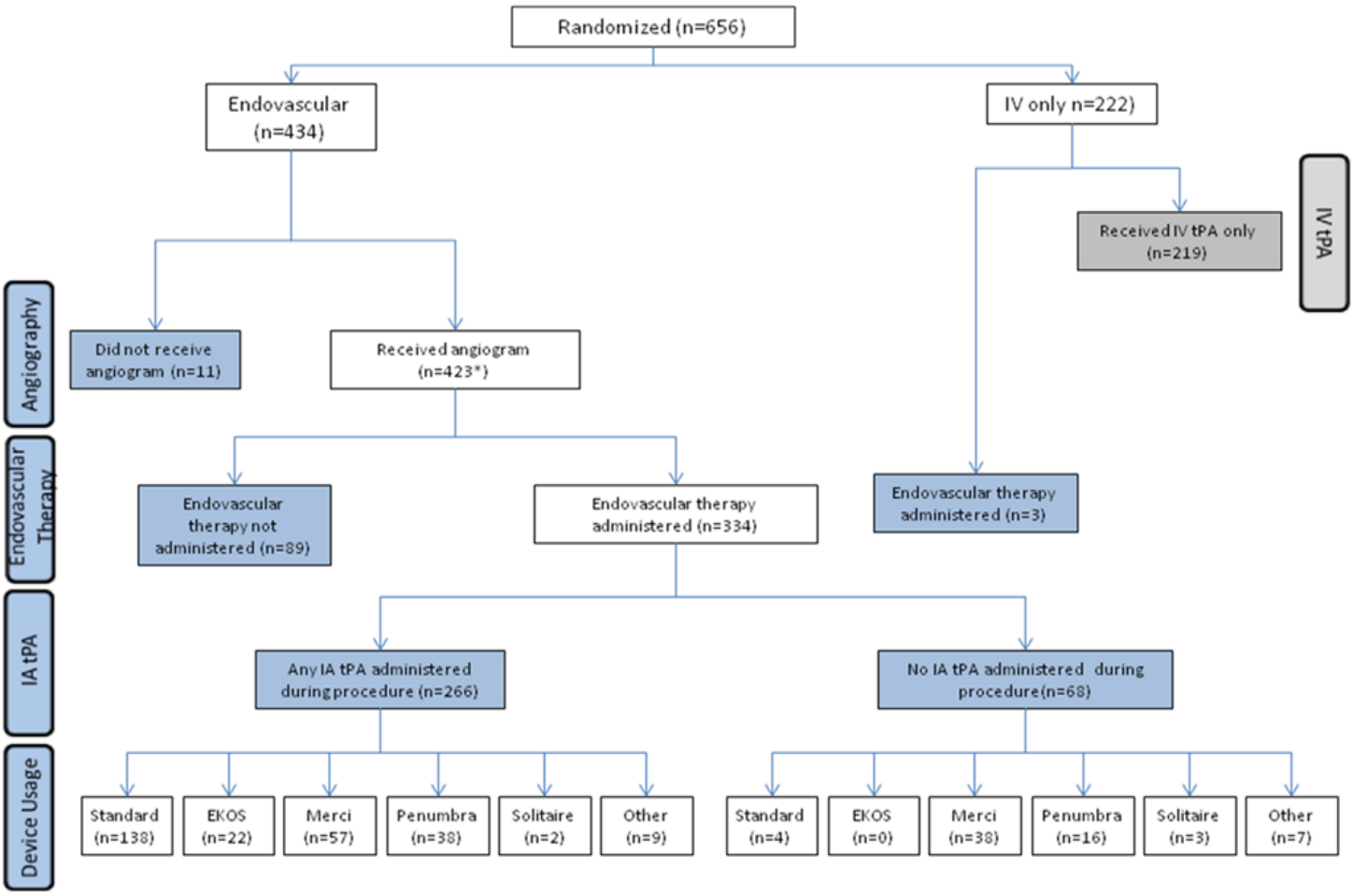
ICHs were subclassified radiographically according to the method used by Dr. Von Kummer and colleagues in the ECASS Trials and in the IMS I Pilot Study (See Supplemental Table 3).[20] The consensus panel of 3 CT reading experts also evaluated the baseline and 24-hour CT angiogram for the occlusions or partial occlusions of the intracranial ICA, MCA, ACA, PCA, vertebral, and basilar arteries. The CT angiogram was read prior to the reading of the CT of the brain to maintain blinding (presence of persisting contrast on 24 hour CT scan in endovascular group).

Angiographic Assessment and Outcomes

All angiograms were collected and assessed for completeness of the angiographic procedure at the University of Cincinnati Angiographic Center by Dr. Thomas A. Tomsick. Dr. Tomsick performed the initial angiographic assessment and reviewed the angiographic data for any safety concerns or protocol deviations. Dr. David Liebeskind at UCLA subsequently reviewed the same angiographic data to provide a second independent assessment of the following vessels pre- and post-treatment. Each artery was classified pre-intra-arterial treatment as shown in Supplemental Table 4. Angiographic outcome was evaluated for both recanalization

of the original primary arterial occlusive lesion (AOL) during and after therapy, as well as for global perfusion post-treatment using the Thrombolysis in Cerebral Infarction or TICI score (Supplemental Table 4),[21] All disagreements in the location of arterial occlusion as well as recanalization and reperfusion grades were adjudicated by review of those cases by both raters.

3) SUPPLEMENTAL FIGURE 1: DIAGRAM OF SUBJECT ACCOUNTABILITY



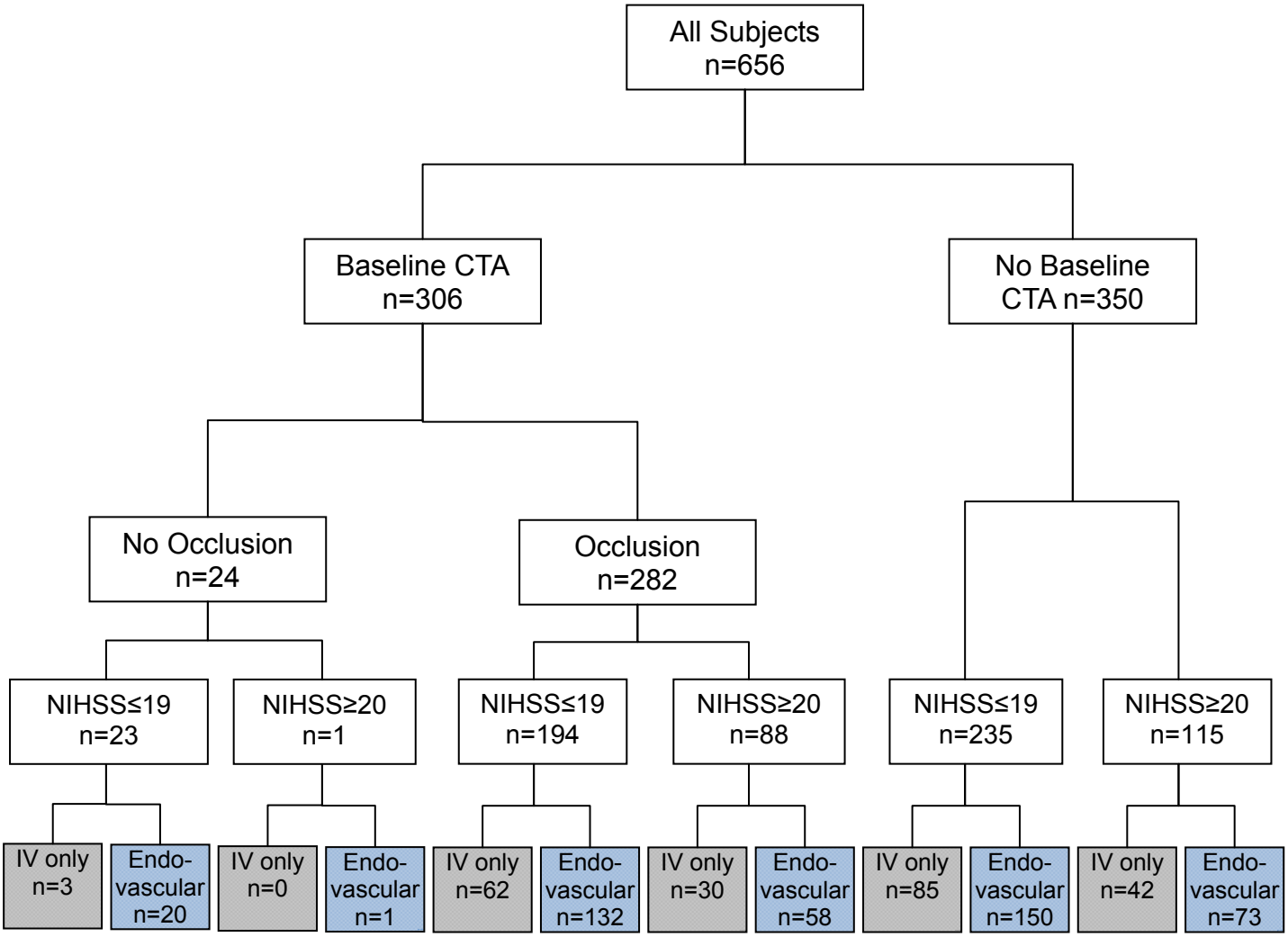
Legend – (S) Figure 1: *Includes 1 subject treated with endovascular therapy but with no available angiogram data.

"Standard" refers to use of a standard microcatheter alone where the intention was to administer intra-arterial t-PA as the primary intervention. Four patients in the Standard category did not receive intra-arterial t-PA for the following reasons: vessel perforation and extravasation with microcatheter manipulation (1), difficult microcatheter access delaying intra-arterial t-PA therapy beyond protocol defined 5 hours (1), standard microcatheter mechanically disrupted the thrombus and no intra-arterial t-PA required (1), and uncontrollable hypertension led to termination of procedure (1).

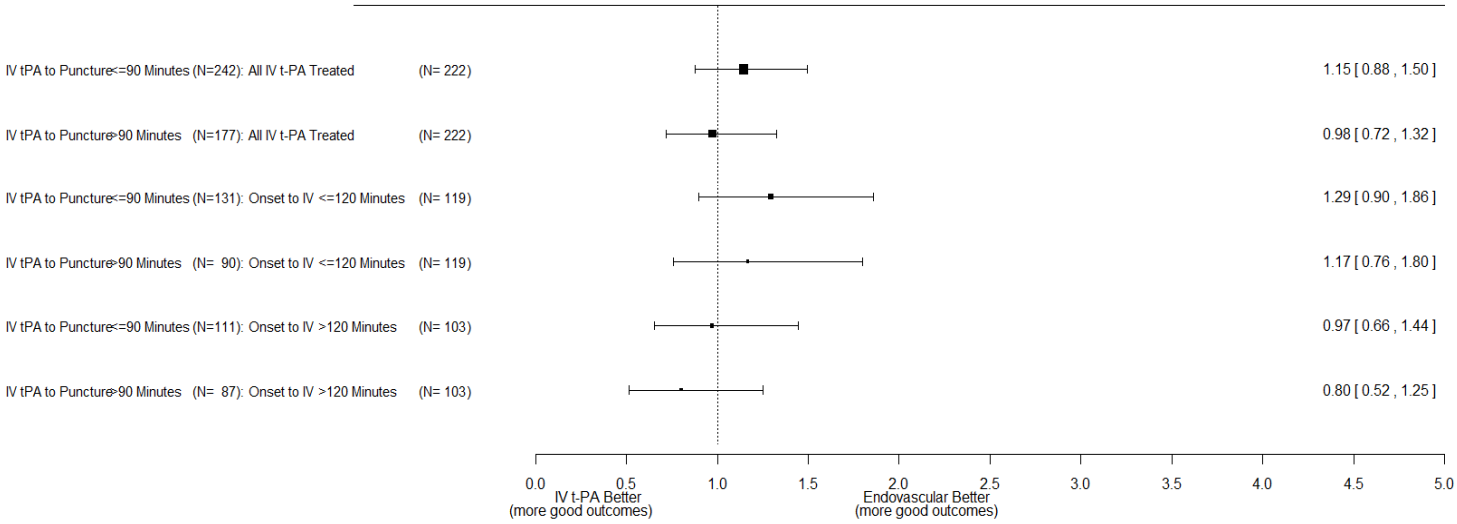
"Other" includes 16 subjects treated with endovascular treatments outside of defined protocol: Solitaire, Penumbra, and intra-arterial t-PA (4), Solitaire and Penumbra (2), Solitaire and Merci (1), Trevo and intra-arterial t-PA (1), Penumbra, Trevo and intra-arterial t-PA (1), Penumbra, Merci and intra-arterial t-PA (2), Penumbra system followed by Merci Retriever (1), Merci, intra-arterial t-PA, and aspiration through catheter (1), EKOS and Penumbra (1), intra-arterial t-PA and penumbra catheter with manual suction (1), and intra-arterial t-PA and then Merci (1).

Reasons that the 11 subjects in the endovascular group did not have an angiogram include: major clinical deterioration (1), large area of developing infarct on repeat CT (1), major improvement after IV t-PA (2), inadvertent overdose of IV t-PA - 100 mg – (1), failure to begin groin puncture and endovascular treatment within protocol-defined 5 hours (2), MRA showed open major arteries (1), CTA showed very tight stenosis in symptomatic ICA which was deemed by investigator to require angioplasty and would result in protocol violation (1), identification that patient did not meet inclusion/exclusion criteria after randomization (1), and randomization error (1). Reasons that the 89 subjects in the endovascular group who had an angiogram but did not receive endovascular therapy include: no thrombus deemed treatable by endovascular therapy by site investigator N = 80 with an additional 9 subjects not receiving treatment for the following reasons: inability to safely access occlusion (3), recanalization during angiogram (2), occlusion thought not responsible for clinical presentation (2), and no documented reason (2). Upon central review of the 80 subjects deemed no thrombus treatable: 33 no thrombus seen, 34 with thrombus deemed not treatable by endovascular therapy, 12 with treatable thrombus, and one with missing reason.

4) SUPPLEMENTAL FIGURE 2: SUBJECT ENROLLMENT BY CT ANGIOGRAPHY (CTA) AND BASELINE NIHSS STRATA



5) SUPPLEMENTAL FIGURE 3: ADJUSTED* RELATIVE RISK FOR PREDEFINED SUBGROUPS (ENDOVASCULAR: IV T-PA ONLY) OF 90-DAY MRS



Legend – (S) Figure 3: * Adjusting for age (continuous), baseline NIHSS cohort, time from onset to IV t-PA initiation (continuous)

5) SUPPLEMENTAL TABLE 1: INCLUSION AND EXCLUSION CRITERIA

Clinical Inclusion Criteria

- Age: 18 through 82 years (i.e., candidates must have had their 18th birthday, but not had their 83rd birthday).
- Initiation of IV t-PA within 3 hours of onset of stroke symptoms. Time of onset is defined as the last time when the patient was witnessed to be at baseline (i.e., subjects who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep).
- An NIHSSS ≥ 10 at the time that IV t-PA is begun or an NIHSSS >7 and <10 with an occlusion seen in M1, ICA or basilar artery on CTA at institutions where baseline CTA imaging is standard of care for acute stroke patients.
- Investigator verification that the subject has received/ is receiving the correct IV t-PA dose for the estimated weight prior to randomization

Clinical Exclusion Criteria

- History of stroke in the past 3 months.
- Previous intra-cranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arteriovenous malformation.
- Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal.
- Hypertension at time of treatment; systolic BP > 185 or diastolic > 110 mm Hg; or aggressive measures to lower blood pressure to below these limits are needed.
- Presumed septic embolus, or suspicion of bacterial endocarditis.
- Presumed pericarditis including pericarditis after acute myocardial infarction.
- Suspicion of aortic dissection.
- Recent (within 30 days) surgery or biopsy of parenchymal organ.
- Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.
- Recent (within 90 days) severe head trauma or head trauma with loss of consciousness.
- Any active or recent (within 30 days) hemorrhage.

- Patients with known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; or oral anticoagulant therapy require coagulation lab results prior to enrollment. Any subject with INR greater than 1.7 or institutionally equivalent prothrombin time is excluded. Patients without history or suspicion of coagulopathy do not require INR or prothrombin time lab results to be available prior to enrollment.
- Females of childbearing potential who are known to be pregnant and/or lactating or who have positive pregnancy tests on admission.
- Baseline lab values: glucose < 50 mg/dl or > 400 mg/dl, platelets <100,000, or Hematocrit <25.
- Patients that require hemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram for whatever reason.
- Patients who have received heparin or a direct thrombin inhibitor (Angiomax™, argatroban, Refludan™, Pradaxa™) within the last 48 hours; must have a normal partial thromboplastin time (PTT) to be eligible.
- Subjects with an arterial puncture at a non-compressible site or a lumbar puncture in the previous 7 days.
- Patients with a seizure at onset of stroke.
- For patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, the mRS score at baseline must be ≤ 2. This excludes patients who live in a nursing home or who are not fully independent for activities of daily living (toileting, dressing, eating, cooking and preparing meals, etc.).
- Other serious, advanced, or terminal illness.
- Any other condition that the investigator feels would pose a significant hazard to the patient if Activase/Actilyse® (Alteplase) therapy is initiated.
- Current participation in another research drug treatment.
- Informed consent is not or cannot be obtained. For example, obtunded patients are not automatically excluded from the study. However, if the next of kin or legal guardian (i.e., the

individual legally empowered in the state where the consent is obtained) cannot provide consent, randomization and entry into the study could not proceed.

Imaging Exclusion Criteria

• High density lesion consistent with hemorrhage of any degree.

• Significant mass effect with midline shift.

• Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline imaging. An ASPECTS of < 4 can be used as a guideline when evaluating >1/3 region of territory involvement. Sulcal effacement and / or loss of grey-white differentiation alone are not contraindications for treatment.

• CT evidence of intraparenchymal tumor.

• Baseline CTA without evidence of an arterial occlusion (Amendment 5 only). NOTE: The trial did not require baseline CTA imaging, if CTA was routinely performed prior to IV t-PA, information from the CTA was to be used to satisfy this exclusion.

Guidelines for Interpretation of the Inclusion/ Exclusion Criteria

The following guidelines apply to the inclusion exclusion and imaging criteria noted above.

• Subjects with no other exclusion criteria that experience unavoidable delay in start of IV t-PA could be included in the trial up to 15 minutes beyond the 3 hour onset of stroke symptoms. This was not considered as a protocol violation.

• The “correction” of baseline glucose or coagulation laboratory values to meet exclusion criteria was not allowed.

• Subjects who have taken Clopidogrel within the last 24 hours from screening for the trial were not excluded.

• Subjects who received low molecular weight heparins (such as Dalteparin, Enoxaparin, Tinzaparin) as DVT prophylaxis or in full dose within the last 24 hours from screening for the trial were excluded.

• Subject who have received GP IIb/IIIa Inhibitors within the within the past 2 weeks from screening for the trial were excluded.

• The preferred baseline imaging modality was CT scan. However, at sites where MR imaging was the standard baseline imaging and the performance of a CT scan will necessitate a delay in treatment a MRI was acceptable with prior approval from the UCCIAC.

• The performance of a CTA was not required or recommended prior to enrollment; however CTA at baseline could be performed at centers where it is standard of care for all acute strokes with prior approval from the UCCIAC.

6) SUPPLEMENTAL TABLE 2: REASONS WHY SUBJECTS WHO RECEIVED IV T-PA AT IMS III SITES WERE NOT ELIGIBLE IN IMS III

Reason	Number (Percent)
1 - Less than 18 years or greater than 82 years old.	1360 (26.1)
2 - Unable to initiate t-PA within 3 hours of onset.	302 (5.8)
3 - NIHSS of less than 10 at the time t-PA is begun.	1385 (26.6)
4 - History of stroke in the past 3 months.	25 (0.5)
5 - Previous intra-cranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arteriovenous malformation.	8 (0.2)
6 - Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal.	1 (0)
7 - Hypertension at time of treatment; systolic BP > 185 or diastolic > 110 mm Hg.	23 (0.4)
8 - Presumed septic embolus, or suspicion of bacterial endocarditis.	1 (0)
9 - Presumed pericarditis including pericarditis after acute myocardial infarction.	3 (0.1)
10 - Suspicion of aortic dissection.	7 (0.1)
11 - Recent (within 30 days) surgery or biopsy of parenchymal organ.	35 (0.7)
12 - Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.	5 (0.1)
14 - Any active or recent (within 30 days) hemorrhage.	11 (0.2)
15 - Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; or oral anticoagulant therapy.	17 (0.3)
16 - Females of childbearing potential who are known to be pregnant and/or lactating.	2 (0)
17 - Baseline lab values - glucose < 50 mg/dl or > 400 mg/dl, platelets <100,000, or Hct <25.	13 (0.3)
18 - Patients that require hemodialysis or peritoneal dialysis.	28 (0.5)

Reason	Number (Percent)
19 - Patients who have received heparin within 48 hours must have a normal partial thromboplastin time (PTT) to be eligible.	5 (0.1)
20 - Subjects with an arterial puncture at a non-compressible site or a lumbar puncture in the previous 7 days.	2 (0)
21 - Patients with a seizure at onset of stroke.	32 (0.6)
22 - Patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations.	73 (1.4)
23 - Other serious, advanced, or terminal illness.	67 (1.3)
24 - Any other condition that the investigator feels would pose a significant hazard to the patient.	93 (1.8)
25 - Current participation in another research drug treatment protocol.	44 (0.8)
26 - Informed consent is not or cannot be obtained.	315 (6.1)
27 - High density lesion consistent with hemorrhage of any degree.	6 (0.1)
28 - Significant mass effect with midline shift.	8 (0.2)
31 - No evidence of arterial occlusion on baseline CTA.	11 (0.2)
95 - Patient was excluded because of entry into a competing trial.	94 (1.8)
96 - Refused consent (or did not want to participate in research).	128 (2.5)
97 - Arrived within 3 hours but unable to randomize within 40 minutes of IV TPA initiation.	281 (5.4)
98 - Other (Not specifically categorized)	812 (15.6)
Total*	**5197**

*36 additional patients received t-PA but no reason was provided why they were not enrolled. These patients are not included in total N or percentages.

7) SUPPLEMENTAL TABLE 3: IMAGING CLASSIFICATION OF HEMORRHAGE

HI Type 1	Small petechiae along margin of the infarct
HI Type 2	More confluent petechiae within the infarcted area but without space-occupying effect
PH Type 1	Hematoma in ≤ 30% of the infarcted area with some slight space occupying effect
PH Type 2	Dense hematoma > 30% total of the infarcted area with substantial space-occupying effect or any hemorrhagic area outside the infarcted area
rPH Type 1	Small or medium sized blood clots located remote from the actual infarct; a mild space occupying effect could be present. Remote primary intracerebral hemorrhage
rPH Type 2	Large confluent dense blood clots in an area remote from the actual infarct; substantial space occupying effect might be present.

8) SUPPLEMENTAL TABLE 4: CLASSIFICATIONS OF ARTERIAL OCCLUSIVE LESION AND REPERFUSION (THROMBOLYSIS IN CEREBRAL INFARCTION SCORE OR TICI)

Baseline Classification of the Arterial Occlusive Lesions (AOL) was coded as follows

0=patent

1 = partial occlusion

2 = complete occlusion

3 = not visualized

4 = not examined

Classification of the Primary Arterial Occlusive Lesion (AOL) was coded for recanalization patency as follows:

0 = patent

1 = partial occlusion

2 = complete occlusion

3 = not visualized

4 = not examined

Classification of TICI Reperfusion was coded as follows:

Grade 0 = No reperfusion

Grade 1 = Perfusion past the initial obstruction, but limited distal branch filling with little or slow distal perfusion.

Grade 2a = Partial Perfusion of less than ½ of the vascular distribution of the occluded artery (e.g., filling and perfusion in one M2 division).

Grade 2b = Partial Perfusion of ½ or greater of the vascular distribution of the occluded artery (e.g., filling and perfusion in 2 or more M2 segments)

Grade 3 = Full perfusion in all branches of previously occluded arteries

9) SUPPLEMENTAL TABLE 5: DOSING OF T-PA AND TREATMENT TIMES

	Endovascular	IV t-PA Alone
All Randomized	434	222
All Subjects		
Total t-PA Dose, mg: mean (SD)	60.3 (14.2)	72.5 (14.3)
Endovascular Group Only		
Time from Onset to Groin Puncture, min: mean (SD)	208 (46.7)	
Received IA Therapy (%)	334 (77)	
Time from Onset to IA Therapy, min: mean (SD)	249.4 (50.6)	
Received IA t-PA (%)	266 (61.3)	
Total IV t-PA dose, mg: mean (SD)	52.1 (12)	
Total IA t-PA dose, mg: mean (SD)	13.3 (6.7)	

10) SUPPLEMENTAL TABLE 6: CUMULATIVE SERIOUS ADVERSE EVENTS BY BODY SYSTEM AND TREATMENT GROUP

	Endovascular (%)	t-PA Alone (%)	RR	RR 95% CI
Total Subjects	434	222		
All Systems	256 (58.9)	126 (56.7)	1.04	0.90, 1.19
Blood and lymphatic system disorders	6 (1.4)	6 (2.7)	0.51	0.17, 1.57
Cardiac disorders	45 (10.3)	22 (9.9)	1.05	0.65, 1.70
Congenital, familial and genetic disorders	4 (0.9)	2 (0.9)	1.02	0.19, 5.54
Eye disorders	1 (0.2)	0 (0)		
Gastrointestinal disorders	17 (3.9)	5 (2.3)	1.74	0.65, 4.65
General disorders and administration site conditions	15 (3.5)	6 (2.7)	1.28	0.50, 3.25
Hepatobiliary disorders	1 (0.2)	0 (0)		
Immune system disorders	1 (0.2)	0 (0)		
Infections and infestations	39 (9.0)	29 (13.0)	0.69	0.44, 1.08
Injury, poisoning and procedural complications	23 (5.3)	9 (4.1)	1.31	0.62, 2.78
Investigations	9 (2.1)	2 (0.9)	2.30	0.50, 10.56
Metabolism and nutrition disorders	5 (1.2)	4 (1.8)	0.64	0.17, 2.36
Musculoskeletal and connective tissue disorders	4 (0.9)	2 (0.9)	1.02	0.19, 5.54
Neoplasms benign, malignant and unspecified (including cysts and polyps)	4 (0.9)	1 (0.5)	2.05	0.23, 18.19
Nervous system disorders	128 (29.4)	69 (31.0)	0.95	0.74, 1.21
Psychiatric disorders	11 (2.5)	6 (2.7)	0.94	0.35, 2.50
Renal and urinary disorders	7 (1.6)	3 (1.4)	1.19	0.31, 4.57
Reproductive system and breast disorders	1 (0.2)	0 (0)		
Respiratory, thoracic and mediastinal disorders	49 (11.2)	26 (11.7)	0.96	0.62, 1.51
Skin and subcutaneous tissue disorders	1 (0.2)	1 (0.5)	0.51	0.03, 8.14
Surgical and medical procedures	20 (4.6)	10 (4.5)	1.02	0.49, 2.15
Vascular disorders	28 (6.5)	14 (6.3)	1.02	0.55, 1.90
Uncoded	3 (0.7)	2 (0.9)	0.77	0.13, 4.56

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