Endovascular Treatment of Acute Ischemic Stroke

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Endovascular Treatment of Acute Ischemic Stroke
Endovasculaire behandeling van acuut herseninfarct

Thesis

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CHAPTER 1

Introduction

INTRODUCTION

Patients with acute ischemic stroke (AIS) present with a sudden loss of neurological function caused by an obstruction in blood flow to a part of their brain. The resultant symptoms are dependent on the location of the occlusion and the eloquence of the brain tissue being supplied downstream. While the rate of neuronal loss in patients with an occlusion of the M1 segment of the middle cerebral artery has been quantified on average to be approximately 2 million neurons per minute (1), it is highly variable between different patients (2).

It has been known for a long time that early and efficient revascularization of the occluded vessel can stop further neuronal loss and reverse the neurological symptoms partly or completely. The underlying principle to explain this was first described by Astrup et al. through a concept of core and penumbra (3). After an acute intracranial occlusion, there starts to develop a core of the infarct which is tissue that is dead and is not going to reverse even with restoration of blood flow, while the penumbra is tissue that is ischemic and non-functioning (contributing to the neurological symptoms) but still alive and likely to die if blood flow is not restored. This penumbral tissue is salvageable and is the target for revascularization therapies. After arterial occlusion, there can be temporal growth of the ischemic core into the penumbral area that is modulated by leptomeningeal collateral blood flow, the key element setting the pace of the ischemic process (Figure 1) (4). Patients with a large vessel occlusion (LVO) present with highly variable ischemic core and penumbra after a given time interval from onset providing evidence for variable collateral circulation (5).

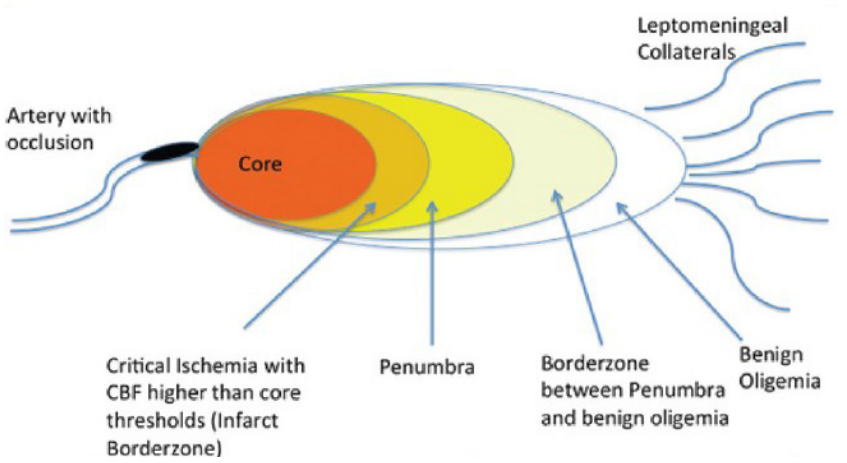

Figure 1. Schematic shows regions beyond an arterial occlusion with border zones among core, penumbra, and benign oligemia. These regions evolve over time and with continued occlusion, penumbra will slowly convert into core. The rate of penumbra dying is related to the degree of decrease in blood flow which in turn is related to the robustness of collaterals. It is likely that other factors (e.g. blood glucose, blood pressure) may also play a role.

Several imaging techniques like CT Perfusion and Perfusion Weighted MRI for measurement of the volume of core and penumbra have been developed. However, accurate measurement especially in a patient suffering from an acute stroke and within a short period of time remains a challenge. In addition, there is lack of standardization of post-processing software with significant variation of results based on what software is used (6, 7).

Thrombolysis

In 1976, a pilot study with intravenous urokinase (initially discovered in 1947), dosed according to body weight, and using angiography to document intracranial occlusion for some but not all patients, showed the intravenous urokinase was an effective thrombolytic agent but associated with an increase in intracranial hemorrhage (ICH) and no clinical improvement (8). In 1957, streptokinase was shown to be effective in thrombolysis of

peripheral emboli. Subsequently, streptokinase was evaluated in 40 stroke patients who were treated within 72 hours of stroke onset with infusions over 3 days (9). There was no significant improvement in clinical outcome and increased rate of ICH (10). About 30 years later streptokinase was evaluated again in the setting of acute ischemic stroke in multiple trials, including the Multicenter Acute Stroke Trial- Europe (MAST-E); Multicenter Acute Stroke Trial- Italy (MAST-I) and the Australian Streptokinase Study (11, 12). None of the trials were able to show benefit over placebo and in fact both the MAST trials showed increased rates of ICH.

Intravenous thrombolysis (IVT) with alteplase has been shown to be beneficial as a reperfusion therapy since 1995 (13). Alteplase or recombinant tissue plasminogen activator (tPA) is a systemic thrombolytic that binds to the fibrin protein threads of the thrombus and activates the local plasminogen. The plasminogen converts to plasmin resulting in thrombolytic action. It does not trigger this conversion in the absence of fibrin and hence, has limited systemic side effects. The initial trial showed benefit up to 3 hours from onset. Subsequently, the European Cooperative Acute Stroke Study (ECASS) III trial showed benefit up to 4.5 hours (14). Published in 2008 and with a median time of IV tPA administration of close to 4 hours, the trial demonstrated improvement in outcomes at 90 days. The Echoplanar Imaging Thrombolytic Evolution Trial (EPITHET) was a small neutral study (15). It compared placebo to IV tPA from 3-6 hours from onset with focus on imaging. Finally, in 2014, the largest of the IV tPA trials - International Stroke Trial (IST)-3 - was published (16). IST-3 took almost a decade to complete and compared IV tPA to placebo in those situations where the treating physician was uncertain regarding benefit of treatment to that particular patient. Consequently, in this study, many of the older subjects were treated early and younger patients were treated late. Although individually many of these studies were neutral, a Cochrane review published in 2000 showed benefit (17). Subsequently, a pooled analysis published in 2010 demonstrated clear treatment effect (18). In addition, there was clear data to suggest that 'time is brain': earlier treatment was associated with better outcomes and larger treatment effect (19). However, it was noted that IVT was not very effective in reperfusion of the most severe of AIS patients that are generally due to LVO (20). Based on known anatomy and pathophysiology, the more proximal the occlusion is, the greater is the amount of brain tissue that is affected and hence, the larger the clinical deficit. As proximal vessels are larger than distal vessels, these get occluded by larger emboli that present a limited surface to the throm-

bolytic agent to act on. In addition, it is quite likely that there is a column of relatively static blood flow around the embolus from the point of the last bifurcation which further limits the access of the thrombolytic agent to the embolus (21). Also, it is quite likely that the effectiveness of alteplase as a thrombolytic is influenced by the characteristics and contents of the thrombus/embolus. It is unlikely that a calcified embolus dislodged from the left atrial appendage in a patient with atrial fibrillation will get dissolved with alteplase. Finally, it seems likely that the time from onset also influences the vulnerability of the clot to alteplase - older clots will be tougher to dissolve.

In parallel to the progress being made in the field of IVT and its implementation, there continued to be dramatic changes in the field of interventional neuroradiology with better tools and easier access to intracranial vasculature. It seemed an obvious step to try to open these LVOs with local intra-arterial application of thrombolytic agents. It was hypothesized that by local delivery, one could have a higher local concentration increasing local effectiveness without increasing systemic side effects. Also, by microcatheter and/or microwire manipulation there may be enhanced drug delivery throughout the clot. The first effort in this direction was in the Prolyse in Acute Cerebral Thromboembolism (PROACT) trials (22, 23). The PROACT trial was conducted to test safety and recanalization efficacy of local intra-arterial delivery of recombinant prourokinase (23). A total of 46 patients were randomized. The PROACT trials tested the safety of endovascular thrombolysis (23). In PROACT II, a total of 180 patients were randomized with blinded follow-up between February 1996 and August 1998 in fifty-four centers in the United States and Canada. All patients had symptoms of acute ischemic stroke of less than 6 hours' duration caused by angiographically proven occlusion of the MCA. The randomization was to 9 mg of IA recombinant prourokinase (r-proUK) plus heparin or heparin only. At three months, 40% of r-proUK patients and 25% of control patients had a modified Rankin score (mRS) of 2 or less. Mortality was 25% for the r-proUK group and 27% for the control group. There were significant differences in the recanalization rates (66% r-proUK group vs. 18% control group). ICH with neurological deterioration within 24 hours occurred in 10% of r-proUK patients and 2% of control patients. While the trial showed a statistically significant benefit, there were many issues. Some of the major concerns were the number of patients that needed to be screened with catheter angiography to randomize one patient and the increased complication rate in the treatment arm.

New techniques: endovascular thrombectomy (EVT)

The PROACT trials tested the usefulness of local, endovascular chemical thrombolysis. While the results did show promising recanalization of the occluded vessel, it was slow and increased the rate of ICH. It seemed logical to develop and test devices that would mechanically remove the clot in an expedient manner establishing reperfusion and not increase hemorrhagic complications.

The MERCI (Mechanical Embolus Removal for Cerebral Ischemia) device was invented in 1995. Two single arm studies (MERCI and Multi MERCI) showed promising results with high recanalization rates (64-69.5%) and similar frequencies of sICH as in the control arm of PROACT II (24, 25). While the device was never formally tested in randomized controlled trials (RCTs), the biggest and most interesting development was the approval of the device by the Food and Drug Administration (FDA) in 2004. This unleashed innovation in the field as subsequent devices needed to only show non-inferiority to the results of the MERCI device related trials. Although the device was considered as a great improvement in neurointervention for a long time, the device was far from perfect, did not always work, was very painful for the patient and did result in a quite a few sub-arachnoid hemorrhages. In several countries and institutions, the evidence for effectiveness of MERCI device was not considered convincing, the treatment was not reimbursed and was not included in professional guidelines. Thus, neurointerventionalists were ready and receptive for alternative technologies.

The next major advancement was thromboaspiration: a large bore catheter was used to aspirate the clot while using a separator to break up the clot. The Penumbra Pivotal Stroke Trial was performed establishing its safety and high rates of revascularization (81.6% of TIMI 2-3) (26). However, the rates of good outcome (mRS 0-2) were generally disappointing low at 25%. It is to be noted that this was a single arm study and hence, no conclusions were possible regarding treatment effect. The Penumbra system was approved by the FDA in 2008. I wrote a paper studying the disconnect between the high rates of reperfusion vs. good outcome rates and was already starting to realize the importance of patient selection (e.g. patients with small to moderate core) as well as efficiency (time is brain) (27).

Contemporaneous to the development, approval and availability of the PenumbraTM system, the SolitaireTM detachable and retrievable stent (stent retriever) was added to the ischemic stroke armamentarium. The original version was designed for the purposes of stent assisted coiling of intracerebral aneurysms and hence was called Solitaire AB (aneurysm bridging). This device became available in Europe and Canada in 2009. Around that time, there has been a few reports of partially deploying the Enterprise stent, which was a detached self-expanding stent, for treatment of acute stroke and the availability of a detachable, retrievable stent was something the neurointerventional field was waiting for. Castano et al. from Spain published the first report on the use of Solitaire for acute stroke in 2009 (28). Unfortunately, the process of approval of this device took several years because of change in requirements by FDA. In the meantime, another similar device called TrevoTM also became available. Both these devices were tested in RCTs against the MERCI device (SWIFT trial and the TREVO2 trial). Both the trials showed the dramatic superiority of stent retrievers over the MERCI device (reduced procedural complications, higher revascularization rates and improved functional outcomes) (29, 30) .

While all these new stent retrievers were being tested, three separate RCTs were being conducted comparing EVT against medical treatment (IV tPA) in different parts of the world: Interventional Management of Stroke (IMS)3, SYNTHESIS EXPANSION, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) (31-33). Unfortunately, very few patients in these trials were treated using the newer generation devices. Most of the patients were treated with either intra-arterial thrombolytics or with the MERCI device. All the three trials were published in the same issue of the New England Journal of Medicine and failed to show the benefit of EVT. I was significantly involved in the IMS3 trial (in the executive committee, author on the main paper and my center was one of the highest enrolling centers). In the IMS3 trial, a total of 656 patients were randomized to IVT and EVT vs. IVT alone in patients with moderate to severe stroke within 3 hours of symptom onset. The study was stopped as it crossed a predefined futility boundary at the time of an interim analysis.

Lessons learned

Several lessons were learnt from the IMS3 trial. Some of the major rectifiable issues were: a. Low rate or recruitment and long duration of the trial. This has multiple issues including loss of interest and there being major changes in technology and perceptions; b. Lack

of documentation of LVO prior to randomization. This resulted in a higher 'noise' level as certain patients who were randomized to the endovascular arm were not amenable to EVT; c. Slow workflow. Even before IMS3, organization of stroke workflow and focusing on efficiency of treatment was my passion. It was clear to me even at that time that firstly, 'time is brain' and secondly, there were significant opportunities to improve workflow. At my institution, we had implemented many system changes to improve efficiency (34, 35). However, many of these improvements were not widely known and implemented and as such, the overall workflow in the trial was quite slow; d. Very low utilization of modern devices (stent retrievers). Only 4 patients were treated using the Solitaire device. In fact, a process was in place for the approval of new stent retriever technology. Unfortunately, following the process took time. Given my extensive experience by that time, when it was finally approved for use within the trial, I was asked to conduct a Solitaire training course for all the centers. The course was quite successful but the trial stopped soon after; e. Enrollment of patients with low ASPECTS (Alberta Stroke Program Early Computed Tomography Score) which indicates extensive signs of infarcted tissue on CT. Realizing the importance of the correct interpretation of the non-contrast CT scan, I set up an educational website (aspectsinstroke.com)(36); f. Lack of understanding of the impact of general anesthesia (GA). At that time many sites were routinely using GA for conducting endovascular thrombectomy. This had many concerns including the resulting delays in treatment and potential harm due to hypotension during induction. We looked at our own data and showed superiority of outcomes in patients treated without GA (37); g. Cherry-picking, which means that the local investigators use their subjective judgement and treat patients that in their opinion have a high likelihood of a good outcome with EVT and start treating them outside of the trial. This hampered enrollment of all eligible patients in a trial. There were possibly many reasons for cherry-picking but the dramatic success and safety of the newer stent retrievers and the inability to use these devices within the trial, in my opinion, played a major role.

Designing and conducting the next generation of trials.

Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial (Principal Investigators: Michael Hill, Mayank Goyal, Andrew Demchuk): This trial was designed to overcome the limitations of the IMS3 trial. The design elements included use of modern stent retriever technology, use of CT Angiography (CTA) to document LVO, use of collaterals on CTA to reduce the likelihood of including low

ASPECTS patients. In addition, the trial was executed by the principal investigators with attention to the following elements: personal visits and connections with each site, training and help with efficiency, monitoring of workflow and working hard to prevent cherry picking.

Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial (Principal Investigators: Jeffrey Saver, Mayank Goyal, Hans-Christof Diener, Elad Levy, Alain Bonafe, Vitor Periera Mendes, Reza Jahan; trial run by Medtronic). This trial was designed with the intention of getting an indication for the Solitaire device by FDA in the event of a positive result. The investigators were able to bring in many of the design elements of ESCAPE into this trial. There were a few differences between the two trials: a. ESCAPE enrolled patients up to 12 hours from onset while in SWIFT PRIME, all patients had to have received IVT b. CT perfusion imaging was used for patient selection in the majority of patients in SWIFT PRIME, c. all patients in the endovascular arm had to be treated using the Solitaire device. This trial was submitted to the Food and Drug Administration (FDA) for their approval of the protocol and based on their recommendations an upper age limit was introduced to match the tPA studies (the then current standard). Additionally, treatment of coexistent carotid stenosis in the neck was considered by FDA to be a second investigational procedure and thus, patients with carotid occlusion/tight stenosis were excluded from the study.

Aims and outline of the thesis

After the publication of the three randomized trials IMS3, SYNTHESIS EXPANSION, MR RESCUE (31-33) in 2013 demonstrating a lack of benefit of EVT, there was a growing opinion among many stroke physicians of the absence of benefit of this treatment. The first aim of this thesis is to describe our research which was to provide new proof for the efficacy of EVT. Secondary aims include: evaluating various sub-groups through the establishment of a patient level database from multiple trials; understanding the importance of workflow, further establishing the importance of 'time is brain' and better understanding the bottlenecks to early treatment; innovate on imaging strategies to allow for faster and better decision making and lastly, innovate and improve on strategies on systems of care in light of evidence supporting EVT. This thesis is divided into four parts.

In the first part, I assess the effect and safety of EVT in AIS using results from the ESCAPE trial (Chapter 2.1), the SWIFT PRIME trial (Chapter 2.2) and perform a patient level meta-analysis from the summation of the results of all the trials allowing for a detailed exploration of the sub-groups (Chapter 2.3).

In the second part, I investigate the importance of workflow in acute stroke and a better understanding of the different bottlenecks. The relationship between time and outcome is explored. Data on workflow from the following trials is presented: IMS3 (Chapter 3.1), ESCAPE (Chapter 3.2) and SWIFT PRIME (Chapter 3.3). In addition, an analysis from a patient level meta-analysis from the summation of the results of all the trials is presented (Chapter 3.4).

In the third part, a detailed analysis of the impact of various imaging factors on outcome is discussed using data from IMS3 (Chapter 4.1) and SWIFT PRIME (Chapter 4.2). To improve decision making and workflow in acute ischemic stroke due to LVO, I propose a new imaging innovation for decision making in acute stroke: multiphase CT angiography (mCTA) (Chapter 4.3). In addition, I present the results of utilizing mCTA for various ASPECTS regions and its usefulness in predicting tissue outcome (Chapter 4.4). In addition, an analysis from a patient level meta-analysis of all the recent randomized trials is presented (Chapter 4.5).

In the fourth part, I evaluate the usefulness of mathematical modeling techniques to optimize systems of care regarding transport of patients to an endovascular capable centre versus going to a centre that is capable of IVT but not EVT (Chapters 5.1 and 5.2).

Finally, the last chapter (Chapter 6) is a general discussion of the thesis and future challenges and opportunities. It is followed by a summary in English and Dutch (Chapter 7).

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CHAPTER 2

Effect And Safety Of Endovascular Treatment In Acute Ischemic Stroke

2.1 - Randomized Assessment Of Rapid Endovascular Treatment Of Ischemic Stroke

2.2 - Stent-Retriever Thrombectomy After Intravenous tPA Versus tPA Alone In Stroke

2.3 - Endovascular Thrombectomy After Large-Vessel Ischaemic Stroke: A Meta-Analysis Of Individual Patient Data From Five Randomised Trials

CHAPTER 2.1

Randomized Assessment Of Rapid Endovascular Treatment Of Ischemic Stroke

Based upon:

Randomized Assessment of Rapid Endovascular Treatment of Ischemic Stroke.

Mayank Goyal, Andrey M. Demchuk, Bijoy K. Menon, Muneer Eesa, Jeremy L. Rempel, John Thornton, Daniel Roy, T.G. Jovin, Robert A. Willinsky, Biggya L. Sapkota, Dar Dowlatshahi, Donal F. Frei, Noreen R. Kamal, Walter J. Montanera, Alexander Y. Poppe, Karla J. Ryckborst, Frank L. Silver, Ashfaq Shuaib, Donatella Tampieri, David Williams, Oh Y. Bang, Blaise W. Baxter, Paul A. Burns, Hana Choe, J.-H. Heo, Christine A. Holmstedt, Brian Jankowitz, Michael Kelly, Guillermo Linares, Jennifer L. Mandzia, Jai Shankar, Sung-Il Sohn, Richard H. Swartz, Philip A. Barber, Shelagh B. Coutts, Eric E. Smith, William F. Morrish, Alain Weill, Suresh Subramaniam, AlimP. Mitha, John H. Wong, Mark W. Lowerison, Tolulope T. Sajobi, and Michael D. Hill for the ESCAPE Trial Investigators.

N Engl J Med. 2015; 372: 1019-30.

Drs. Goyal and Hill contributed equally to this article.

ABSTRACT

Background

Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment. We evaluated rapid endovascular treatment in addition to standard care in patients with acute ischemic stroke with a small infarct core, a proximal intracranial arterial occlusion, and moderate-to-good collateral circulation.

Methods

We randomly assigned participants to receive standard care (control group) or standard care plus endovascular treatment with the use of available thrombectomy devices (intervention group). Patients with a proximal intracranial occlusion in the anterior circulation were included up to 12 hours after symptom onset. Patients with a large infarct core or poor collateral circulation on computed tomography (CT) and CT angiography were excluded. Workflow times were measured against predetermined targets. The primary outcome was the score on the modified Rankin scale (range, 0 [no symptoms] to 6 [death]) at 90 days. A proportional odds model was used to calculate the common odds ratio as a measure of the likelihood that the intervention would lead to lower scores on the modified Rankin scale than would control care (shift analysis).

Results

The trial was stopped early because of efficacy. At 22 centers worldwide, 316 participants were enrolled, of whom 238 received intravenous alteplase (120 in the intervention group and 118 in the control group). In the intervention group, the median time from study CT of the head to first reperfusion was 84 minutes. The rate of functional independence (90-day modified Rankin score of 0 to 2) was increased with the intervention (53.0%, vs. 29.3% in the control group; P<0.001). The primary outcome favored the intervention (common odds ratio, 2.6; 95% confidence interval, 1.7 to 3.8; P<0.001), and the intervention was associated with reduced mortality (10.4%, vs. 19.0% in the control group; *P*=0.04). Symptomatic intracerebral hemorrhage occurred in 3.6% of participants in intervention group and 2.7% of participants in control group (*P*=0.75).

Conclusions

Among patients with acute ischemic stroke with a proximal vessel occlusion, a small infarct core, and moderate-to-good collateral circulation, rapid endovascular treatment improved functional outcomes and reduced mortality. (Funded by Covidien and others; ESCAPE Clinical*Trials*.gov number, NCT01778335.)

Ischemic stroke is a devastating condition with a high burden of neurologic disability and death. As a systemic treatment, intravenous alteplase has been shown to be better than conservative care.[1,2] Among patients with a proximal vessel occlusion in the anterior circulation, 60 to 80% of patients die within 90 days after stroke onset or do not regain functional independence despite alteplase treatment.[3,4] The major reason for the limited efficacy of alteplase is the modest rate of early reperfusion among patients with a large-vessel occlusion.[5,6]

Local treatment of large-vessel occlusion began with intraarterial delivery of thrombolytic drugs.[7] The Prolyse in Acute Cerebral Thromboembolism (PROACT) II study was the first positive trial of endovascular treatment involving patients with angiographically visualized occlusion of the middle cerebral artery.[8] Unfortunately, subsequent trials did not confirm the clinical benefit even with the addition of first-generation thrombectomy devices.[3,9,10] Key lessons learned from these previous trials are the need for proof of proximal vessel occlusion,[11] rapid and effective imaging methods to exclude patients with a large infarct core,[12-14] an efficient workflow to achieve fast recanalization,[15,16] and high reperfusion rates.[17-19]

Recent studies have shown the superiority of retrievable stents over the previous generation of thrombectomy devices.[17,18] The recently reported Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) used this technology, and the results of that trial showed clinical benefit with endovascular treatment.[4] The Endovascular Treatment for Small Core and Anterior *Circulation* Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial was designed to test whether patients with acute ischemic stroke, who were selected on the basis of results of computed tomography (CT) and CT angiography (CTA), would benefit from rapid endovascular treatment involving contemporary endovascular techniques.[20]

METHODS

Trial Design

The ESCAPE trial was a multicenter, prospective, randomized, open-label, controlled trial with blinded outcome evaluation (PROBE design).[20] Participants were assigned, in a 1:1 ratio, to receive endovascular treatment plus guideline-based care (intervention group) or guideline-based care alone (control group) (see the Methods section in the Supplementary Appendix, available with the full text of this article at NEJM.org). This academic-investigator-initiated trial was designed to answer a practical question regarding a patient with acute ischemic stroke who has just undergone neurovascular imaging with noncontrast CT and CTA: "Should this patient undergo endovascular thrombectomy?" (Fig. S3 in the Supplementary Appendix).

The trial was monitored by an independent data and safety monitoring board. The study funders, including Covidien, were not involved in the design or conduct of the study, the preparation or review of the protocol, the collection or analysis of the data, or the preparation or review of the manuscript. All the authors collected data, provided comments on the analysis, contributed to the writing of the manuscript, and were independent of the sponsors. All the authors vouch for the accuracy and completeness of the data and data analyses and for the fidelity of this report to the study protocol, available at NEJM.org.

Sites were selected for participation after visits by the principal investigators and documentation of fast treatment times and efficient work-flow. The principal investigator at each site signed a formal letter stating a commitment to attempt to enroll consecutive patients who were eligible for the ESCAPE trial.[21] The ethics board at each site approved the trial. In jurisdictions where it was permitted, the consent process was deferred when the participant lacked the capacity to provide consent and a legally authorized representative was unavailable.

Randomization was performed with the use of a real-time, dynamic, Internet-based, randomized minimization procedure (minimal sufficient balance method)[22] to achieve distri-

bution balance with regard to age, sex, baseline National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating greater stroke severity), site of arterial occlusion, baseline Alberta Stroke Program Early Computed Tomography Score (ASPECTS), and status with respect to intravenous alteplase treatment. The ASPECTS scale is a 10-point scoring system to quantify early ischemic changes in the middle-cerebral-artery territory, with a score of 10 indicating normal and 1 point subtracted for each abnormal region (details are available at www.aspectsinstroke.com).[23,24]

Participants

Eligible participants were adults (no upper-age limit) with a disabling ischemic stroke who had been functioning independently in the community (score on the Barthel Index [range, 0 to 100, with higher scores indicating a greater ability to complete activities of daily living] ≥90) before the stroke. Enrollment could occur up to 12 hours after the onset of stroke symptoms. Noncontrast CT and CTA (preferably multiphase) were performed to identify participants with a small infarct core, an occluded proximal artery in the anterior circulation, and moderate-to-good collateral circulation.[14,25-28] Multiphase CTA is less vulnerable to patient motion than CT perfusion, requires no additional contrast, and allows for quick determination of collateral status[12] (Fig. S2 in the Supplementary Appendix). The use of magnetic resonance imaging for patient selection was discouraged. A small infarct core was defined as an ASPECTS of 6 to 10. Proximal artery occlusion in the anterior circulation was defined as occlusion of the middle-cerebral-artery trunk and its immediate branches, with or without intracranial occlusion of the internal carotid artery (Fig. S4 in the Supplementary Appendix). Moderate-to-good collateral circulation was defined as the filling of 50% or more of the middle-cerebral-artery pial arterial circulation on CTA (preferably on multiphase CTA).

Imaging was performed at the endovascular center; for patients transferred from other hospitals, imaging was repeated. Before and during screening, participants were treated with intravenous alteplase when clinically appropriate as part of standard care (Fig. S3 in the Supplementary Appendix). We did not keep a log of patients who were screened for the trial.[29]

Treatments

Participants in the intervention group underwent rapid endovascular treatment. A cerebral angiogram was obtained. The neurointerventionist used available thrombectomy devices to achieve reperfusion. The use of retrievable stents was recommended. During thrombus retrieval, suction through a balloon guide catheter in the relevant internal carotid artery was also recommended. The control group received the current standard of care as described in the Canadian or local guidelines for the management of acute stroke[30,31] (see the Methods section in the Supplementary Appendix). Participants in both groups received intravenous alteplase within 4.5 hours after the onset of stroke symptoms if they met accepted local guidelines for intravenous alteplase treatment.

Weekly monitoring of imaging and treatment speed, with regular feedback to sites by teleconference, ensured adherence to participant eligibility criteria and workflow metrics. Guidance on rapid, effective endovascular treatment and high-quality imaging methods was provided. The target time from study noncontrast CT to groin puncture was 60 minutes or less and from study noncontrast CT to first reperfusion (defined as first reflow in the middle cerebral artery) was 90 minutes or less. These aggressive targets were chosen to emphasize speed and ensure rapid imaging acquisition and interpretation, quick transfer of patients to the angiography suite, and fast reperfusion. If there were clear patient-related factors (e.g., vessel tortuosity) or workflow factors (e.g., unavailability of the intervention team) that would prevent meeting the time targets, it was recommended that patients not be enrolled.

Clinical Assessments and Outcomes

All participants had standard assessments of demographic characteristics, medical history, laboratory values, and stroke severity (NIHSS score). Details of the assessments have been published previously[20] and are also available in the study protocol. The primary outcome-the score on the modified Rankin scale at 90 days after randomization-was assessed by trained personnel who were unaware of the treatment-group assignments. The modified Rankin scale is a graded interval scale (range, 0 [no symptoms] to 6 [death]) for the assessment of neurologic functional disability.[32] Secondary and safety outcomes included early recanalization and reperfusion, intracranial hemorrhage, angiographic complications, neurologic disability at 90 days, and death. Interpretation of the imaging was performed

at an external core laboratory by personnel who were unaware of the treatment-group assignments (when they interpreted the CT images), clinical data, and outcomes. External, independent clinical monitors validated the clinical data.

Statistical Analysis

The trial was powered to detect a shift in the distribution of scores on the modified Rankin scale at 90 days between the intervention and control groups, with scores of 5 (bedbound with severe disability) and 6 (death) combined, with the assumption that the differential effect would lead to a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 1.8. A total required sample of 500 participants was anticipated. One formal interim analysis after the enrollment of 300 participants was planned. The stopping rule for efficacy was defined with the use of O'Brien-Fleming boundaries on the binary outcome of a modified Rankin score at 90 days of 0 to 2 versus 3 to 6.20 The primary analysis was unadjusted and was performed in the intention-to-treat population. P values of less than 0.05 were considered to indicate statistical significance, and all tests of hypotheses were two-sided. No adjustments were made for multiple comparisons. Adjusted estimates of effect were calculated, with adjustment for age, sex, baseline NIHSS score, baseline ASPECTS, location of occlusion (internal carotid artery plus middle cerebral artery vs. middle cerebral artery only), and status with respect to intravenous alteplase treatment (yes vs. no). The assessment of effect modification (heterogeneity of treatment effect) was performed with the inclusion of multiplicative interaction terms. All analyses were performed with the use of Stata software, version 12.1 (StataCorp). Figures were drawn with the use of both Stata software, version 12.1, and R software (R Development Core Team 2014, www.r-project.org). Further details are provided in the statistical analysis plan (available at NEJM.org).

Table 1. Baseline Characteristics and Process Measures.*

Variable	Intervention (N= 165)	Control (N= 150)
Demographic characteristics		
Age-yr		
Median	71	70
Interquartile range	60-81	60-81
Female sex-no. (%)	86 (52.1)	79 (52.7)
White race-no. (%)†	144 (87.3)	131 (87.3)
Medical history-no. (%)		
Hypertension	105 (63.6)	108 (72.0)
Diabetes mellitus	33 (20.0)	39 (26.0)
Atrial fibrillation	61 (37.0)	60 (40.0)
Clinical characteristics		
NIHSS score ‡		
Median	16	17
Interquartile range	13-20	12-20
Systolic blood pressure at hospital arrival-mm Hg		
Median	147	146
Interquartile range	131-159	125-169
Glucose level at hospital arrival-mmol/liter§		
Median	6.6	6.7
Interquartile range	5.8-7.7	5.7-7.8
Imaging characteristics		
ASPECTS on CT-median (interquartile range)¶	9 (8-10)	9 (8-10)
Location of occlusion on CTA-no./total no. (%)‖		
ICA with involvement of the M1 middle-cerebral-artery segment	45/163 (27.6)	39/147 (26.5)
M1 or all M2 middle-cerebral-artery segments	111/163 (68.1)	105/147 (71.4)
Single M2 middle-cerebral-artery segment	6/163 (3.7)	3/147 (2.0)
Ipsilateral cervical carotid occlusion-no. (%)	21 (12.7)	19 (12.7)
Process times-min**		
Stroke onset to randomization		
Median	169	172
Interquartile range	117-285	119-284
Stroke onset to study CT		
Median	134	136
Interquartile range	77-247	76-238
Stroke onset to start of IV alteplase		
Median	110	125
Interquartile range	80-142	89-183
Study CT to groin puncture		
Median	51	
Interquartile range	39-68	

Study CT to first reperfusion††		
Median	84	
Interquartile range	65-115	
Stroke onset to first reperfusion††		
Median	241	
Interquartile range	176-359	
Treatment with IV alteplase-no. (%)	120 (72.7)	118 (78.7)

* The intervention group was assigned to endovascular treatment plus standard care, and the control group was assigned to standard care alone. CT denotes computed tomography, CTA CT angiography, ICA internal carotid artery, and IV intravenous.

† Race was self-reported.

‡ Scores on National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits.

§ To convert the values to milligrams per deciliter, divide by 0.05551.

¶ The Alberta Stroke Program Early Computed Tomography Score (ASPECTS) is an imaging measure of the extent of ischemic stroke. Scores ranges from 0 to 10, with higher scores indicating a smaller infarct core (details are available at www.aspectsinstroke.com).

‖ In one participant in the intervention group, the location of the occlusion on CTA was not determined by the core laboratory. Occlusion of the ICA with involvement of the M1 middle-cerebral-artery segment could occur with or without involvement of the A1 anterior-cerebral-artery segment (see Fig. S4 in the Supplementary Appendix). The M1 middle-cerebral-artery segment extends from the origin to the site of bifurcation or trifurcation (the anterior temporal artery is considered a branch of the M1 segment). The M2 middle-cerebral-artery segments extend from the site of bifurcation or trifurcation to the origin of the cortical branches.

** For the time from stroke onset to the start of IV alteplase, data were missing for 1 patient in the intervention group. For the time from study CT to groin puncture, 161 patients were included in the analysis. For the time from study CT to first reperfusion and the time from stroke onset to first reperfusion, 145 patients were included in the analysis.

†† First reperfusion was defined as the first visualization of reflow in the middle cerebral artery, usually on deployment of a retrievable stent.

RESULTS

An unplanned interim analysis was conducted after the release of the MR CLEAN results, which showed efficacy of endovascular therapy (see the Methods section in the Supplementary Appendix). The ESCAPE trial was stopped early on the advice of the data and safety monitoring board because the early termination of the study prespecified boundary for efficacy had been crossed.

Patients

At 22 centers in Canada (11 centers), the United States (6), South Korea (3), Ireland (1), and the United Kingdom (1), a total of 316 participants underwent randomization before the trial was stopped: 165 participants were assigned to the intervention group, 150 participants were assigned to the control group, and 1 participant was excluded owing to improper consent procedures. The trial enrolled 1.44 participants per center per month from February 2013 through October 2014. One participant in the control group crossed over to receive endovascular treatment. In the intervention group, 14 participants did not receive any interventional therapy. Four participants (1.3%) were lost to follow-up; missing data on outcomes in these participants were not imputed (Fig. S1 in the Supplementary Appendix). Baseline characteristics were similar in the two treatment groups (Table 1, and Table S1 in the Supplementary Appendix). Imaging protocol violations, identified by personnel who interpreted the images at the core laboratory, occurred in 26 participants (8.3%): 11 of 308 participants in whom the ASPECTS could be evaluated (3.6%) had a score of less than 6 on the ASPECTS scale, 20 of 315 participants (6.3%) had poor collateral circulation, and 14 of 315 participants (4.4%) had inappropriate target-vessel occlusion (some participants had >1 protocol violation). Collateral circulation was assessed with the use of multiphase CTA in a majority of participants. A total of 56 participants (17.8%) were enrolled with deferral of consent procedures. Monitoring of appropriate source documentation materials (with regard to informed consent, inclusion and exclusion criteria, randomization information, demographic characteristics, and assessments at baseline [NIHSS score and Barthel Index score] and at day 90 [modified Rankin score, NIHSS score, and Barthel Index score]) was completed for all randomly assigned participants.

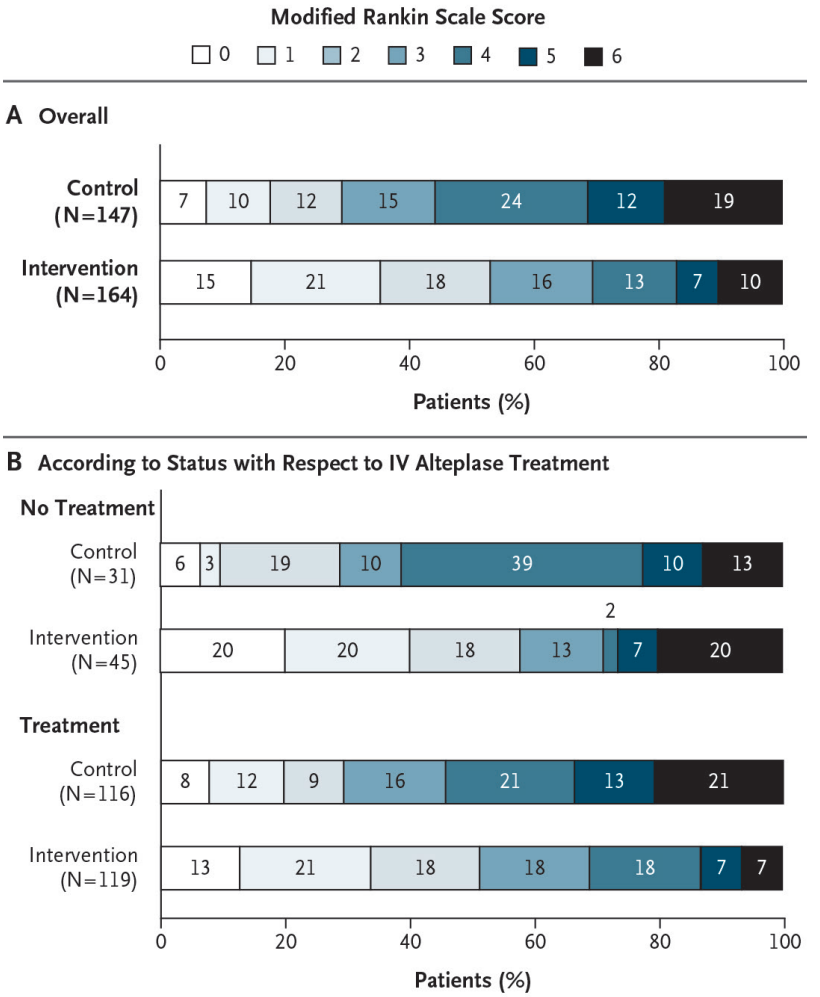

Figure 1. Scores on the Modified Rankin Scale at 90 Days in the Intention-to-Treat Population.

Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death. Panel A shows the distribution of scores at 90 days in the intervention and control groups in the overall trial population. A significant difference between the intervention and control groups was noted in the overall distribution of scores (unadjusted common odds ratio, indicating the odds of improvement of 1 point on the modified Rankin scale, 2.6; 95% confidence interval, 1.7 to 3.8), favoring the intervention. Panel B shows the distribution of scores at 90 days in the intervention and control groups according to status with respect to intravenous (IV) alteplase treatment. In this analysis, there was no evidence of heterogeneity of effect (P= 0.89 for interaction by the Wald test).

Primary Outcome

Analysis of the primary end point showed a common odds ratio (indicating the odds of improvement of 1 point on the modified Rankin scale) of 2.6 (95% confidence interval [CI], 1.7 to 3.8) favoring the intervention (P<0.001) (Fig. 1A and Table 2). The median 90-day modified Rankin score was 2 in the intervention group and 4 in the control group (P<0.001). The proportion of patients with a modified Rankin score of 0 to 2 at 90 days was 53.0% in the intervention group and 29.3% in the control group (rate ratio, 1.8; 95% CI, 1.4 to 2.4; P<0.001). Mortality at 90 days was 10.4% in the intervention group and 19.0% in the control group (rate ratio, 0.5; 95% CI, 0.3 to 1.0; P = 0.04) (Fig. S5 in the Supplementary Appendix). The rate of symptomatic intracerebral hemorrhage was 3.6% in the intervention group and 2.7% in the control group (rate ratio, 1.4; 95% CI, 0.4 to 4.7; P = 0.75). Device-related or procedural complications were observed in 18 patients: 4 had a serious adverse event and 14 had a nonserious adverse event (Table 3, and Table S2 in the Supplementary Appendix).

Table 2. Primary and Secondary Efficacy Outcomes.

Outcome	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Effect Variable	Unadjusted Value (95% CI)	Adjusted Value (95% CI)†
Primary outcome: modified Rankin score at 90 days‡				Common odds ratio	2.6 (1.7–3.8)	3.1 (2.0–4.7)
Modified Rankin score of 0–2 at 90 days — no./total no. (%)§	87/164 (53.0)	43/147 (29.3)	23.8 (13.2–34.4)	Rate ratio	1.8 (1.4–2.4)	1.7 (1.3–2.2)
NIHSS score of 0–2 at 90 days — no./total no. (%)	79/153 (51.6)	31/134 (23.1)	28.4 (17.8–39.2)	Rate ratio	2.2 (1.6–3.2)	2.1 (1.5–3.0)
Barthel Index score of 95–100 at 90 days — no./total no. (%)¶	94/163 (57.7)	49/146 (33.6)	24.1 (13.3–34.9)	Rate ratio	1.7 (1.3–2.2)	1.7 (1.3–2.2)
TICI score of 2b or 3 at final angiogram — no./total no. (%)‖	113/156 (72.4)					
Modified AOL score of 2 or 3 — no./total no. (%)**		43/138 (31.2)				
NIHSS score at 24 hours — median (interquartile range)††	6 (3–14)	13 (6–18)		Beta coefficient	4.0 (2.2–5.8)	4.1 (2.6–5.6)
NIHSS score at 90 days — median (interquartile range)††	2 (1–8)	8 (3–19)		Beta coefficient	6.5 (3.2–9.8)	6.5 (3.5–9.6)
EQ-5D visual-analogue scale score at 90 days — median (interquartile range)††‡‡	80 (60–90)	65 (50–80)		Beta coefficient	9.4 (3.5–15.2)	9.9 (3.8–16.0)

* Differences (intervention group - control group) are shown as percentage points.

† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.

‡ The primary analysis involved 164 participants in the intervention group and 147 participants in the control group. Scores on the modified Rankin scale of functional disability range from 0 (no symptoms) to 6 (death). The common odds ratio was estimated from an ordinal logistic-regression model and indicates the odds of improvement of 1 point on the modified Rankin scale, with a common odds ratio greater than 1 favoring the intervention. The proportional odds assumption was tested and found to be valid.

§ A modified Rankin score of 0 to 2 indicates functional independence.

¶ The Barthel Index is an ordinal scale for measuring performance of activities of daily living. Scores range from 0 to 100, with 0 indicating severe disability and 95 or 100 no disability that interferes with daily activities.

‖ A Thrombolysis in Cerebral Infarction (TICI) score of 2b or 3 indicates successful reperfusion (see Table S3 in the Supplementary Appendix).

** A modified Arterial Occlusive Lesion (AOL) score of 2 or 3 indicates partial or complete recanalization (see Table S3 in the Supplementary Appendix).

†† Treatment effect was estimated with the use of simple linear regression.

‡‡ The EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale is a continuous scale measure of self-reported quality of life. Scores range from 0 to 100, with 0 indicating the worst possible quality of life and 100 the best possible quality of life.

Table 3. Reported Serious Adverse Events.

Event	Intervention (N=165)	Control (N=150)	Difference (95% CI)*	Rate Ratio (95% CI)	Adjusted Rate Ratio (95% CI)†
Death — no./total no. (%)	17/164 (10.4)	28/147 (19.0)	8.6 (0.8 to 16.6)	0.5 (0.3 to 1.0)	0.5 (0.3 to 0.8)
Large or malignant middle-cerebral-artery stroke — no. (%)‡	8 (4.8)	16 (10.7)	5.8 (0.1 to 11.7)	0.5 (0.2 to 1.0)	0.3 (0.1 to 0.7)
Symptomatic intracerebral hemorrhage — no. (%)‡§	6 (3.6)	4 (2.7)	1.0 (–2.9 to 4.8)	1.4 (0.4 to 4.7)	1.2 (0.3 to 4.6)
Hematoma at access site — no. (%)¶	3 (1.8)	0			
Perforation of the middle cerebral artery — no. (%)	1 (0.6)	0			

* Differences (intervention group - control group) are shown as percentage points.

† Adjusted estimates were calculated with the use of multiple regression analyses. Estimates were adjusted for age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to intravenous alteplase treatment, as prespecified in the protocol and statistical analysis plan.

‡ Two hemicraniectomy procedures were performed. The indications for hemicraniectomy were malignant middle-cerebral-artery ischemic stroke (one patient in the control group) and symptomatic intracerebral hemorrhage (one patient in the intervention group).

§ Symptomatic intracerebral hemorrhage was clinically determined at the study site.

¶ Hematoma occurred in two participants at the site of groin puncture. Neck hematoma occurred in the single participant in whom direct carotid access was used, after femoral access was unsuccessful.

Secondary Outcomes and Subgroup Analyses

Secondary clinical and imaging end points favored the intervention group. The rate of patients with a score on the Barthel Index of 95 to 100 at 90 days was 57.7% in the intervention group versus 33.6% in the control group, the rate of patients with a 90-day NIHSS score of 0 to 2 was 51.6% versus 23.1%, and the median 90-day score on the EuroQoL Group 5-Dimension Self-Report Questionnaire (EQ-5D) visual-analogue scale (range, 0 to 100, with higher scores indicating better quality of life) was 80 versus 65 (Table 2).

There was no evidence of heterogeneity of effect across any of the prespecified subgroups (defined according to age, sex, baseline NIHSS score, baseline ASPECTS, occlusion location, and status with respect to alteplase treatment) or according to the presence or absence of cervical carotid occlusion. All variables showed a direction of effect in favor of the intervention (Fig. 2, and Fig. S6 in the Supplementary Appendix). However, the absolute proportion of good outcomes varied substantially according to subgroup (Fig. 1B, and Fig. S7 in the Supplementary Appendix).

A total of 49 patients underwent randomization 6 or more hours after stroke onset; in the analysis of a modified Rankin score of 0 to 2 at 90 days, the direction of effect favored the intervention in these patients (rate ratio, 1.7; 95% CI, 0.7 to 4.0), but the between-group difference was not significant.

Of 165 participants assigned to the intervention group, 151 (91.5%) underwent endovascular treatment, and 120 (72.7%) received intravenous alteplase. General anesthesia was used in 15 participants (9.1%). Retrievable stents were used in 130 of the 151 participants (86.1%) who under went an endovascular procedure; 100 of these 130 participants (77.0%) received a Solitaire stent (Covidien). In the intervention group, the median time from symptom onset to first reperfusion was 241 minutes (interquartile range, 176 to 359), the median time from study CT to first reperfusion was 84 minutes (interquartile range, 65 to 115), and the median time from groin puncture to first reperfusion was 30 minutes (interquartile range, 18 to 46). Successful reperfusion (as defined by a core-laboratory-adjudicated Thrombolysis in Cerebral Infarction [TICI] score of 2b or 3, indicating complete filling of the expected vascular territory) was observed in 113 of 156 participants (72.4%) in the intervention group: 79 of 112 participants (70.5%) who received

intravenous alteplase and 34 of 44 participants (77%) who did not. (For details on the TICI scale, see Table 3 in the Supplementary Appendix.)

In the control group, follow-up CTA was performed in 138 participants (median time from symptom onset to follow-up CTA, 425 minutes [interquartile range, 355 to 564]). Successful recanalization (as defined by a core-laboratory-adjudicated modified Arterial Occlusive Lesion score of 2 or 3 on CTA, indicating partial or complete recanalization of the occluded artery) was observed in 43 of 138 participants (31.2%): 41 of 110 (37.3%) who received intravenous alteplase and 2 of 28 (7%) who did not. (For details on the modified Arterial Occlusive Lesion scale, see Table S3 in the Supplementary Appendix.)

DISCUSSION

We found that among participants with acute ischemic stroke with a small infarct core, a proximal intracranial occlusion in the anterior circulation, and moderate-to-good intracranial collateral circulation, rapid endovascular treatment improved the clinical outcome and reduced mortality. The trial confirms the benefit of endovascular treatment reported recently in the MR CLEAN trial.[4]

The ESCAPE trial attempted to deliver rapid endovascular therapy to patients who were selected for inclusion on the basis of imaging. Post hoc analysis of the Interventional Management of Stroke (IMS) III trial and the Solitaire FR Thrombectomy for Acute Revascularization (STAR) trial showed that achieving faster reperfusion, as compared with slower reperfusion, was associated with a better clinical outcome.[16,33] The ESCAPE trial achieved shorter interval times than those seen in past trials, with a median time from study noncontrast CT to first reperfusion of 84 minutes. A prespecified efficiency target for the time from noncontrast CT to reperfusion encouraged fast image acquisition and interpretation and fast decision making.[16,34-37] Critical to the achievement of rapid treatment was parallel decision making and action. For example, participants in the intervention group underwent groin puncture while alteplase was being infused, and complete reperfusion was achieved in some participants before the alteplase infusion was finished. The primary emphasis was on achieving early reperfusion.[15,16,34,35]

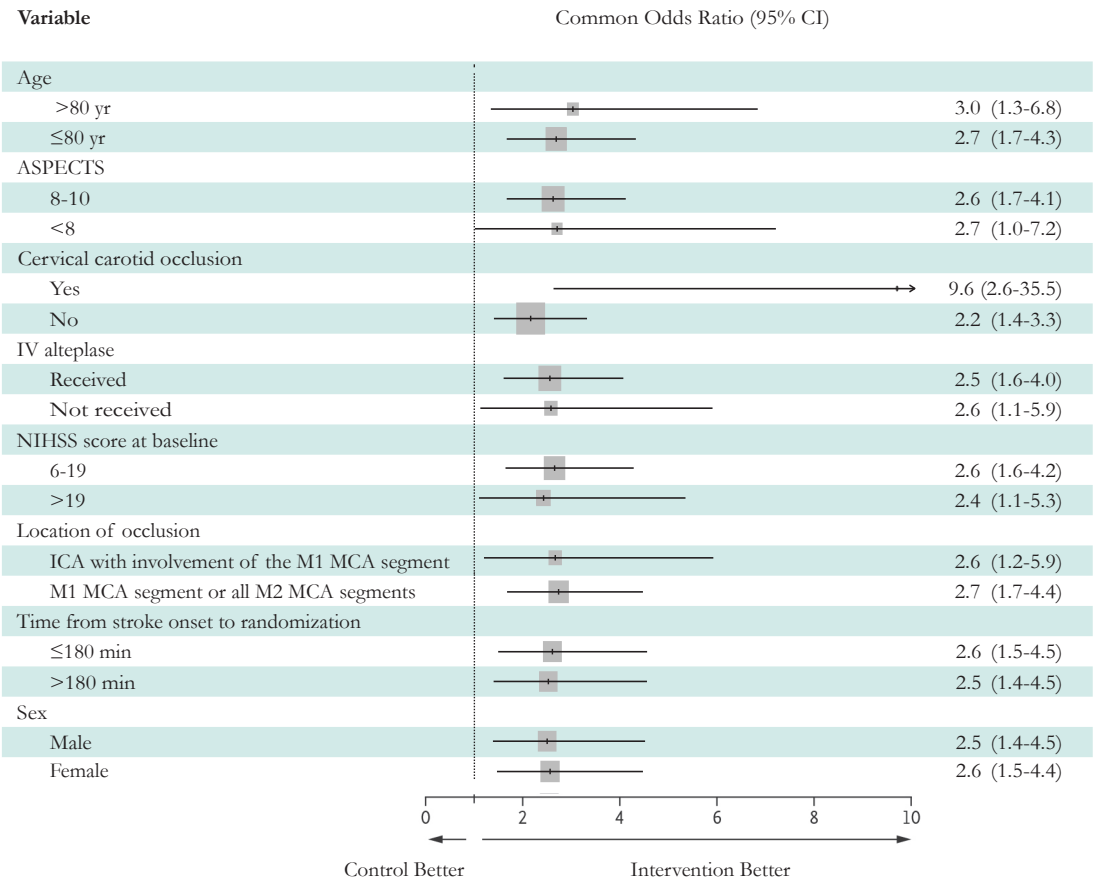

Figure 2. Subgroup Analyses

A forest plot shows that the difference in the primary clinical outcome (common odds ratio indicating the odds of improvement of one point on the modified Rankin scale at 90 days, analyzed with the use of ordinal logistic regression) favored the intervention group across all prespecified subgroups. The thresholds for age and National Institutes of Health Stroke Scale (NIHSS) score (range, 0 to 42, with higher scores indicating more severe neurologic deficits) were chosen at the 75th percentile, and the threshold for time from stroke onset to randomization was chosen just above the median. The threshold for the Alberta Stroke Program Early Computed Tomography Score (ASPECTS; range, 0 to 10, with higher scores indicating a smaller infarct core) was prespecified. For cervical carotid occlusion, $P = 0.049$ for interaction by the Wald test. Other P values were greater than 0.10 for interaction. ICA denotes internal carotid artery, and MCA middle cerebral artery.

Imaging-related selection criteria focused on the population with a small infarct core at baseline, which was defined by both modest early ischemic change on noncontrast CT and moderate-to-good collateral circulation distal to the occlusion.[26] A new technique of collateral assessment, multiphase CTA, was used in a majority of patients (Fig. S2 in the Supplementary Appendix).[12] This imaging approach resulted in a low number of imaging protocol violations and enabled the meeting of workflow time targets.

There was no evidence of heterogeneity of treatment effect across prespecified subgroups.

Endovascular treatment appeared to benefit all ages (the oldest person enrolled in the trial was 93 years of age), both sexes, patients with moderate strokes and those with severe strokes, patients who received intravenous alteplase and those who did not, and patients with and those without occlusion in the internal carotid artery (Fig. 2, and Fig. S6 in the Supplementary Appendix). Although eligibility criteria allowed enrollment up to 12 hours after symptom onset, the median time from symptom onset to first reperfusion was 241 minutes. A total of 49 participants (15.5%) underwent randomization 6 or more hours after symptom onset, and the study was not powered to assess endovascular therapy among patients presenting 6 to 12 hours after symptom onset.

The incidence of asymptomatic hemorrhagic infarction was greater in the intervention group than in the control group (Table S2 in the Supplementary Appendix), possibly owing to early reperfusion.[38] The rate of more serious parenchymal hematomas or symptomatic hemorrhage was not higher in the intervention group than in the control group. Device-related or procedural complications were uncommon.

MR CLEAN and the ESCAPE trial showed benefit and low complication rates with endovascular treatment that was performed predominantly with retrievable stents. Factors that distinguish the ESCAPE trial from MR CLEAN and prior trials of endovascular treatment for stroke include the use of imaging to exclude participants with a large infarct core and poor collateral circulation, a shorter interval from symptom onset to treatment initiation, a low rate of general anesthesia (9% in the ESCAPE trial vs. 38% in MR CLEAN), and a higher rate of successful reperfusion (TICI score of 2b or 3). The longer time from alteplase administration to randomization (approximately 114 minutes)

in MR CLEAN indicated that most patients underwent randomization after the alteplase infusion was completed.[4] These differences may account for the higher proportions of good outcomes and the larger effect size observed in the ESCAPE trial.

There are limitations of our study. First, we purposefully did not require screening logs (which tend to yield poor-quality data) and cannot provide an estimate of how many patients were ineligible on the basis of imaging criteria. Second, a majority of participants were enrolled at selected endovascular centers that are capable of implementing efficient workflow and imaging processes. This level of efficiency and expertise is not currently widespread, which limits the immediate generalizability of our results. Although the time targets used in our trial may appear daunting, the history of intervention for acute coronary syndromes suggests that such efficiency in workflow is widely attainable.[35,39,40]

In conclusion, the ESCAPE trial, in which fast and efficient workflow, innovative imaging, and effective thrombectomy devices were used, provides evidence of the benefit of endovascular treatment in patients with moderate-to-severe ischemic stroke.

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Supplementary Appendix

Supplementary Table 1 – Additional Baseline Characteristics

	Intervention n=165	Control n=150
Past Medical History – no. (%)		
Hyperlipidemia	58 (35.2)	66 (44.0)
Smoking (past or current)	80 (48.8)	73 (49.3)
Ischemic heart disease	40 (24.2)	31 (20.7)
Congestive heart failure	24 (14.6)	24 (16.0)
Past stroke	17 (10.3)	17 (11.3)
Clinical – median (IQR)		
DBP (mm Hg) at hospital arrival	80 (20)	80 (24)
Creatinine (μM)	84 (28)	84 (27)
Onset-to-randomization time – no. (%)		
< 3 hours	88 (53.3)	78 (52.0)
3-5.9 hours	48 (29.1)	52 (35.7)
6-8.9 hours	17 (10.3)	15 (10.0)
9-12 hours	12 (7.3)	5 (3.3)
Process times min – median (IQR)		
IV alteplase to randomization†	24 (65)	20.5 (86)
IV alteplase to randomization (drip and ship) (n=57)*	120 (90)	134 (108)
IV alteplase to randomization (mother ship) (n=153)	17 (22)	16 (18.5)
IV alteplase-to-groin-puncture (n=116)	50.5 (67)	---
IV alteplase-to-first-reperfusion (n=101)	85 (83)	---
Groin-puncture-to-first-reperfusion (n=144)	30 (27.5)	---

IQR: interquartile range; DBP: diastolic blood pressure; μM = μmol/L; SD = standard deviation; CT: Computed Tomography
† 16 subjects were randomized prior to receiving IV tPA
*1 missing alteplase time in the drip and ship intervention group

All averages are presented as median and inter-quartile range. Proportions are presented as %. First reperfusion is defined as the first visualization of MCA flow, usually on the deployment of a retrievable stent.

Supplementary Table 2a – Serious Adverse Events

Serious Adverse Events* - no. (%)	**Intervention (N=165)**	**Control (N=150)**
Angioedema (orolingual)	0 (0)	1 (0.7)
Atrial fibrillation	3 (1.8)	1 (0.7)
Cancer	2 (1.2)	2 (1.3)
Carotid endarterectomy	2 (1.2)	0 (0)
Congestive heart failure / pulmonary edema	4 (2.4)	3 (2.0)
Fall	1 (0.6)	1 (0.7)
GI bleed	2 (1.2)	1 (0.7)
Myocardial infarction	2 (1.2)	1 (0.7)
Pneumonia	7 (4.2)	9 (6.0)
Limb deep venous thrombosis / pulmonary thromboembolism	2 (1.2)	2 (1.3)
Recurrent stroke	8 (4.9)	3 (2.0)
Sepsis	1 (0.6)	2 (1.3)
Systemic embolus	1 (0.6)	0 (0)
Seizure	0 (0)	1 (0.7)

*Serious adverse events (SAEs) were those that resulted in death, a prolonged hospital stay, re-admission to hospital, or were severe or life threatening. The SAEs listed here are in addition to those shown in Table 3.

Supplemental Table 2b – Selected Non-serious and Radiological Adverse Events

Non-serious Adverse Events* – no. (%)	Intervention (N=165)	Control (N=150)
Associated with Intervention**		
Access site hematoma (all femoral)	12 (7.2)	0 (0)
Carotid dissection	1 (0.6)	0 (0)
Cranial nerve palsy (cavernous sinus syndrome)	1 (0.6)	0 (0)
Sub-arachnoid hemorrhage	1 (0.6)	0 (0)
Common Adverse Events		
Urinary Tract Infection	20 (12.1)	30 (20.0)
Headache	27 (16.4)	22 (14.7)
Pneumonia	12 (7.3)	15 (10.0)
Atrial fibrillation	10 (6.1)	12 (8.0)
Myocardial infarction	0 (0)	1 (0.7)
Limb deep venous thrombosis / pulmonary thromboembolism	3 (1.8)	2 (1.3)
Gastrointestinal hemorrhage	2 (1.2)	3 (2.0)
Angioedema (orolingual)	1 (0.6)	1 (0.7)
Radiological Safety Outcome measures – no. (%) [core lab determined]		
Radiological ICH		
PH-2	4 (2.4)	1 (0.7)
PH-1	4 (2.4)	2 (1.3)
rPH-1	1 (0.6)	1 (0.7)
rPH-2	0 (0)	2 (1.3)
HI-2	25 (15.2)	9 (6.1)
HI-1	27 (16.4)	11 (7.3)
Radiological SAH	5 (3.0)	2 (1.3)

Core lab determined ICH types were scored according to the ECASS criteria. PH: parenchymal hematoma; rPH: remote parenchymal hematoma; HI: hemorrhagic infarction; SAH: sub-arachnoid hemorrhage; CT: computed tomography

*Non-serious adverse events were those that did not result in death, a prolonged hospital stay, re-admission to hospital, and were not severe or life threatening.

**18 patients suffered adverse events associated with intervention. Of these, 4 were judged to be serious and are listed in table 3; 14 were non-serious and are listed in Table S2b above. One patient suffered both a serious and non-serious adverse event and is represented in both tables.

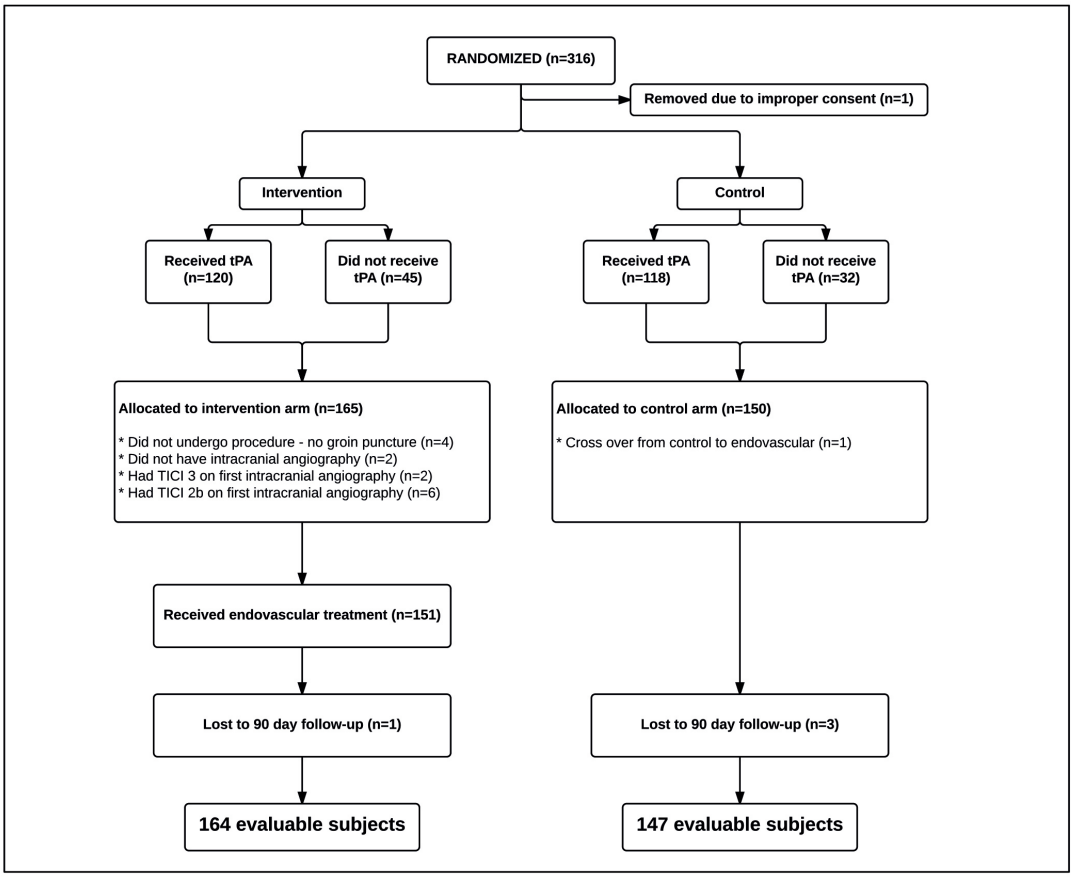
Supplementary Table 3a: The Thrombolysis in Infarction Score (TICI) [5]

Score	TICI
0	No perfusion
1	Penetration With Minimal Perfusion. The contrast material fails to opacify the entire cerebral bed distal to the obstruction for the duration of the angiographic run.
2a	Only partial filling (<2/3) of the entire vascular territory is visualized.
2b	Complete filling of all of the expected vascular territory is visualized, but the filling is slower than normal.
3	Complete Perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as into the obstruction *and* clearance of contrast material from the involved bed is as rapid as from an uninvolved other bed of the same vessel or the opposite cerebral artery.

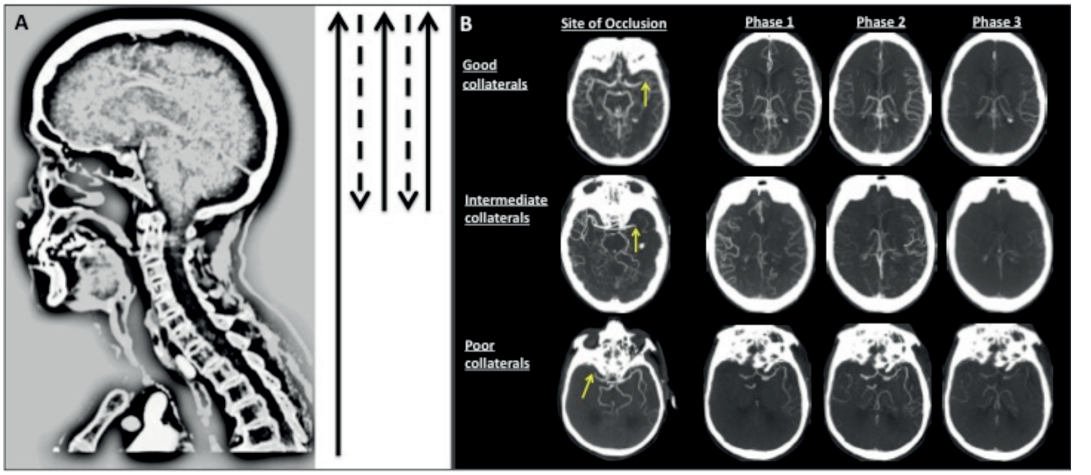
Supplementary Table 3b: The modified Arterial Occlusive Lesion (mAOL) score on follow-up CTA to assess recanalization of the occlusive lesion (thrombus) seen on the baseline CTA.

Score	mAOL
0	Primary occlusive lesion remains same
1	Debulking of thrombus without recanalization
2	Partial or Complete recanalization of the primary lesion with thrombus/occlusion in the distal vascular tree
3	Complete recanalization of the primary occlusion with no thrombus in the vascular tree at or beyond the primary occlusive lesion

Supplementary Figure 1: Consort Diagram

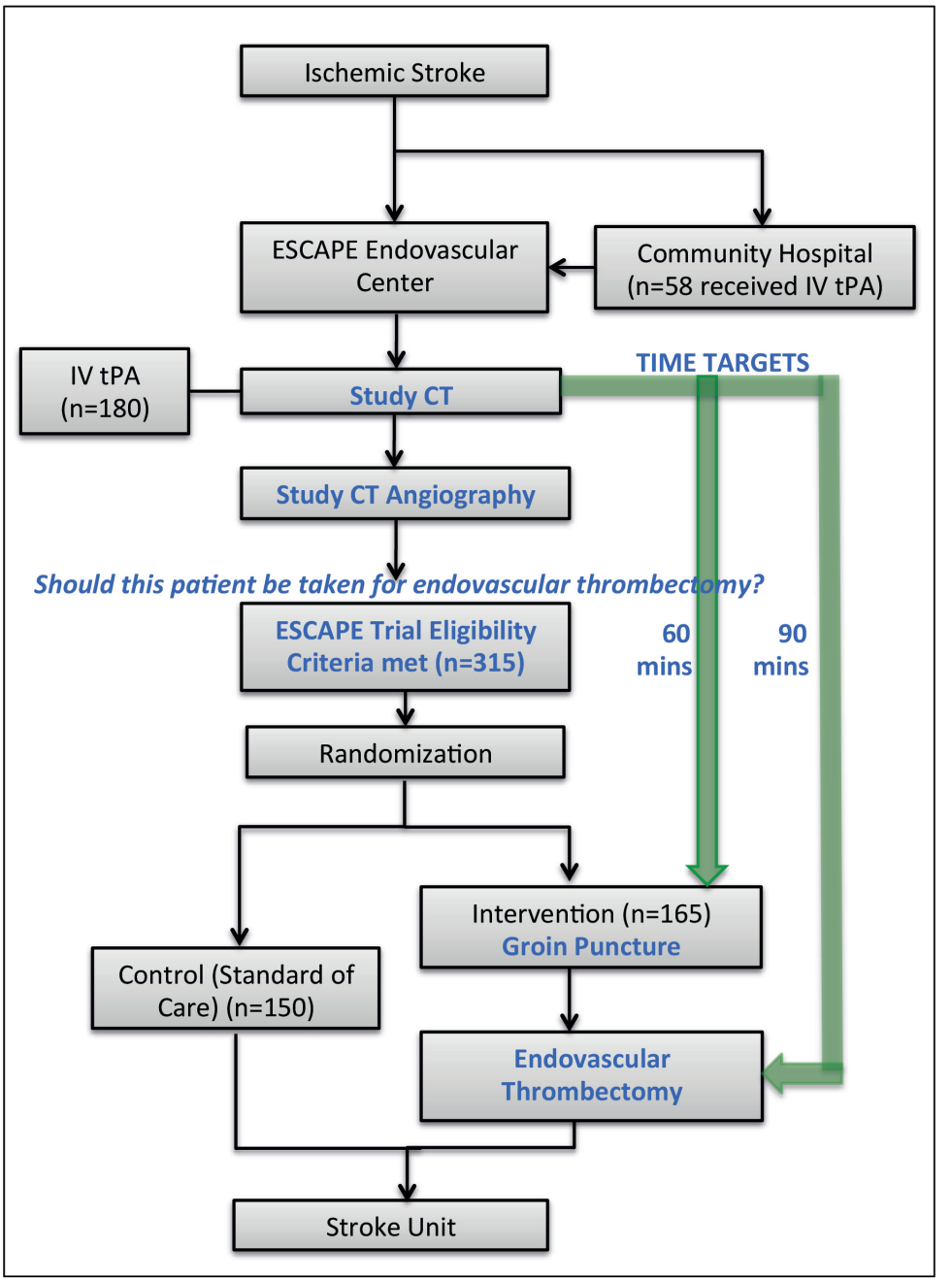


Supplementary Figure 2: The figure on the left shows the technique of multi-phase CTA. A solid arrow represents each image acquisition phase. Arrows with dash lines represent the scanner moving back to base of skull. The first phase (long solid arrow) is a conventional arch to vertex CT-angiogram. The next two phases (short solid arrows) are sequential skull base to vertex acquisitions acquired in the mid venous and late venous phase. The figure on the right shows collateral assessment using the multi-phase CTA technique. The upper row shows a patient with a left M1 MCA occlusion (arrow) and good collaterals (backfilling arteries) on multi-phase CTA. The middle row shows a patient with a left M1 MCA occlusion (arrow) and intermediate collaterals. The lower row shows a patient with a right M1 MCA occlusion (arrow) and poor collaterals (minimal backfilling arteries) on multi-phase CTA; this patient would have been excluded from the trial.

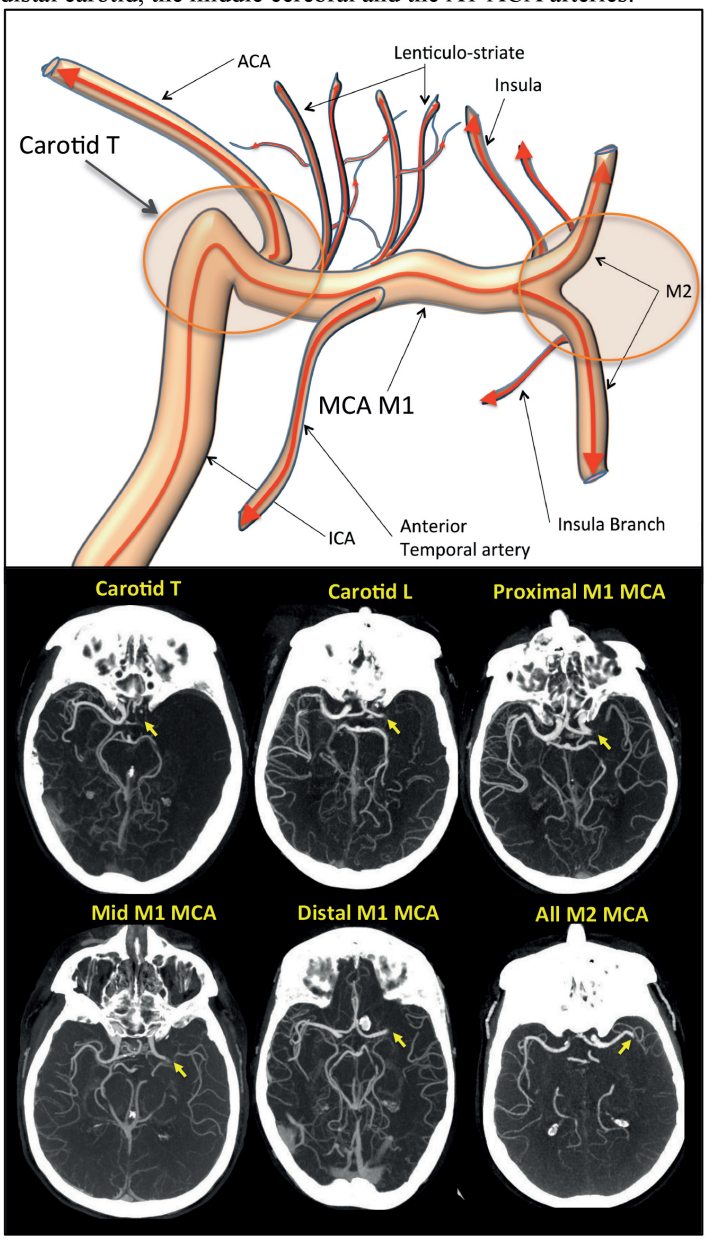


Modified with permission from: Menon BK d'Esterre C, Qazi E, Almekhlafi MA, Hahn L, Demchuk AM, Goyal M. Multi-phase CTA: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke. Radiology, 2015, Ahead of Print, 10.1148/radiol.15142256. Published online: January 29, 2015

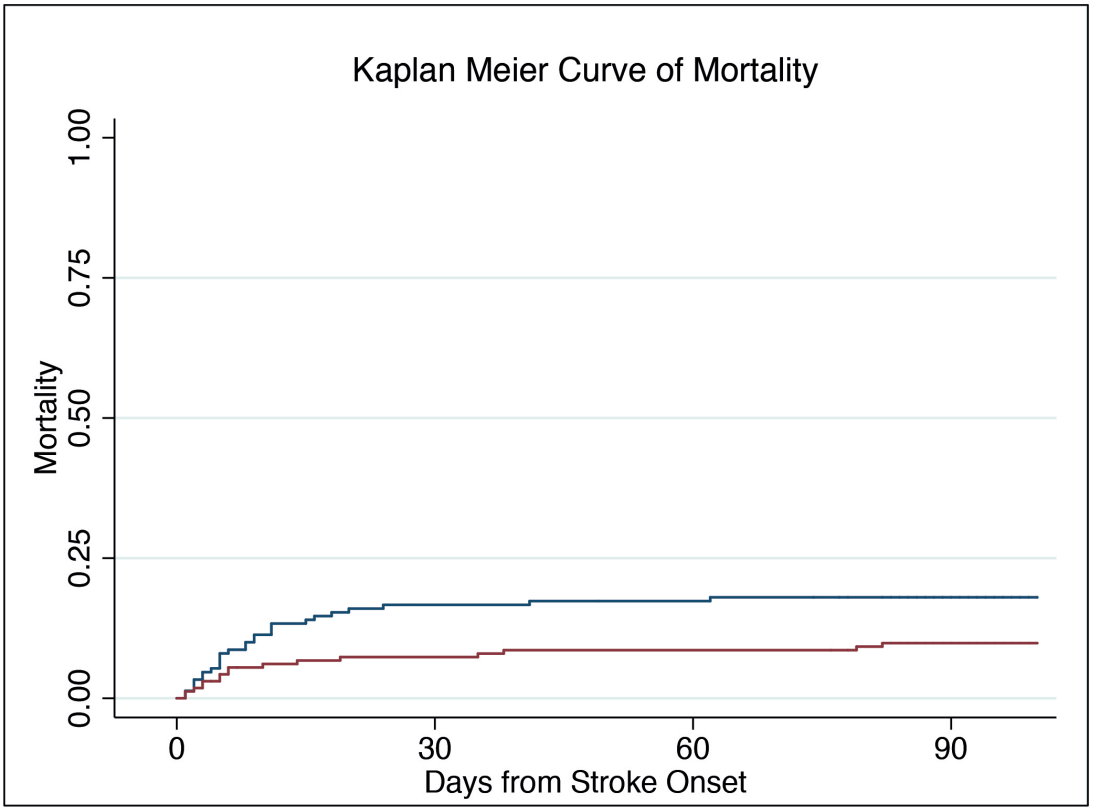
Supplementary Figure 3: Flow chart showing steps in the ESCAPE trial leading up to randomization. Intravenous alteplase (tPA) administration happened in parallel whenever indicated.



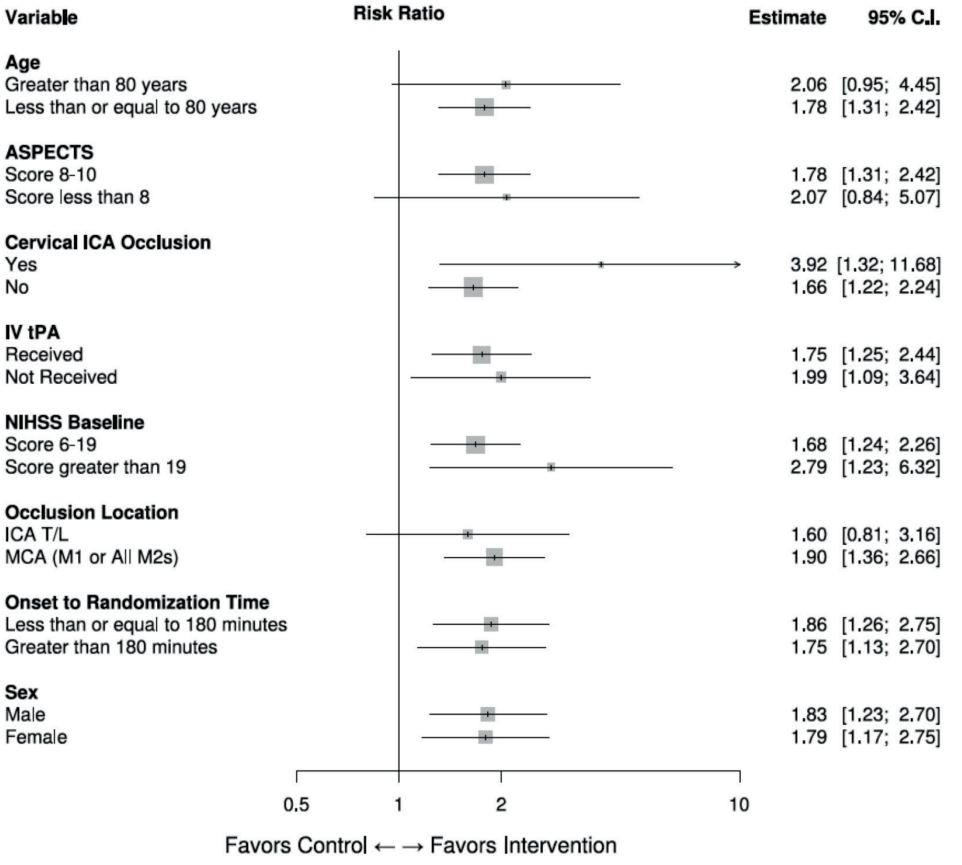
Supplementary Figure 4: The upper panel shows the carotid T segment, MCA M1 and M2 segments along with arterial branches arising from these segments. The lower panel shows occlusions in the proximal intracranial anterior circulation that were eligible to be included in the ESCAPE trial. A carotid L occlusion occurs when the thrombus occludes the distal carotid and the middle cerebral but not the A1-ACA arteries; a carotid T occlusion occurs when the thrombus occludes the distal carotid, the middle cerebral and the A1-ACA arteries.



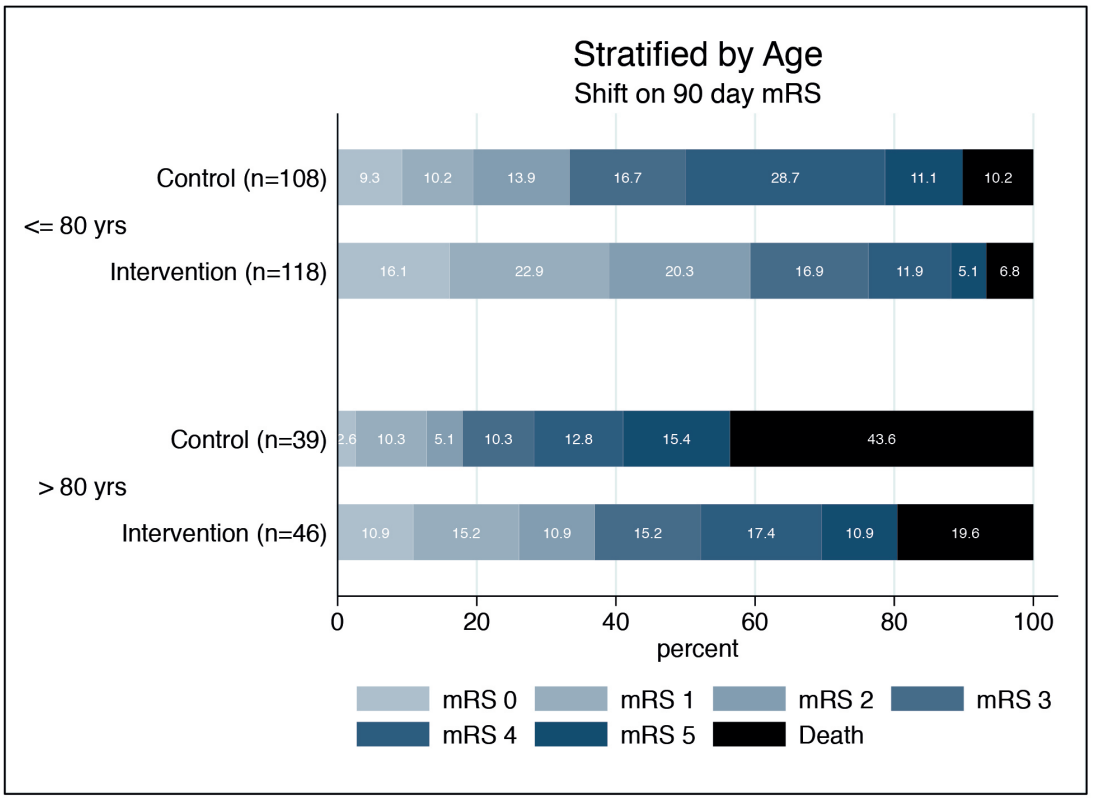
Supplementary Figure 5 - Kaplan Meier curve shows a mortality benefit favoring intervention (adjusted Hazard ratio of 0.4 (95%CI 0.2-0.8) [Adjusted for age, sex, baseline NIHSS score, baseline ASPECTS score, IV alteplase use, baseline occlusion location]



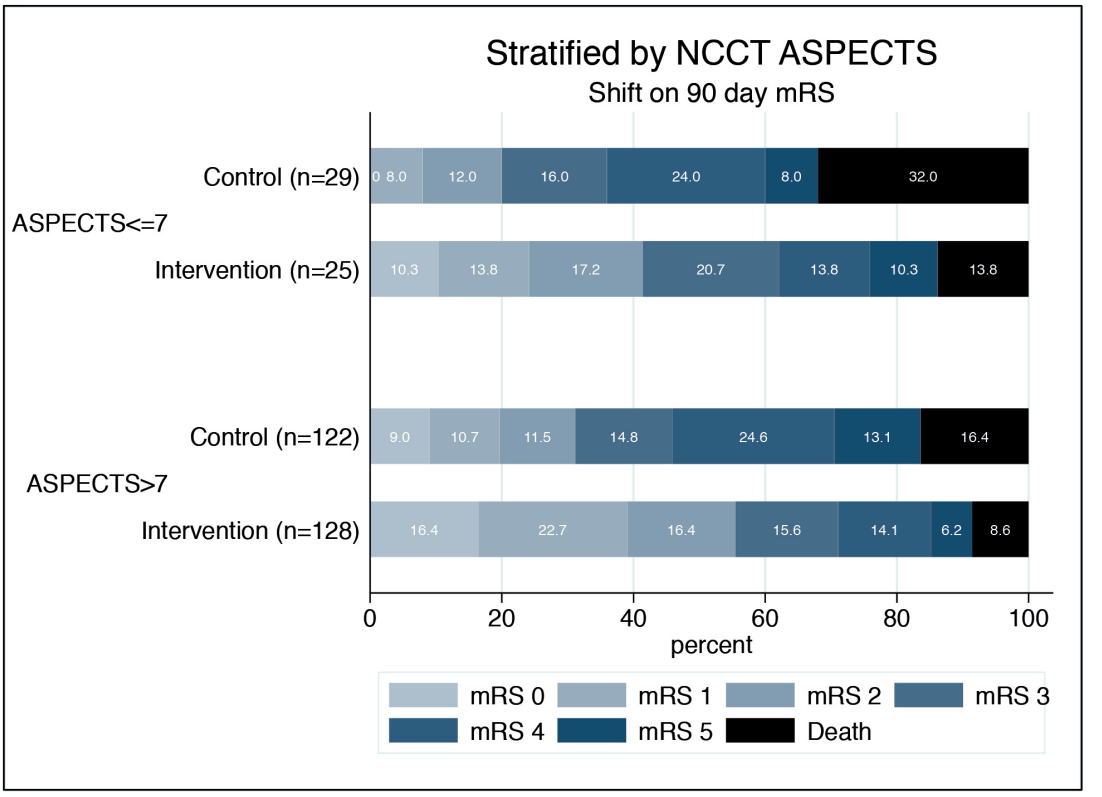
Supplementary Figure 6: Forest plot showing that the difference in mRS 0-2 at 90 days favors the intervention group over the control group, stratified by pre-specified variables. Thresholds for age and NIHSS score were chosen at the 75th percentile, onset-to-randomization time just above the median. Threshold for ASPECTS was pre-defined. All $p_{interaction} > 0.10$, Mantel-Haenszel χ^2 test.



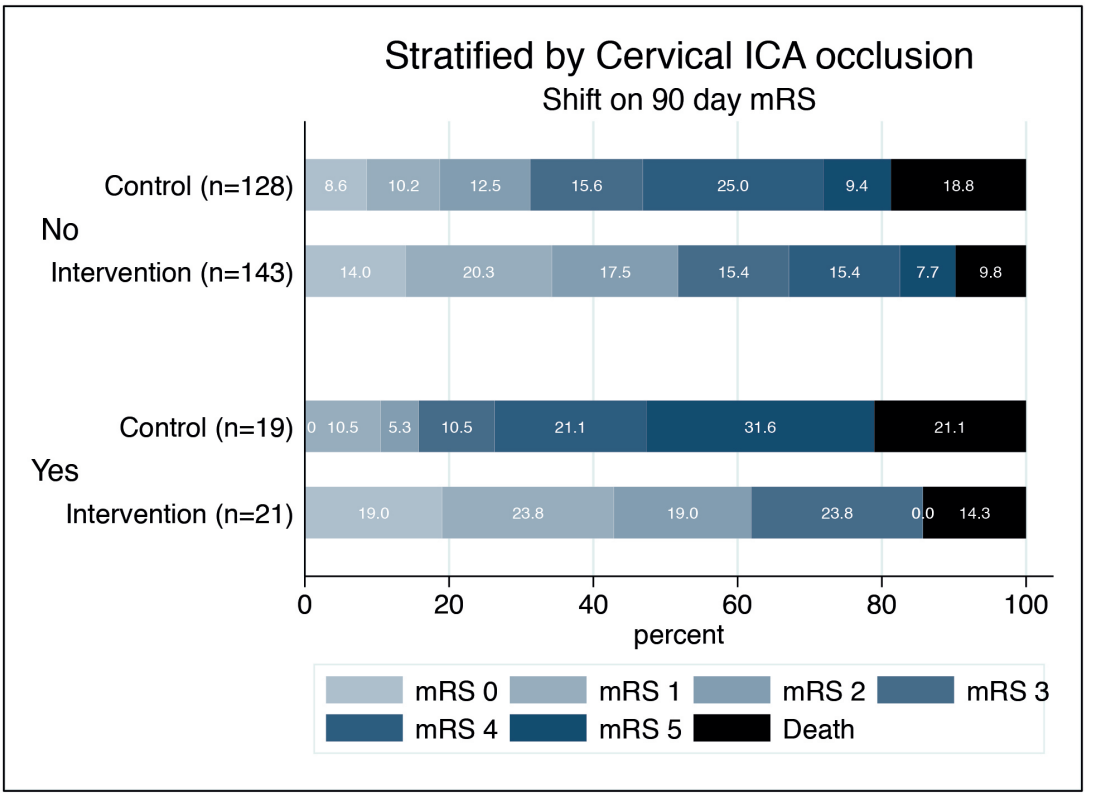
Supplementary Figure 7a: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects with age ≤ 80 years vs. > 80 years. Threshold for age was chosen at the 75th percentile. There is no evidence of heterogeneity of treatment effect between these subgroups. ($p_{interaction}$=0.382, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



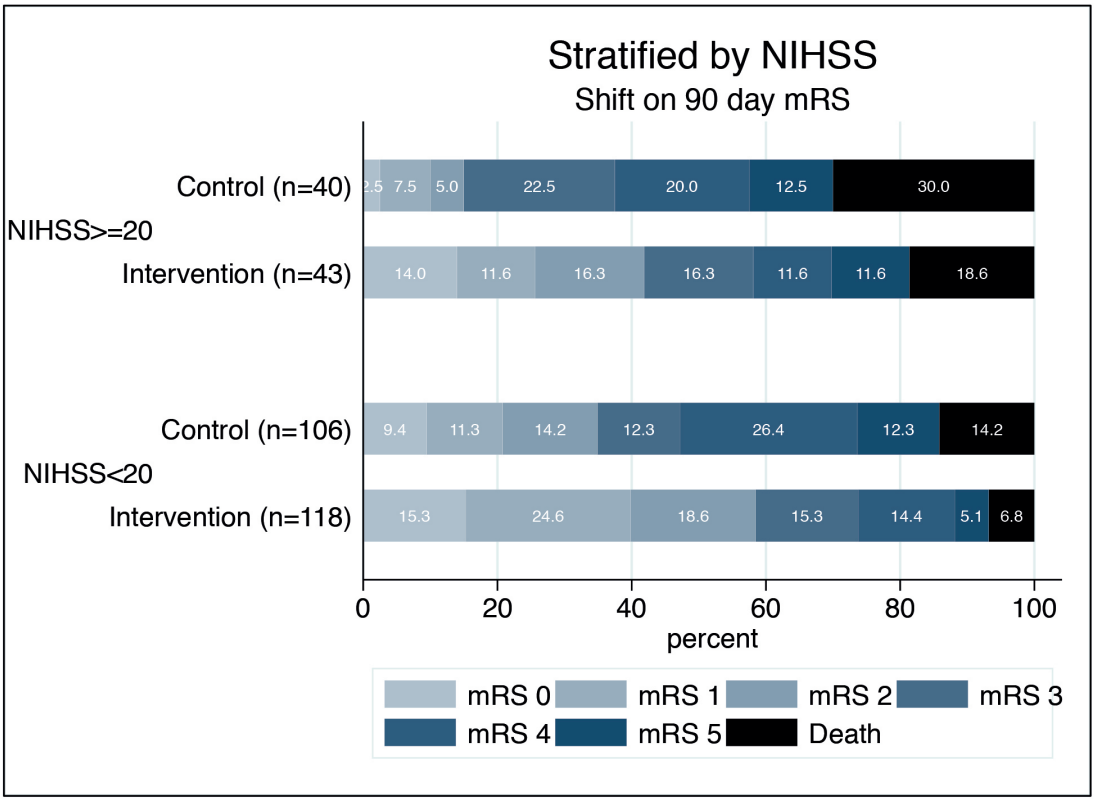
Supplementary Figure 7b: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects with baseline non-contrast CT ASPECTS ≤ 7 vs. > 7. Nine subjects had CT ASPECTS 0-5 (protocol violators) and are included in the ASPECTS ≤ 7 group for this analysis. Threshold for ASPECTS was pre-defined. There is no evidence of heterogeneity of treatment effect between these subgroups. ($p_{interaction}$=0.914, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



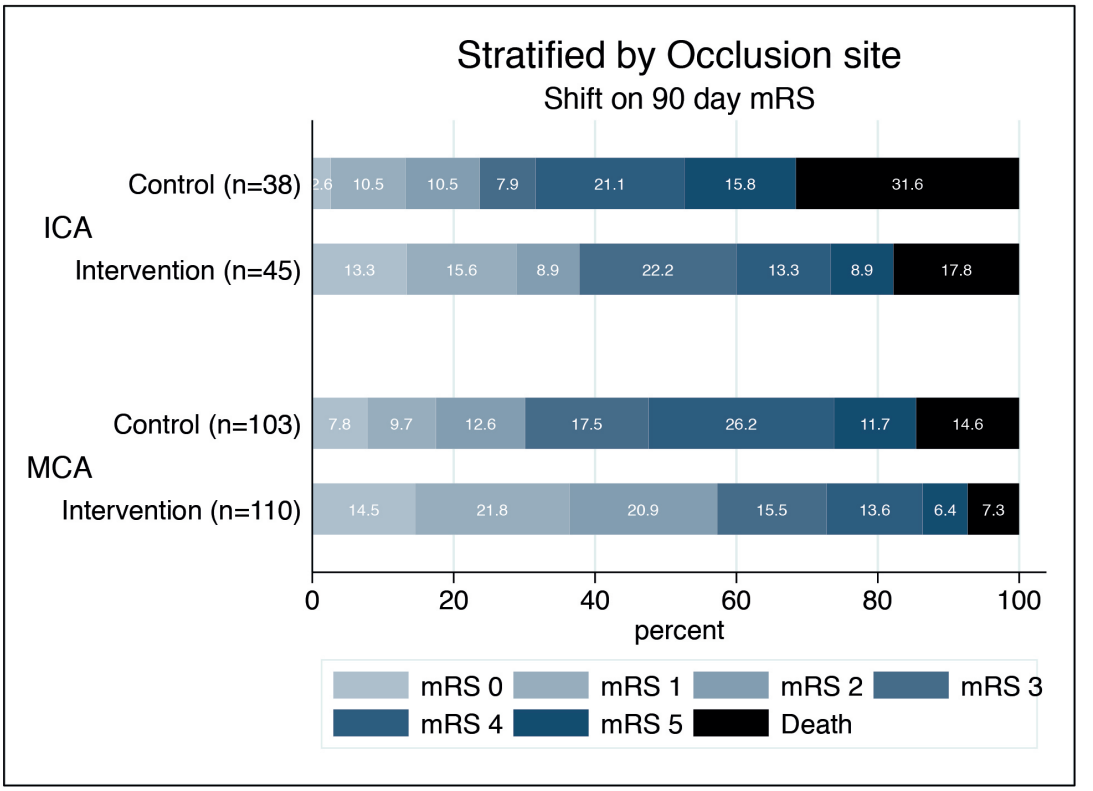
Supplementary Figure 7c: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects stratified by presence or absence of cervical ICA occlusion. There is borderline evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.049, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



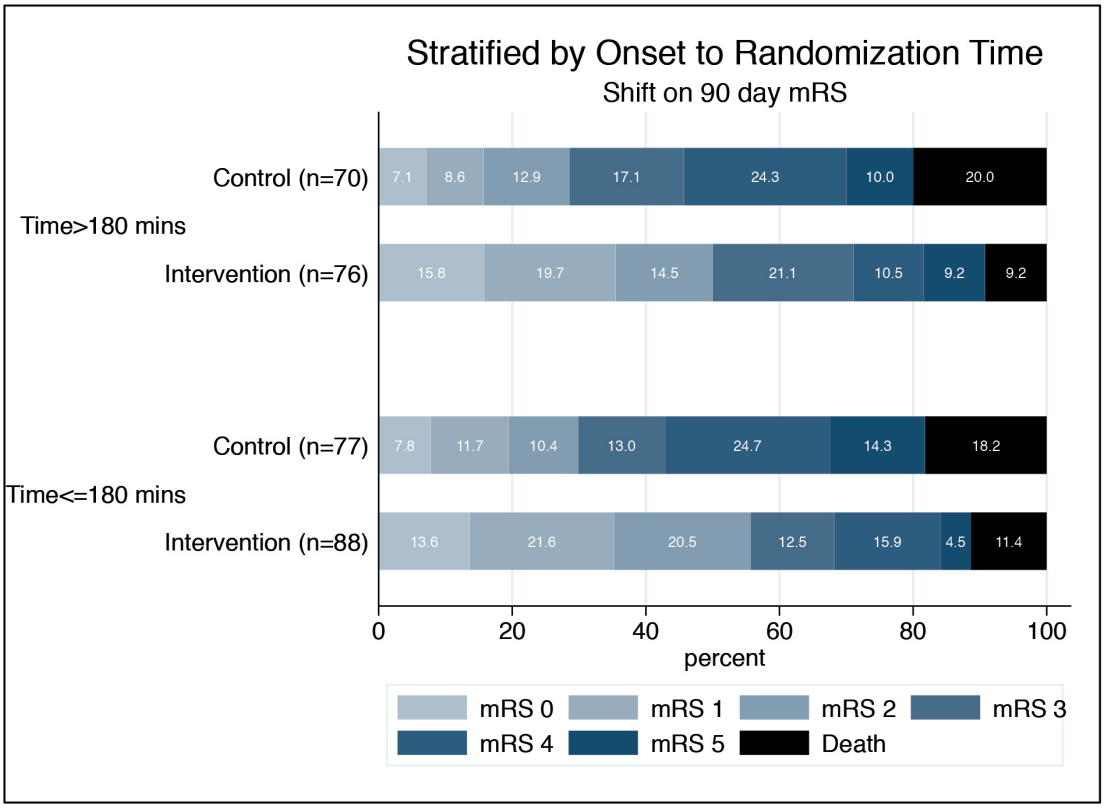
Supplementary Figure 7d: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects stratified by baseline NIHSS. Threshold for NIHSS was chosen at the 75th percentile. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.994, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



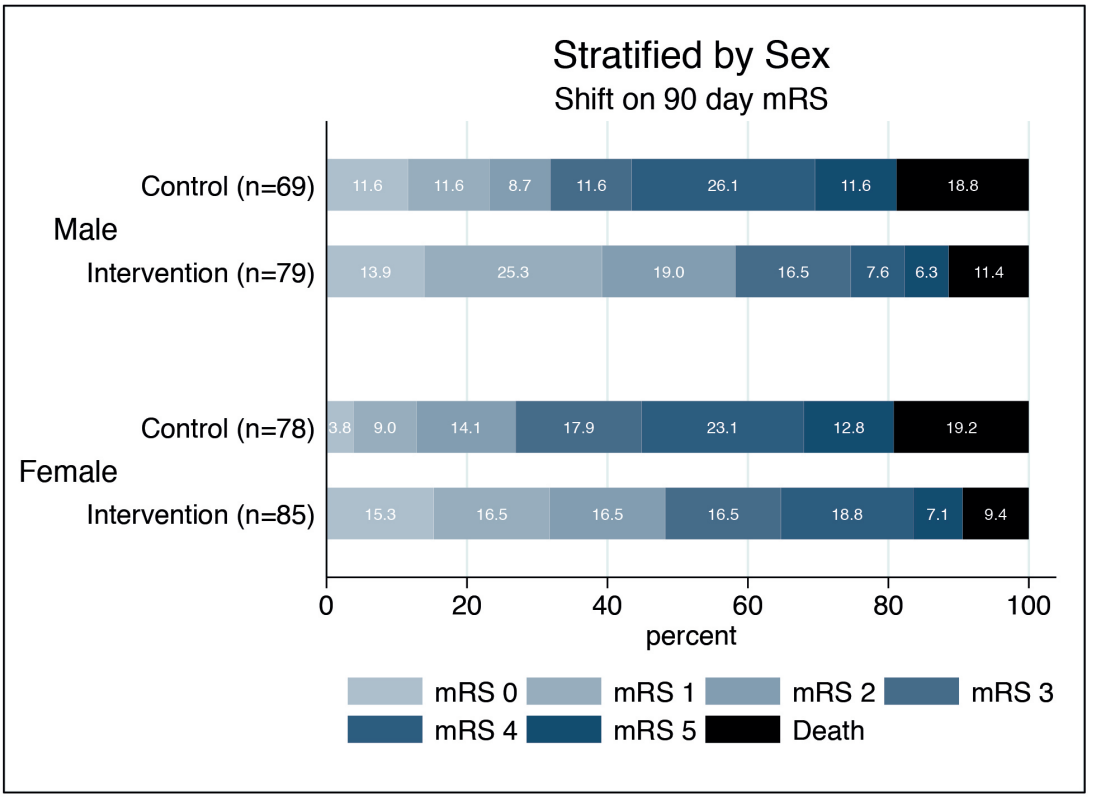
Supplementary Figure 7e: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects stratified by occlusion location (carotid 'T' or 'L' occlusion vs. MCA M1 or both M2 segments). There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.796, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



Supplementary Figure 7f: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects stratified by time from stroke symptom onset to randomization. Threshold for time was chosen just above the 50th percentile. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.983, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



Supplementary Figure 7g: Figure shows benefit in the intervention group when compared to the control group across the 90-day mRS distribution in subjects stratified by sex. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.827, Wald test). Categories 5 and 6 were merged for ordinal logistic regression.



CHAPTER 2.2

Stent-Retriever Thrombectomy After Intravenous T-Pa Vs. T-Pa Alone In Stroke

Based upon:

Stent-Retriever Thrombectomy after Intravenous t-PA vs. t-PA Alone in Stroke

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ABSTRACT

Background

Among patients with acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, less than 40% regain functional independence when treated with intravenous tissue plasminogen activator (t-PA) alone. Thrombectomy with the use of a stent retriever, in addition to intravenous t-PA, increases reperfu sion rates and may improve long-term functional outcome.

Methods

We randomly assigned eligible patients with stroke who were receiving or had received intravenous t-PA to continue with t-PA alone (control group) or to undergo endovascular thrombectomy with the use of a stent retriever within 6 hours after symptom onset (intervention group). Patients had confirmed occlusions in the proximal anterior intracranial circulation and an absence of large ischemic-core lesions. The primary outcome was the severity of global disability at 90 days, as assessed by means of the modified Rankin scale (with scores ranging from 0 [no symptoms] to 6 [death]).

Results

The study was stopped early because of efficacy. At 39 centers, 196 patients under went randomization (98 patients in each group). In the intervention group, the median time from qualifying imaging to groin puncture was 57 minutes, and the rate of substantial reperfusion at the end of the procedure was 88%. Thrombectomy with the stent retriever plus intravenous t-PA reduced disability at 90 days over the entire range of scores on the modified Rankin scale ($P<0.001$). The rate of functional independence (modified Rankin scaJe score, 0 to 2) was higher in the inter vention group than in the control group (60% vs. 35%, $P<0.001$). There were no significant between-group differences in 90-day mortality (9% vs. 12%, $P=0.50$) or symptomatic intracranial hemorrhage (0% vs. 3%, $P=0.12$).

Conclusions

In patients receiving intravenous t-PA for acute ischemic stroke due to occlusions in the proximal anterior intracranial circulation, thrombectomy with a stent retriever within 6 hours after onset improved functional outcomes at 90 days. (Funded by Covidien; SWIFT PRIME Clinical*Trials*.gov number, NCT01657461.)

Intravenous tissue plasminogen actlvator (t-PA) administered within 4.5 hours after the onset of acute ischemic stroke improves outcomes.[1-3] However, intravenous t-PA has multiple constraints, including unresponsiveness of large thrombi to rapid enzymatic digestion, a narrow time window for administration, and the risk of cerebral and systemic hemorrhage. Among patients with occlusions of the intracranial internal carotid artery or the first segment of the middle cerebral artery (or both), intravenous t-PA results in early reperfusion in only 13 to 50%.[4-7]

Neurovascular thrombectomy is a reperfusion strategy that is distinct from pharmacologic fibri nolysis. Endovascular mechanical treatments can remove large, proximal clots rapidly and result in higher rates of reperfusion than intravenous t-PA alone. Three initial trials of endovascular thera pies did not show a benefit for thrombectomy over intravenous t-PA or supportive medical care, but they were limited by the use of intraarterial delivery of t-PA or the use of early-generation devices with modest reperfusion efficacy (or both), the failure of two trials to use vessel imaging to confirm the presence of an appropriate target occlusion, and the slow initiation of endovascular intervention.[8-10]

The Solitaire revascularization device (Covidien) is a self-expanding stent used to retrieve thrombi and restore blood flow. In multicenter registries and one randomized trial, this stent retriever, as compared with early-generation mechanical thrombectomy devices, was associated with faster and more frequent reperfusion, reduced intracranial hemorrhage, and improved disability outcome.[11-15]

We performed the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial to establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with intravenous t-PA versus intravenous t-PA alone in patients with acute ischemic stroke. This trial was among several contemporaneous trials launched worldwide to test new-generation strategies for mechanical thrombectomy.[16-18] Our trial was conducted in multiple countries and health systems as a registration trial capable of supporting expansion of regulatory labeling. We used a uniform device procedure in the intervention group and tested intracranial neurovascular thrombectomy alone rather than in combination with cervical stenting.

METHODS

Trial Design

In this international, multicenter, prospective, randomized, open clinical trial, we compared in travenous t-PA followed by neurovascular tbrom bectomy with the use of a stent retriever with intravenous t-PA alone in patients with acute is chemic stroke. All the patients had confirmed oc clusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both on vessel imaging and an absence of large ischemic-core lesions. Patients were randomly assigned in a 1:1 ratio to one of two treatment groups: intravenous t-PA plus stent retriever (in tervention group) or intravenous t-PA alone (control group). Using a minimization algorithm, we balanced the numbers of patients in the two treatment groups with respect to four factors: investigational site, baseline severity according to the National Institutes of Health Stroke Scale (NIHSS) score (5.17 vs. >17, on a scale of O to 42, with higher scores indicating greater severity), age (<70 years vs. 70 years), and occlusion location (middle cerebral artery vs. internal carotid artery). Details of the study design have been published previously.[1,9] The study was conducted and reported with fidelity to the study protocol, available with the full text of this article at NEJM.org. (An overview of the study procedure is provided in Fig. Sl in the Supplementary Appendix, available at NEJM.org.)

The trial was approved by the institutional review board at each site. Enrolled patients provided written informed consent, or at select sites, there was an exception from explicit informed consent in emergency circumstances.

The trial was funded by Covidien and designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance per formed by the sponsor. The first and subsequent drafts of the manuscript were written by the first and second authors, incorporating input from all the authors. The academic authors had unrestricted access to the data, performed the data analysis with the primary and the independent study statisticians, and attest to the integrity of the trial and the completeness and accu-

racy of the reported data. The trial was monitored by an independent data and safety monitoring board.

PATIENTS AND PARTICIPATING CENTERS

The study was performed at 39 centers in the United States and Europe. All study centers were required to have performed at least 40 mechanical-thrombectomy procedures, including at least 20 procedures with the Solitaire stent retriever, annually. Entry criteria selected patients who had acute ischemic stroke with moderate-to-severe neurologic deficits; had imaging-confirmed oc clusion of the intracranial internal carotid artery, the first segment of the middle cerebral artery, or both; met the imaging eligibility requirements; were receiving or had received intravenous t-PA; and were able to undergo initiation of endovascular treatment within 6 hours after the time that they were last known to be well before the onset of acute stroke symptoms. Qualifying imaging had to be performed at a study hospital; imaging was repeated for patients who were transferred from outside hospitals. Detailed study inclusion and exclusion criteria are provided in Table Sl in the Supplementary Appendix.

To identify patients with salvageable tissue, at trial launch the entry criteria regarding imaging selection required patients to have a target-mismatch penumbral profile, with a small core of tissue that was likely to be irreversibly injured and a large region of hypoperfused tissue that was likely to be salvageable. Penumbral imaging analysis was performed with the use of RAPlD (iSchemaView), an operator-independent image postprocessing system.[20] After the enrollment of the first 71 patients, these criteria were revised to use a small-to-moderate core-infarct strategy (Table Sl in the Supplementary Appendix) to accommodate study sites with limited perfusion imaging capability and to ensure accelerated treatment delivery. Study sites with advanced imaging capability were still encouraged to obtain penumbral imaging and to exclude patients who did not meet the target-mismatch profile.

INTERVENTION

In the intervention group, neurovascular throm bectomy was performed with the use of the Solitaire FR (Flow Restoration) or Solitaire 2 device. Concomitant stenting of the cervical internal carotid artery was not permitted, although angioplasty could be performed

to permit intracranial access. A studywide continuous quality-improvement program emphasized the speed and quality of the neurointerventional workflow, including rapid patient transfer to the neuroangiography suite and procedure performance. The study target for the time from qualifying imaging to groin puncture was within 70 minutes.

OUTCOME MEASURES

The primary study-outcome measure was disability at 90 days, as assessed by means of the modified Rankin scale, a global measure of disability on a seven-level scale, with scores ranging from 0 (no symptoms) to 6 (death) (Fig. 1). (Details on the use of this scale are provided in the Supplementary Appendix.)

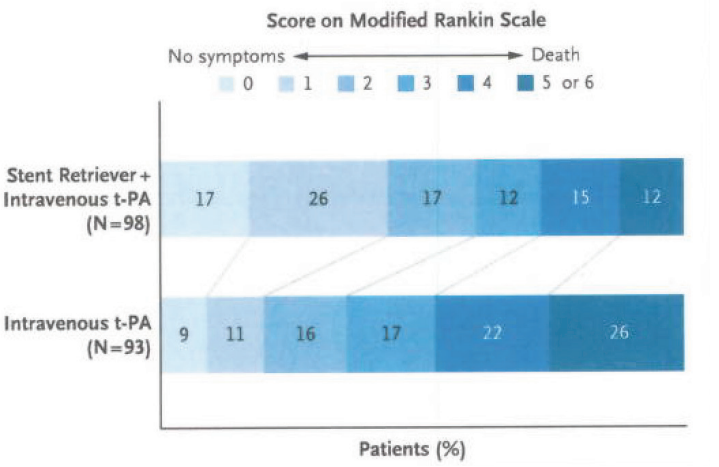

Figure 1. Functional Outcomes at 90 Days, According to the Score on the Modified Rankin Scale.

Shown are the 90-day scores on the modified Rankin scale for the patients in the two treatment groups. Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability (able to carry out all usual activities, despite some symptoms), 2 slight disability (able to look after own affairs without assistance but unable to carry out all previous activities), 3 moderate disability (requires some help but able to walk unassisted), 4 moderately severe disability (unable to attend to bodily needs with out assistance and unable to walk unassisted), 5 severe disability (requires constant nursing care and attention, bedridden, and incontinent), and 6 death. Persons with a score of 0, 1, or 2 are considered to be independent in daily function. Neurovascular thrombectomy with the use of a stent retriever was associated with a significant shift in the distribution of scores toward lesser disability ($P<0.001$ by the Cochran-Mantel-Haenszel test), including an absolute increase of 25 percentage points in the proportion of patients who were functionally independent at 90 days ($P<0.001$.) The term t-PA denotes tissue plasminogen activator.

Secondary clinical efficacy outcomes were the rate of death at 90 days, the rate of functional independence (modified Rankin scale score, 5.2) at 90 days, and the change in the NIHSS score at 27 hours after randomization. The technical efficacy outcomes regarding revascularization were substantial reperfusion, as assessed by means of catheter angiography in the intervention group and defined as a modified Thrornbolysis in Cerebral Infarction score of 2b (50 to 99% reperfu sion) or 3 (complete reperfusion)[21]; and successful reperfusion at 27 hours in the two study groups, which was defined as reperfusion of 90% or more of the initial perfusion-lesion volume, as assessed by means of perfusion imaging (computed tomography [CT] or magnetic resonance imaging [MRJ]) at 27 hours after randomization. Prespecified safety outcomes were all serious adverse events through study completion and symptomatic intracranial hemorrhage at 27 hours after randomization.

Clinical And Radiologic Assessment

Clinical assessments were performed at baseline, 27 hours after randomization, 7 to 10 days (or at discharge if earlier), 30 days, and 90 days. Clinical evaluations included the score on the modified Rankin scale for assessing global disability and the NIHSS score for assessing neurologic deficit. Entry and outcome neurovascular images were assessed in a blinded manner by staff at the core imaging laboratories (iSchemaView for penumbral and volumetric imaging and Synarc for parenchymal and angiographic imaging).

Table 1. Demographic and Clinical Characteristicsofthe Patients.*

Characteristic	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)
Age-yr	66.3±11.3	65.0±12.5
Male sex-no./total no. (%)	45/96 (47)	54/98 (55)
Race-no./total no. (%) †		
White	83/92 (90)	79/90 (88)
Black	8/92 (9)	10 /90 (11)
Asian or other	1/92 (l)	1/90 (l)
Hispanic ethnic group-no. (%) †	7/92 (8)	8/90 (9)
NIHSS score ‡		
Median	17	17
Interquartile range	13- 19	13-20
Prestroke score of 0 or 1 on modified Rankin scale-no./total no. (%) §	93/94 (99)	96/98 (98)
Medical history-no./total no. (%)		
Hypertension	56/97 (58)	66/98 (67)
Diabetes mellitus	15/97 (15)	12/98 (12)
Current or past tobacco use	39/93 (42)	41/96 (43)
Atrial fibrillation	38/97 (39)	35/98 (36)
Myocardial infarction	11/97 (11)	8/98 (8)
Serum glucose-mg/dl, ¶	131±47	131±46
Administration of intravenous t-PA at outside hospital-no./total no. (%)	35/94 (37)	31/98 (32)
Interval from symptom onset to start of intravenous t-PA-min		
Median	117	110.5
Interquartile range	80-155	85-156
Parenchymal imaging variable		
ASPECTS value ‖		
Median	9	9
Interquartile range	8-10	7- 10
Penumbral imaging performed-no./total no. (%)	75/97 (77)	83/98 (85)
Target-mismatch profile-no./total no.(%)**	64/75 (85)	69/83 (83)

Table 1. (Continued)

Characteristic	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)
Site of intracranial-artery occlusion-no./total no. (%)		
Internal carotid artery	15/94 (16)	17/93 (18)
Middle cerebral artery		
First segment	72/94 (77)	62/93 (67)
Second segment ††	6/94 (6)	13/93 (14)
Process time-min		
Stroke onset to randomization		
Median	188	190.5
Interquartile range	130-268	141-249
Stroke onset to groin puncture		
Median	NA	224
Interquartile range	NA	165-275
Stroke onset to first deployment of stent retriever		
Median	NA	252
Interquartile range	NA	190-300
Arrival in emergency department to groin puncture		
Median	NA	90
Interquartile range	NA	69-120
Qualifying image to groin puncture		
Median	NA	57
Interquartile range	NA	40-80

* Plus- minus values are means ±SD. There were no significant differences between the two groups. One patient in the group that received intravenous tissue plasminogen activator (t-PA) alone requested the deletion of all data. Three additio nal patients in the group that received intravenous t-PA alone (1 patient who died and 2 who withd re w) are missing some baseline data owing to early study exit, including data on the prestroke modified Rankin Scale score, the hospital site of intravenous t-PA ad ministrat io n, and site of intracranial-artery occlusion for all 3 patients, and data on sex, race, and ethnic group for l. Data on race and ethnic group were missing for all 13 patients in France owing to national regulations. Data regarding the location of the arterial occlusion were missing for 7 pa-tients be cause the core laboratory considered that imaging could not be assessed with complete reliability . Two patients were deemed by the core laboratory to not have occlusions in the internal carotid artery or the first or second segment of the middle cerebral arte ry. A total of37 patients did not have baseline penumbral imaging performed, after a protocol amendment making penumbra! imaging optional. Data regarding additional baseline characteristics are shown in Table S4 in the Supplementary Appendix. NA denotes not applicable.

† Race and ethnic group were self-reported.

‡ Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficit.

§ Scores on the modified Rankin scale for the assessment of global disability range from 0 (no symptoms) to 6 (death).

¶ To convert the values for glucose to millimoles per liter, multiply by 0.05551.

‖ The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core.

** The target-mismatch profile was defined as meeting the following criteria as assessed on CT perfusion or diffusion imaging and perfusion MRI: the core infarct lesion measured SO m l or less , the volume of tissue with a time to maxi mum delay of more than 10 seconds was100 ml or less, and the mismatch volume was at least 15 ml and the mis match ratio was more than 1.8:1.0.

†† These occlusions were classified as first-segment occlusions by the treating site at the time of study entry but as second-segment occlusions by the core imaging laboratory.

Statistical Analysis

For the primary outcome, we analyzed the score on the modified Rankin scale at 90 days using simultaneous success criteria of the overall dis tribution of the score (shift in disability levels) and the proportion of patients who were functionally independent. Both criteria needed to be met in order for the study to be declared positive. The statistical hypothesis on the scale shift was that the distribution over the entire range of scores (except for scores of 5 or 6, which were collapsed into a single group) among patients in the intervention group would be more favorable than the distribution in the control group, as analyzed by means of the Cochran-Mantel-Haenszel test.

A simultaneous requirement for success was that the difference in the proportion of patients with a score of 0 to 2 nominally meet a pre-specified minimum, which varied according to the final sample size at trial discontinuation or completion, with a larger benefit required with a smaller sample size (Table S2 in the Supplementary Appendix). Missing final scores on the modified Rankin scale were handled with the use of the last-observation-carried-forward approach when a score was available from the 30-day visit or the visit at 7 to 10 days. Power and sample size were determined with the use of the dual success criteria, incorporating a group sequential-analysis plan with five interim analyses for efficacy, futility, and safety. (Details are provided in Table S2 in the Supplementary Appendix and in the full statistical analysis plan in the protocol.)

After the preliminary results of the Multi-center Randomized Clinical Trial of Endovascu lar Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) and the Endovascular Treatment for Small Core and Anterior *Circulation* Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times (ESCAPE) trial were reported,[16,18]

our data and safety monitoring board recommended holding enrollment, and the first interim efficacy analysis was performed slightly early (including 196 rather than 200 patients). In February 2015, the study was halted when the interim efficacy analysis showed that the prespecified stopping-criteria boundary for efficacy had been crossed. A test to determine whether the data across clinical sites could be pooled showed no evidence of heterogeneity of treatment effect (P=0.73 by the Breslow-Day test), so pooled study results are presented. All P values are two-sided.

RESULTS

Characteristics Of The Patients

From December 2012 through November 2014, 196 patients underwent randomization (98 in each group) at 39 centers in the United States and Europe. Reasons for exclusion are listed in Table S3 in the Supplementary Appendix.

The demographic and clinical characteristics of the two treatment groups at baseline were well balanced (Table 1, and Table S4 in the Supplementary Appendix). Figure S2 in the Supplementary Appendix shows the enrollment and follow-up of patients in the trial.

Intervention

In the intervention group, the time from symptom onset to groin puncture was 224 minutes (interquartile range, 165 to 275), the time from the start of intravenous t-PA to groin puncture was 77 minutes (interquartile range, 50 to 142), and the time from study-qualifying brain imaging to groin puncture was 57 minutes (interquar tile range, 40 to 80). In the intervention group, the stent retriever was deployed in 87 patients (89%); the reasons for nondeployment are listed in Table S5 in the Supplementary Appendix. Among these 87 patients, the median time from groin puncture to first deployment of the stent retriever was 24 minutes (interquartile range, 18 to 33). General anesthesia was used in 36 patients (37%) in the intervention group.

Primary Outcome

Treatment with thrombectomy with the use of the stent retriever met both of the simultaneous success criteria. Thrombectomy treatment was associated with a favorable shift in the distribution of global disability scores on the modified Rankin scale at 90 days (P<0.001 by the Cochran Mantel-Haenszel test, which was lower than the P value of 0.01 that was specified for early stopping; number needed to treat for one additional patient to have a less-disabled outcome, 2.6). The shift toward better outcomes was consistent in direction across all the score levels of the modified Rankin scale (Fig. 1). The proportion of patients who were functionally independent (modified Rankin scale score, 5.2) at 90 days was higher in the intervention group than in the control group, with an absolute difference of 25 percentage points, which exceeded the 12-percent-age-point boundary that was prespecified for early stopping. Results remained significant in sensitivity analyses that used multiple imputation and worst-case and best-case scenarios to account for missing data (Table S6 in the Supplementary Appendix) and in analyses that were adjusted for imbalances in baseline prognostic features (Table S7 and Fig. S3 in the Supplementary Appendix).

Secondary Outcomes

Prespecified secondary clinical efficacy outcomes and technical efficacy outcomes regarding revascularization are shown in Table 2; additional pre-specified and post hoc outcomes are shown in Tables Sl0 and S13 in the Supplementary Appendix. The proportion of outcomes indicating functional independence at 90 days was significantly higher in the intervention group than in the control group, with an absolute difference of 25 percentage points (95% confidence interval [CI], 11 to 38) and a risk ratio of 1.70 (95% CI, 1.23 to 2.33; P<0.001; number needed to treat for one additional patient to be functionally independent, 4.0). Mortality at 90 days did not differ significantly between the intervention group and the control group (9% and 12%, respectively; *P*=0.50).

In the intervention group, substantial reperfusion (50 to 99%) or complete reperfusion (100%) at the end of the procedure occurred in 73 of the 83 patients (88%) who underwent placement of the stent retriever (Table S9 in the Supplementary Appendix). A total of 4 additional patients who underwent the intervention did not have a final angiogram that could be assessed. Successful reperfusion (. 90%) at 27 hours, assessed by means of

perfusion CT or MRI, was more frequent in the intervention group than in the control group (53 of 64 patients [83%] vs. 21 of 52 [40%], P<0.001).

Table 2. Primary and Secondary Outcomes.*

Outcome	Intravenous t-PA Alone (N=98)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	PValue
Primary outcome : scoreon modified Rankin scale at 90 days†				<0.001
No . of patients with data	93	98		
Median score	3	4		
Interquartile range	2-5	1-4		
Secondary outcomes				
Clinical efficacy outcome				
Functional independence at 90 days-no./ total no.(%)‡	33/93 (35)	59/98 (60)	1.70 (l. 23- 2.33)	
Change in NIHSS score at 27 hr				
No. of patients with data	92	97		
Mean change	- 3.9±6.2	-8.5±7.1		<0.001
Death at 90 days- no./total no. (%)§	12/97 (12)	9/98 (9)	0.74 (0.33-1.68)	0.50
Revascularization outcome ¶				
Substantial reperfusion immediately after thrombectomy-no./ total no. (%)	NA	73/83 (88)	NA	NA
Successful reperfusion at 27 hr no./total no. (%)	21/52 (40)	53/64 (83)	2.05 (l.45-2.91)	<0.001

* Plus-minus values are means ±SD. CI denotes confidence interval, and NA not applicable.

† Shown are the results of the prespecified Cochran-Mantel-Haenszel test for the shift in disability score. Similar results were found in the analysis of the common odds ratio (odds ratio, 2.63; 95% CI, 1.57 to 4.40; P<0.001).

‡ Functional independence was defined as a score of 0, 1, or 2 on the modified Rankin scale.

§ One patient in the group that received intravenous t-PA alone requested the deletion of all data, including vital status.

¶ Substantial reperfusion was defined as reperfusion of at least 50% and a modified Thrombolysis in Cerebral Infarction score of 2b (50 to 99% reperfusion) or 3 (complete reperfusion). Successful reperfusion was defined as reperfusion of at least 90%, as assessed with the use of perfusion CT or MRI. Data on successful reperfusion were not obtained for all the patients after the adoption of the protocol amendment making penumbral imaging optional.

Safety

The rates of serious adverse events (36% in the intervention group and 31% in the control group, *P*=0.54) and symptomatic intracranial hemorrhage (0% and 3%, respectively; *P*=0.12) did not differ significantly between the treatment groups (Table 3, and Table S11 in the Supplementary Appendix). There was no significant between-group difference in the rate of all intracranial hemorrhage subtypes that were assessed radiologically, but there were numerically more subarachnoid hemorrhages in the intervention group than in the control group (four patients and one patient, respectively; *P*=0.37). No serious adverse events and seven nonserious adverse events were adjudicated to be device-related (Table S12 in the Supplementary Appendix).

Table 3. Safety Outcomes.*

Outcome	Intravenous t-PA Alone (N=97)	Stent Retriever plus Intravenous t-PA (N=98)	Risk Ratio (95% CI)	PValue
	no. of patients (%)			
Primary safety outcomes				
Any serious adverse event at 90 days†	30 (31)	35 (36)	1.15 (0.78-1.72)	0.54
Symptomatic intracranial hemorrhage at 27 hr	3 (3)	0	0.00 (NA)	0.12
Additional safety outcomes at 27 hr				
Parenchymal hematoma	7 (7)	5 (5)	0.71 (0.23- 2.15)	0.57
Type 1	3 (3)	4 (4)	1.32 (0.3 5.74)	1.00
Type 2	4 (4)	1 (1)	0.25 (0.03- 2.17)	0.21
Subarachnoid hemorrhage	1 (1)	4 (4)	3.96 (0.45- 34.79)	0.37

* NA denotes not applicable.

† A serious adverse event was an adverse event that led to death, a life-threatening illness or injury, permanent impairment of a body structure or a body function, inpatient or prolonged hospitalization, medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function, or fetal distress, fetal death or a congenital anomaly or birth defect. Serious adverse events that are classified according to organ system are shown in Table S11 in the Supplementary Appendix. None of the serious adverse events were adjudicated by the clinical-events committee to be device-related. Nonserious adverse events that were deemed to be device-related are shown in Table S12 in the Supplementary Appendix.

Subgroup Analyses

Within the constraints of the study sample size, no evidence of heterogeneity of treatment effect was detected in any of the eight prespecified sub groups (Fig. 2, and Fig. S4 in the Supplementary Appendix). The benefit of thrombectomy with the stent retriever plus intravenous t-PA over intravenous t-PA alone was also observed in the pre-specified subgroup of patients who received in travenous t-PA within 3 hours after symptom onset (P<0.001) (Table S8 in the Supplementary Appendix).

DISCUSSION

Our study showed that in patients with acute ischemic stroke with confirmed large-vessel occlusions of the anterior circulation who were treated with intravenous t-PA, treatment with the stent retriever within 6 hours after symptom onset improved functional outcomes at 90 days. For every 2.6 patients who were treated, 1 additional patient had an improved disability outcome; for every 4.0 patients who were treated, 1 additional patient was functionally independent at 90-day follow-up.

These findings confirm and extend those of recent trials.[16-18] Our trial emphasized speedy endovascular therapy in patients selected by means of imaging, similar to the protocol used in the ESCAPE trial,[18] and achieved onset-to-reperfusion times that were faster than those in MR CLEAN[16] and in studies of early-generation interven tions.[8-10] The median time from arrival in the emergency department to groin puncture of 90 minutes was faster than the 120-minute target that is recommended in current multisociety guidelines.[22] In our trial, study sites were provided with a prespecified efficiency target of performing groin puncture within 70 minutes after qualifying imaging, and continuous central review encouraged rapid workflow. For patients with intravenous t-PA that was initiated at study centers, groin puncture and stent retriever deployment could take place while t-PA was infusing.

Several aspects of the treatment and treatment response were distinctive in our study. The rate of substantial or complete reperfusion (88%) among patients undergoing intracranial intervention was higher in this trial than in previous trials. The high reperfusion rate is

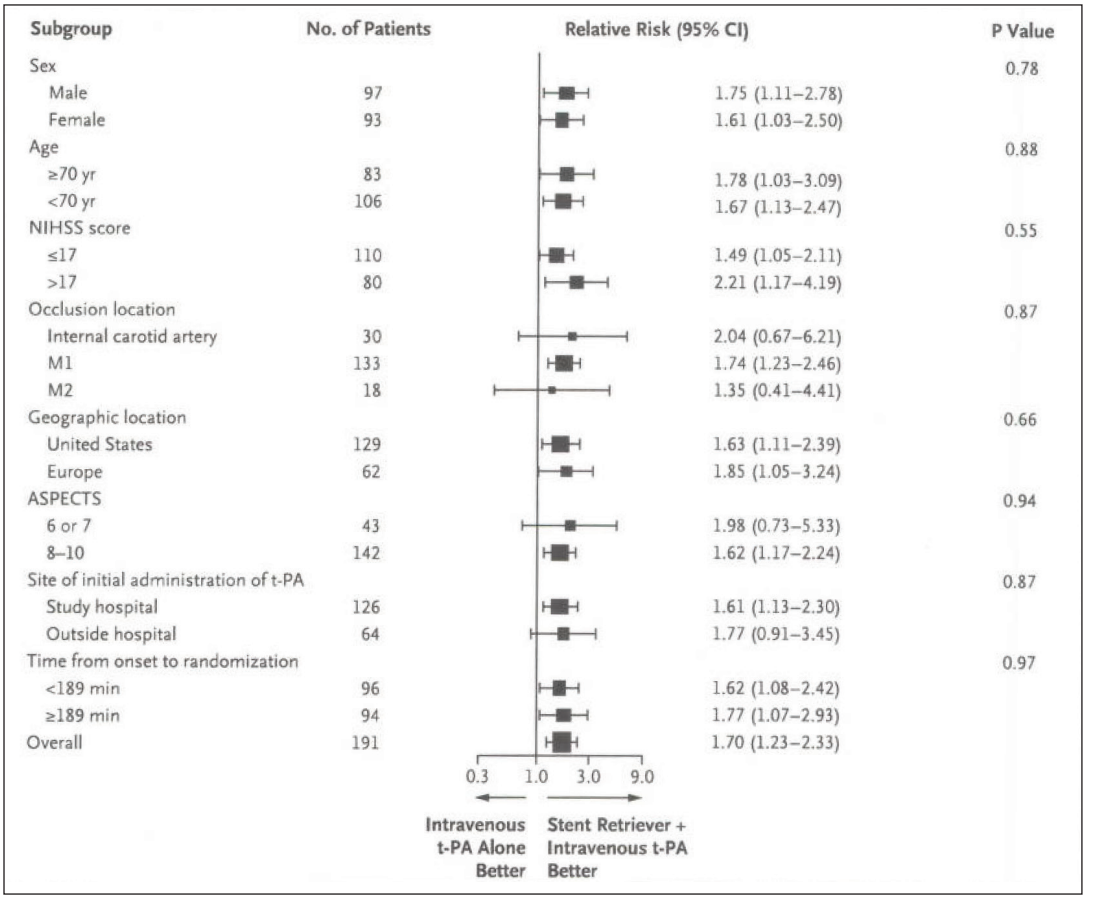

Figure 2. Analysis of Functional Independence at 90 Days in Prespecified Subgroups.

Functional independence was defined as a score on the modified Rankin scale of 0, l, or 2. P values were based on the Breslow-Day test for homogeneous odds ratios across subgroups. Squares indicate point estimates for treatment effects, and the size of the square is proportional to the precision of the estimate. Scores on the National Institutes of Health Stroke Scale (NIHSS) range from 0 to 42, with higher scores indicating more severe neurologic deficits. The threshold of 17 was the threshold used in stratifying randomization. The Alberta Stroke Program Early CT Score (ASPECTS) ranges from 0 to 10, with higher scores indicating a smaller infarct core; a score of 6 or 7 indicates moderate infarct core, and a score of 8 or higher small infarct core. For the time from stroke onset to randomization, the median value was prespecified as the cutoff point for analysis and was found to be 189 minutes. M1 denotes first segment of the middle cerebral artery, and M2 second segment of middle cerebral artery.

probably due in part to the more homogeneous patient population (more occlusions in the first segment of the middle cerebral artery and fewer intracranial or cervical occlusions of the internal carotid artery) and the more homogeneous intervention (an effective stent retriever and no other device classes and no intraarterial fibrinolytic agent) in this trial than in earlier trials. The frequency of functional independence in the intervention group was high in our trial (60%) and was greater than that observed in MR CLEAN (33%) and similar to that observed in the ESCAPE trial (53%) and the Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND IA) trial (71%).[17] The high frequency of this outcome probably reflects the earlier start of the intervention,[21-26] the exclusion of patients with large core infarcts on the basis of imaging,[27-28] and the greater reperfusion rate in our trial, as compared with the other trials.

No significant differences in treatment effect were detected across all the prespecified sub-groups, including such factors as age, sex, degree of neurologic deficit, site of occlusion, and size of infarct core on qualifying imaging, although the moderate sample size limited the power of this analysis. We also performed a prespecified analysis comparing patients who received intravenous t-PA at an outside hospital and were transferred to a study center for thrombectomy with those who received both the intravenous t-PA and the endovascular intervention at the study center. One third of the patients were treated with intravenous t-PA at an outside hospital. These patients had less favorable outcomes overall; however, their relative benefit from endovascular therapy did not differ significantly from that observed in patients who received intravenous t-PA at the study site (Fig. 2, and Fig. S4 in the Supplementary Appendix).

The rates of serious adverse events did not differ significantly between the study groups overall or within major organ categories, and no device-specific serious adverse events were observed. The most common nonserious device-specific adverse event was transient, intraprocedural vasospasm without clinical sequelae. Rates of symptomatic hemorrhage were low and did not differ significantly between the two treatment groups. Subarachnoid hemorrhage and intracerebral hematomas as assessed radiologically were also uncommon.

Our study has several limitations. First, we studied a homogeneous cohort of patients treated with intravenous t-PA; additional trials are needed to delineate the effects of

stent-retriever therapy in other populations of patients with acute ischemic stroke, including those who are ineligible for intravenous t-PA, those who present more than 6 hours after symptom onset (including those who awaken after having had a stroke), and those with occlusions in the second segment of the middle cerebral artery or the posterior circulation. Second, study conduct included a continuous quality-improvement program to improve endovascular workflow efficiency at the participating sites. Implementation of similar quality-improvement programs in routine care settings,[29] as has been done on a broad scale for intravenous t-PA,[30] would be required to ensure similar stent-retriever outcomes in regular practice. Finally, all the enrolling sites were tertiary care centers with established stroke-intervention programs staffed by experienced neuro interventionalists. These results may not be generalizable to clinical sites without requisite neurointerventional expertise.

In conclusion, we found that in patients with acute ischemic stroke due to large-vessel occlusion who had small or moderate ischemic cores, emergency neurovascular thrombectomy with the stent retriever was safe and effective in achieving reperfusion and substantially reduced the degree of disability and increased the proportion of patients with functional independence 3 months after stroke.

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Supplementary Appendix

Additional Methods Information (if needed)

Modified Rankin Scale outcome ratings

The modified Rankin Scale was assessed in a formally operationalized manner by use of the Rankin Focused Assessment - Ambulation (RFA-A). The 90 day mRS was assessed by study personnel certified in the scoring of the mRS using the RFA-A, and blinded to treatment assignment. Each site was required to have at least 1 RFA-certified assessor who would not have any study-related responsibilities other than to perform 90 day blinded assessments. Study standard operating procedures specified that: "The evaluator performing and recording the 90day assessments must be blinded to subject's treatment group assignment. Site investigators cannot act as the blinded assessors for a subject even if they are naïve of the subject's treatment allocation and/or they were not involved in the treatment of said subject. Similarly, designated blinded assessors who conduct a subject's 30-day assessment must disqualify themselves from also performing the 90-day endpoint assessment because of the possibility that they became unblinded to treatment assignment in the course of the 30-day evaluation. The blinded assessors also must have no vested interest in the outcome of the assessment. They must not be involved in any part of the study other than in performing the 90-day assessments."

Table S1. Study Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Age 18 – 80.
2. Clinical signs consistent with acute ischemic stroke.
3. Prestroke Modified Rankin Score ≤ 1.
4. NIHSS ≥ 8 and < 30 at the time of randomization.
5. Initiation of IV t-PA within 4.5 hours of onset of stroke symptoms (onset time is defined as the last time when the patient was witnessed to be at baseline), with investigator verification that the subject has received / is receiving the correct IV t-PA dose for the estimated weight prior to randomization.
6. Thrombolysis in Cerebral Infarction (TICI) 0-1 flow in the intracranial internal carotid, M1 segment of the MCA, or carotid terminus confirmed by CT or MR angiography that is accessible to the Solitaire™ FR Device. (Note: M1 segment of the MCA is defined as the arterial trunk from its origin at the ICA to the first bifurcation or trifurcation into major branches neglecting the small temporopolar branch.)
7. Subject is able to be treated within 6 hours of onset of stroke symptoms and within 1.5 hours (90 minutes) from CTA or MRA to groin puncture.
8. Subject is willing to conduct protocol-required follow-up visits.
9. An appropriate signed and dated Informed Consent Form (or enrollment under exception from explicit informed consent if permitted under country regulations)
10. Subject is affiliated with a social security system (if required by individual country regulations).
11. Subject meets national regulatory criteria for clinical trial participation.

Exclusion Criteria:

1. Subject who is contraindicated to IV t-PA as per local national guidelines.
2. Female who is pregnant or lactating or has a positive pregnancy test at time of admission.
3. As applicable by French law, subject who is a protected individual such as an incompetent adult or incarcerated person.
4. Rapid neurological improvement prior to study randomization suggesting resolution of signs/symptoms of stroke.
5. Known serious sensitivity to radiographic contrast agents.
6. Known sensitivity to Nickel, Titanium metals or their alloys.
7. Current participation in another investigation drug or device treatment study.
8. Known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency. (A subject without history or suspicion of coagulopathy does not require INR or prothrombin time lab results to be available prior to enrollment.)
9. Renal Failure as defined by a serum creatinine > 2.0 mg/dl (or 176.8 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. Life expectancy of less than 90 days.
12. Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT or MRI scan is normal.
13. Suspicion of aortic dissection.
14. Subject with a co-morbid disease or condition that would confound the neurological and functional evaluations or compromise survival or ability to complete follow-up assessments.
15. Subject currently uses or has a recent history of illicit drug(s) or abuses alcohol (defined as regular or daily consumption of more than 4 alcoholic drinks per day).
16. Known history of arterial tortuosity, pre-existing stent, and/or other arterial disease which would prevent the device from reaching the target vessel and/or preclude safe recovery of the device.

Imaging Exclusion Criteria*

1. Computed tomography (CT) or Magnetic Resonance Imaging (MRI) evidence of hemorrhage on presentation.
2. CT or MRI evidence of mass effect or intra-cranial tumor (except small meningioma).
3. CT or MRI evidence of cerebral vasculitis.
4. CT showing hypodensity or MRI showing hyperintensity involving greater than 1/3 of the middle cerebral artery (MCA) territory (or in other territories, >100 cc of tissue) on presentation.
5. **Baseline non-contrast CT or DWI MRI evidence of a moderate/large core defined as extensive early ischemic changes of Alberta Stroke Program Early CT score (ASPECTS) < 6.†
6. CT or MRI evidence of a basilar artery (BA) occlusion or posterior cerebral artery (PCA) occlusion.
7. CTA or MRA evidence of carotid dissection or complete cervical carotid occlusion requiring stenting at the time of the index procedure (i.e., mechanical thrombectomy).
8. Imaging evidence that suggests, in the opinion of the investigator, the subject is not appropriate for mechanical thrombectomy intervention (e.g., inability to navigate to target lesion, moderate/large infarct with poor collateral circulation, etc.).

*Qualifying imaging had to be obtained at the study hospital. Patients with initial imaging at an outside hospital had to undergo additional qualifying CT or MR imaging at the study hospital.

**Before imaging entry criteria revision, this criterion stated: "Core Infarct and hypoperfusion: a) MRI- or CT-assessed core infarct lesion greater than 50 cc; b) Severe hypoperfusion lesion (10 sec or more Tmax lesion larger than 100 cc); c) Ischemic penumbra < 15 cc and mismatch ratio ≤1.8." After imaging entry criteria revision, sites could enroll based on ASPECTS findings only, but were still encouraged to obtain perfusion imaging and use this information if available. A total of 71 patients were enrolled under the initial imaging entry criteria and 125 patients under the revised imaging entry criteria.

†ASPECTS, range 0 to 10, with higher scores indicating smaller infarct core

Table S2. Interim Analysis Bounds

Evaluable Sample Size	Stopping for Safety	Stopping for Efficacy		Stopping for Futility	
	Two-Sided Alpha for Mortality	Two-Sided Alpha for Rankin Shift	Effect Size Δ for mRS 0-2	Effect Size φ for mRS mean value	Effect size Δ for mRS 0-2
200	0.0036	0.0200	12.0%	0.00	0.0%
300	0.0058	0.0125	10.0%	0.00	0.0%
400	0.0094	0.0150	9.0%	0.10	n/a
500	0.0147	0.0150	8.0%	0.14	n/a
600	0.0203	0.0150	6.0%	0.14	n/a
750 (final)	0.0340	0.0350	5.0%	n/a	n/a

Table S3. Results of Pre-screening and Screening

In the SWIFT-PRIME Trial, all sites performed pre-screening of study patients. Sites were asked to maintain a log of pre-screened patients who did not qualify for the study. However, as pre-screening occurred prior to study informed consent, some sites were not permitted by their Institutional Review Boards to submit pre-screening logs to the study database, and central monitoring to confirm accuracy was not performed on any pre-screening data.

At a subset of sites, to promote rapid workflow, informed consent was elicited from patients prior to knowing if they were fully study-eligible. These patients were thereby enrolled in a screening phase, during which additional information about their clinical history and imaging analysis proceeded. Subjects not meeting study eligibility criteria did not proceed to the randomized study phase. Beginning with Revision F, after enrollment of the first 71 patients, sites collected information on adverse events occurring in the first 72 hours among these screened but not randomized patients.

Overall, pre-screening log data were received on 1470 patients from 33 sites, including 28 of the 39 sites that enrolled one or more patients in the randomized trial phase. Table S3a shows the leading pre-screening reasons for non-enrollment.

a. Leading Pre-Screening Reasons for Non-Enrollment

Reason for Non-Enrollment	Number of Patients
NIHSS < 8	413
No intracranial ICA or M1 MCA occlusion	345
Age under 18 or over 80	208
Absence of target mismatch	68
Hemorrhage	35

b. Leading Post-Consent Reasons for Non-Enrollment

Post-consent screening phase data were collected on 77 patients at 15 sites. Among these patients, 94 reasons for non-enrollment were recorded. Table S3b shows the leading post-consent screening reasons for non-enrollment.

Reason for Non-Enrollment	Number of Patients
No intracranial ICA or M1 MCA occlusion	28
Absence of target mismatch	17
NIHSS not between 8-29	9
>1/3 MCA infarct signs	6
Rapid neurologic improvement	4

Among the 77 post-consent screened but not enrolled patients, 6 serious adverse events and 36 nonserious adverse events occurred in the first 72 hours. The leading serious adverse event was malignant edema, occurring in 2 patients.

Table S4. Additional Demographic and Clinical Characteristics of the Patients

Characteristic	Intravenous tPA Alone (N=98)	Solitaire + IV tPA (N = 98)
Prestroke mRS		
Median (IQR)	0 (0-0)	0 (0-0)
0 – no. (%)	78/94 (83.0)	81/98 (82.7)
1 – no. (%)	15/94 (16.0)	15/98 (15.3)
2 - no. (%)	1/94 (1.1)	2/98 (2.0)
Medical history – no. (%)		
Hyperlipidemia	22/97 (22.7)	24/98 (24.5)
Peripheral Arterial Disease	5/97 (5.2)	7/98 (7.1)
Neurologic History – no. (%)		
Prior Ischemic Stroke	1/97 (1.0)	3/98 (3.1)
Hemorrhagic Stroke	0/97 (0)	0/98 (0)
Transient Ischemic Attack	5/97 (5.2)	3/98 (3.1)
Side of occlusion, left – no. (%)	48/94 (51.1)	40/93 (43.0)
Systolic blood pressure – mm Hg, median (IQR)	148.5 (135-165)	150 (135 - 166)
Parenchymal Imaging		
Malignant profile – no. (%)*	9/75 (12.0)	13/83 (15.7)

*Malignant profile was defined as MRI or CT-assessed core infarct >50cc and/or Tmax>10s lesion more than 100cc.

Table S5a-b. Reasons for Nontreatment with Solitaire and Concomitant or Alternative Endovascular Therapies in Patients Allocated to Solitaire Arm

a. *Nontreatment with Solitaire*: Among the 98 patients allocated to Solitaire, 11 were not treated with Solitaire. Reasons for nontreatment were:

- Resolution of target occlusion between entry CTA/MRA and catheter angiography - 7
  - Complete resolution – 6
  - Partial resolution – 1
- No target occlusion at entry* – 2
  - M2 MCA stenosis
  - M1 MCA stenosis
- Unable to access target occlusion – 2
  - Cervical ICA dissection (missed at screening) – 1
  - Vessel perforation from guidewire/microcatheter manipulation and procedure then stopped

*In these 2 patients, a nontarget lesion was found at catheter angiography and was later determined by the Core Lab to also have been the index lesion at enrollment.

b. *Concomitant or Alternative Endovascular Therapy*: Among the 98 patients allocated to Solitaire, concomitant or alternative endovascular therapy was performed in 7. These procedures were:

- Among 87 patients allocated to, and treated with, Solitaire
  - Cervical ICA angioplasty without stenting (allowed per protocol) - 4
- Among 11 patients allocated to, but not treated with, Solitaire
  - Among patients with tandem cervical ICA and target intracranial artery occlusions at entry, with resolution of the intracranial occlusion after IV tPA
    - Cervical ICA angioplasty without stenting – 1
    - Cervical stenting – 1
  - Among patients adjudicated by Core Lab to have an isolated M2 MCA stenosis at entry, rather than an intracranial target occlusion
    - Intracranial stenting - 1

Table S6a. Distribution of Modified Rankin Scale Scores at 3 Months, with Missing Data Assigned Using Multiple Imputation

In this sensitivity analysis, all missing 90 day mRS values – including those imputed in the primary analysis by last observation carried forward -- were assigned using a multiple imputation model under an ordinal outcome (mRS at day 90) with the following predictors: treatment arm, time from onset to IV tPA, baseline NIHSS, age, occlusion location and any post-randomization mRS data (day 7-10 and day 30). (No imputation was made for the 1 patient with all study data deleted at patient request.)

Outcome	Intravenous tPA Alone (N = 97)	Solitaire + IV tPA (N = 98)	P Value*
mRS median (IQR)	3 (2 – 5)	2 (1 – 4)	0.0004
mRS 0 - %	8.2	17.3	
mRS 1 - %	11.0	25.7	
mRS 2 - %	16.6	17.9	
mRS 3 - %	17.5	11.4	
mRS 4 - %	20.8	15.4	
mRS 5/6 - %	25.8	12.2	

*Ordinal logistic regression on pooled multiply imputed data

Table S6b. Distribution of Modified Rankin Scale Scores at 3 Months, with Missing Data Assigned Using Worst Case Scenario

In this sensitivity analysis, 90 day mRS values for 4 patients in the IV tPA arm without an mRS available from any post-randomization visit, final mRS values were assigned using a worst case scenario of 6. (No imputation made for the 1 patient with all study data deleted at patient request.)

Outcome	Intravenous tPA Alone (N = 97)	Solitaire + IV tPA (N = 98)	P Value*
mRS median (IQR)	3 (2 – 5)	2 (1 – 4)	<0.0001
mRS 0 - no. (%)	8 (8.2)	17 (17.3)	
mRS 1 - no. (%)	10 (10.3)	25 (25.5)	
mRS 2 - no. (%)	15 (15.5)	17 (17.3)	
mRS 3 - no. (%)	16 (16.5)	12 (12.2)	
mRS 4 - no. (%)	20 (20.6)	15 (15.3)	
mRS 5/6 - no. (%)	28 (28.9)	12 (12.2)	

Table S6c. Distribution of Modified Rankin Scale Scores at 3 Months, with Missing Data Assigned Using Best Case Scenario

In this sensitivity analysis, 90 day mRS values for 4 patients in the IV tPA arm without an mRS available from any post-randomization visit, final mRS values were assigned using a best case scenario of 0. (No imputation made for the 1 patient with all study data deleted at patient request.)

Outcome	Intravenous tPA Alone (N = 97)	Solitaire + IV tPA (N = 98)	P Value*
mRS median (IQR)	3 (2 – 4)	2 (1 – 4)	0.0017
mRS 0 - no. (%)	12 (12.4)	17 (17.3)	
mRS 1 - no. (%)	10 (10.3)	25 (25.5)	
mRS 2 - no. (%)	15 (15.5)	17 (17.3)	
mRS 3 - no. (%)	16 (16.5)	12 (12.2)	
mRS 4 - no. (%)	20 (20.6)	15 (15.3)	
mRS 5/6 - no. (%)	24 (24.7)	12 (12.2)	

Table S7. Independent Predictors of Distribution of Modified Rankin Scale Scores at 3 Months, Adjusting for Stratification and Additional Baseline Variables.

Term	Odds ratio	P-value
Solitaire treatment group	2.77	<0.001
NIHSS at baseline ≥ 17	0.32	<0.001
Age <70	1.72	0.048
M1 occlusion location	1.86	0.043
History of carotid artery stenosis	1.49	0.29
Platelet count at baseline	1.00	0.94

In the cumulative logistic regression model, adjustment was made for the randomization stratification variables (age, NIHSS, and occlusion location) and all baseline variables differing between groups in bivariate analysis at $p < 0.1$ (history of carotid stenosis, platelet count at baseline). Model results show that, after adjustment, assignment to the Solitaire treatment group remains a strong independent determinant of mRS outcome, increasing the odds of reduced disability 2.8-fold.

Table S8. Distribution of Modified Rankin Scale Scores at 3 Months Among Patients Receiving IV tPA within 3 Hours of Onset

Outcome	Intravenous tPA Alone (N = 76)	Solitaire + IV tPA (N = 84)	P Value*
mRS median (IQR)	3 (2 – 5)	2 (1 – 4)	0.0009
mRS 0 - no. (%)	6 (7.9%)	14 (16.7%)	
mRS 1 - no. (%)	9 (11.8%)	23 (27.4%)	
mRS 2 - no. (%)	13 (17.1%)	14 (16.7%)	
mRS 3 - no. (%)	14 (18.4%)	10 (11.9%)	
mRS 4 - no. (%)	14 (18.4%)	13 (15.5%)	
mRS 5/6 - no. (%)	20 (26.3%)	10 (11.9%)	

Table S9. Modified Thrombolysis in Cerebral Infarction (TICI) Outcomes in Patients Undergoing

Solitaire Stent Retriever Therapy. Data are from 83 endovascular arm patients found to have persisting target occlusion at catheter angiography in whom a Solitaire device was inserted through the arterial sheath site and in whom the Core Lab deemed the final outcome angiogram assessable. (Data do not reflect 4 patients who had Solitaire deployed but in whom the Core Lab deemed the final outcome angiogram non assessable.)

mTICI Grade	Post-Treatment (N=83)
0 - No anterograde flow beyond the point of occlusion	4 (4.8%)
1 - Perfusion past initial obstruction but limited distal branch filling with little or slow distal perfusion	1 (1.2%)
2a - Perfusion of less than half of the vascular distribution of the occluded artery	5 (6.0%)
2b - Perfusion of half or greater of the vascular distribution of the occluded artery	16 (19.3%)
3 - Full perfusion with filling of all distal branches	57 (68.7%)

Table S10a. Additional Clinical and Imaging Outcomes

Outcome	Intravenous tPA Alone	Solitaire + IV tPA	P value
Clinical Efficacy Outcomes			
NIHSS at 90 days – median (IQR) [N]	5 (0-32) [75]	1 (0-22) [88]	<0.001
Barthel Index at 90 days – median (IQR) [N]	90 (0-110) [77]	100 (10-100) [88]	0.003
Parenchymal Imaging Efficacy Outcomes			
Infarct volume at 27 hrs – median (IQR) [N]	35.3 (0 – 406.6) [94]	32 (0 – 530.5) [97]	0.09
Infarct growth at 27 hrs – median (IQR) [N]*	25.7 (-7.4-276.7) [72]	14.8 (-17.5-516.5) [82]	0.02

*Infarct growth = 27 hr infarct volume – baseline RAPID-assessed core infarct volume. Baseline RAPID-assessed core volumes: 1) Perfusion CT imaged patients: regions with cerebral blood flow reduced by more than 70%, 2) MR imaged patients: regions with apparent diffusion coefficient < 620×10^{6} mm^2/s on diffusion sequences

Table S10b. Additional Imaging Correlation Analysis

	N	Correlation (r)	P value
Baseline RAPID-assessed core infarct volume vs 27h infarct volume*	58	0.46	<0.001

*Baseline RAPID-assessed core volumes: 1) Perfusion CT imaged patients: regions with cerebral blood flow reduced by more than 70% compared with contralateral side, 2) MR imaged patients: regions with apparent diffusion coefficient < 620 on diffusion sequences

Table S11. Serious Adverse Events by Body System*

Body System – no (%)	IV tPA alone (N=97)	IV tPA + Solitaire (N=98)
All Systems	30 (30.9)	35 (35.7)
Nervous system disorders	18 (18.6)	15 (15.3)
Respiratory, thoracic and mediastinal disorders	8 (8.2)	6 (6.1)
Cardiac disorders	5 (5.2)	8 (8.2)
Vascular disorders	7 (7.2)	5 (5.1)
Infections and infestations	6 (6.2)	5 (5.1)
Renal and urinary disorders	4 (4.1)	4 (4.1)
Gastrointestinal disorders	2 (2.1)	4 (4.1)
Injury, poisoning and procedural complications	3 (3.1)	3 (3.1)
Blood and lymphatic system disorders	0 (0.0)	3 (3.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	2 (2.1)	0 (0.0)
Psychiatric disorders	1 (1.0)	1 (1.0)

*A serious adverse event was an adverse event that led to: 1) death, 2) a life-threatening illness or injury, 3) permanent impairment of a body structure or a body function, 4) inpatient or prolonged hospitalization, 5) medical or surgical intervention to prevent permanent life-threatening illness or injury or permanent impairment to a body structure or a body function, or 6) fetal distress, fetal death or a congenital anomaly or birth defect.

Table S12. Device-Related Adverse Events

No serious adverse events were adjudicated by the Clinical Events Committee as device-related. A total of 7 nonserious adverse events in 5 patients adjudicated by the Clinical Events Committee as device- related.

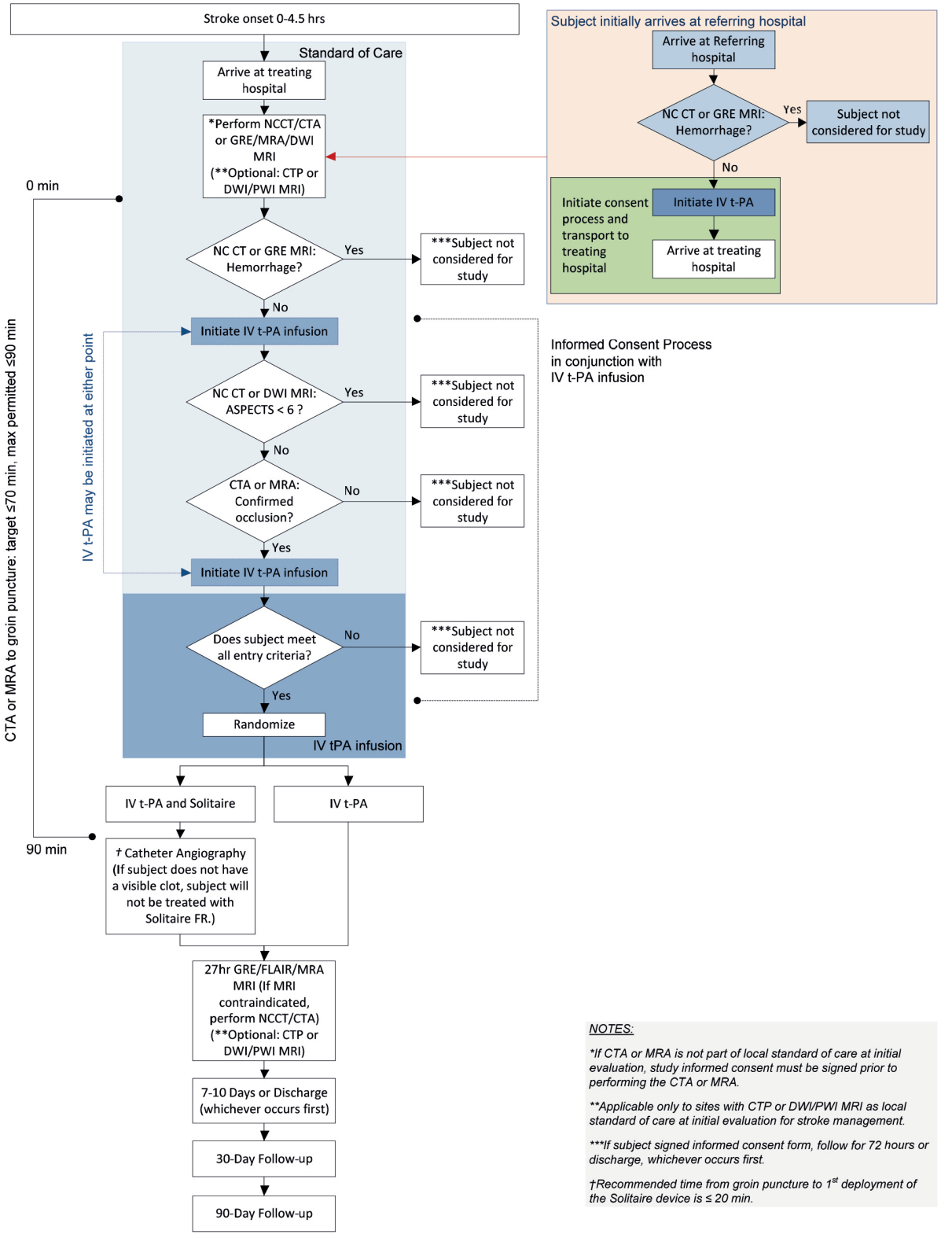
Nonserious Adverse Event Type	Number of Events	Severity	Outcome
Cerebral vasospasm	4	Moderate -3, Mild 1	Recovered without sequelae
Intraventricular hemorrhage	1	Mild	Recovered without sequelae
Subarachnoid hemorrhage	1	Mild	Recovered without sequelae
Subarachnoid contrast extravasation	1	Mild	Recovered without sequelae

Table S13. Treatment Effect Magnitudes

Outcome	Number Needed to Treat	Benefit per Hundred Treated
Dichotomizations of the mRS		
0 vs 1-6	11.5	8.7
0-1 vs 2-6	4.3	23.4
0-2 vs 3-6	4.0	24.7
0-3 vs 4-6	5.1	19.7
0-4 vs 5-6	7.4	13.5
0-5 vs 6	27.0	3.7
Transitions across multiple mRS levels*		
All 7 levels (0,1,2,3,4,5,6)	2.5	40.5
Primary endpoint 6 levels (0,1,2,3,4,5/6)	2.6	39.1

Number needed to treat (NNT) values reflecting transitions across multiple mRS levels were derived by calculating the geometric mean of the NNT values derived by the algorithmic joint outcome table method (Stroke 2009;40:2433-7) and the permutation test method (Stroke 2012;43:664-9).

Figure S1. Overview of Study Procedures (after Revision F)



NOTES:

**If CTA or MRA is not part of local standard of care at initial evaluation, study informed consent must be signed prior to performing the CTA or MRA.*

***Applicable only to sites with CTP or DWI/PWI MRI as local standard of care at initial evaluation for stroke management.*

****If subject signed informed consent form, follow for 72 hours or discharge, whichever occurs first.*

†Recommended time from groin puncture to 1st deployment of the Solitaire device is ≤ 20 min.

Figure S2. Enrollment and Follow-up (CONSORT diagram)

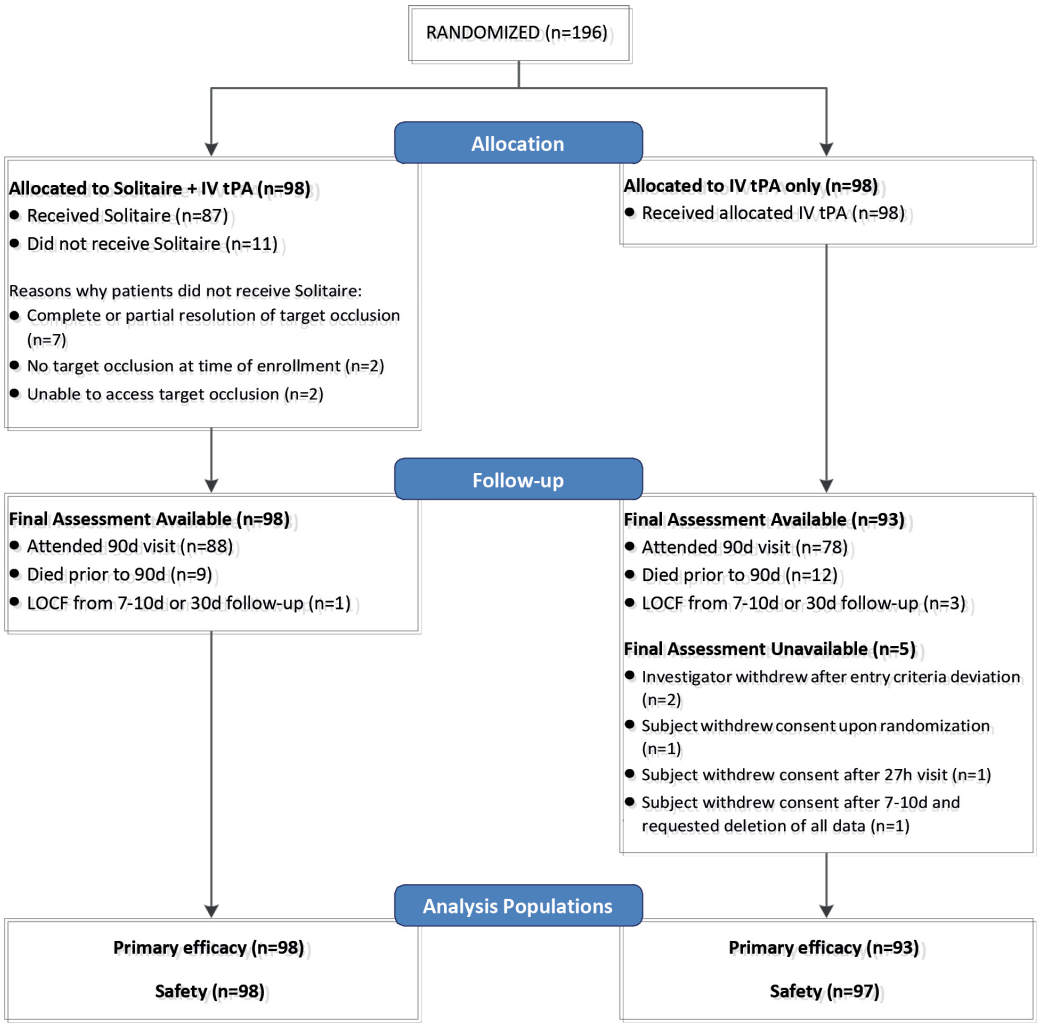


Figure S3. Distribution of Modified Rankin Scale Scores at 3 Months, with Adjustment for Stratification Variables. Adjustment was made for the randomization stratification variables (age, NIHSS, and occlusion location). Favorable shift in mRS outcomes was present, $p < 0.0001$ (ordinal logistic regression).

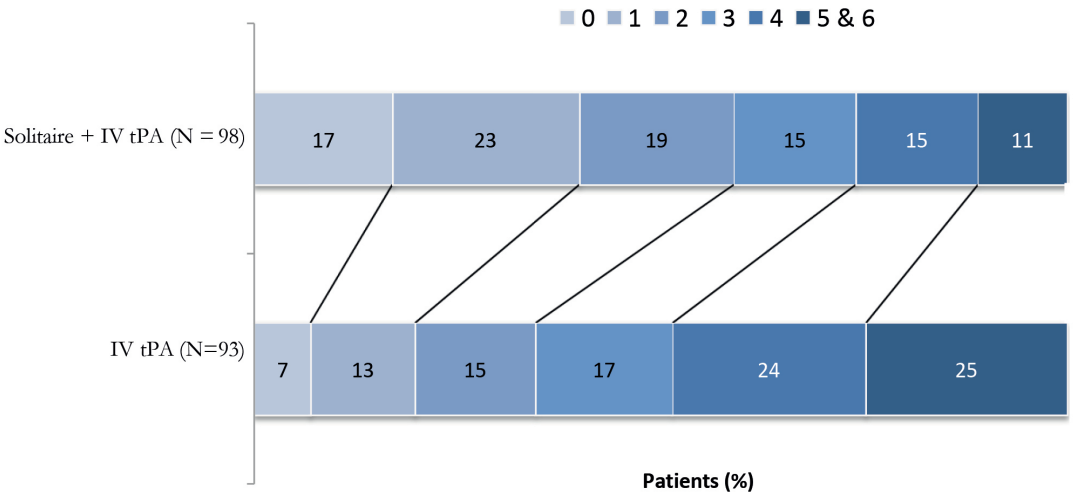


Figure S4. Distribution of Modified Rankin Scores at 90 Days in Prespecified Subgroups

This series of figures shows the distribution of modified Rankin Scale scores at 90 days among the 8 prespecified subgroups, using prespecified cutpoints for continuous variables. These groups and cutpoints are:

- Gender (Male versus Female)
- Age (< 70 versus ≥ 70)
- NIHSS (≤ 17 versus > 17)
- Occlusion location (M1 versus ICA)
- Geographic region (U.S, Europe)
- ASPECTS (6-7, 8-10)
- Site of IV tPA Start (study hospital vs outside hospital)
- Time to Randomization (< Median versus ≥ Median)

Figure S4a. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patients Stratified by Gender. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.99, Breslow-Day test).

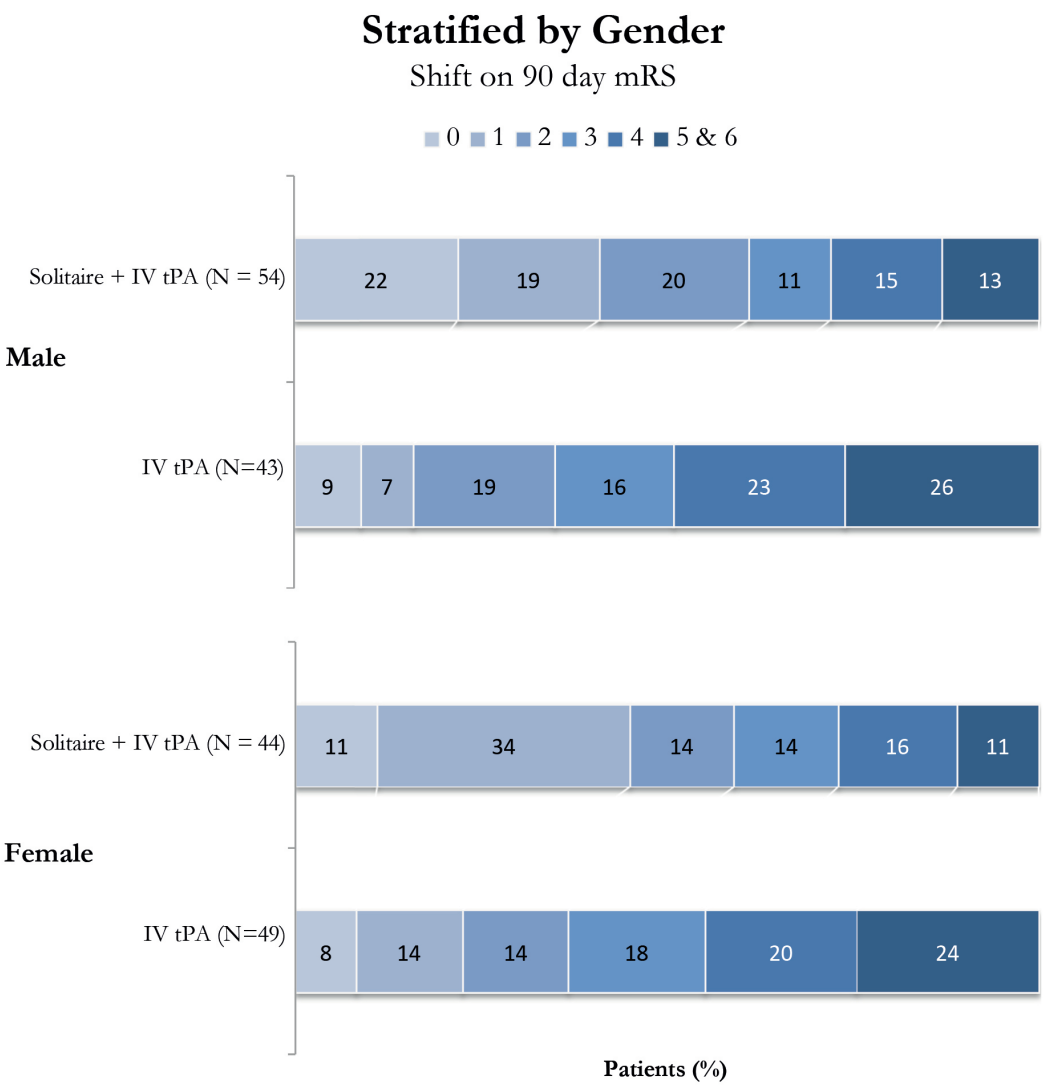


Figure S4b. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patients Stratified by Age. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.24, Breslow-Day test).

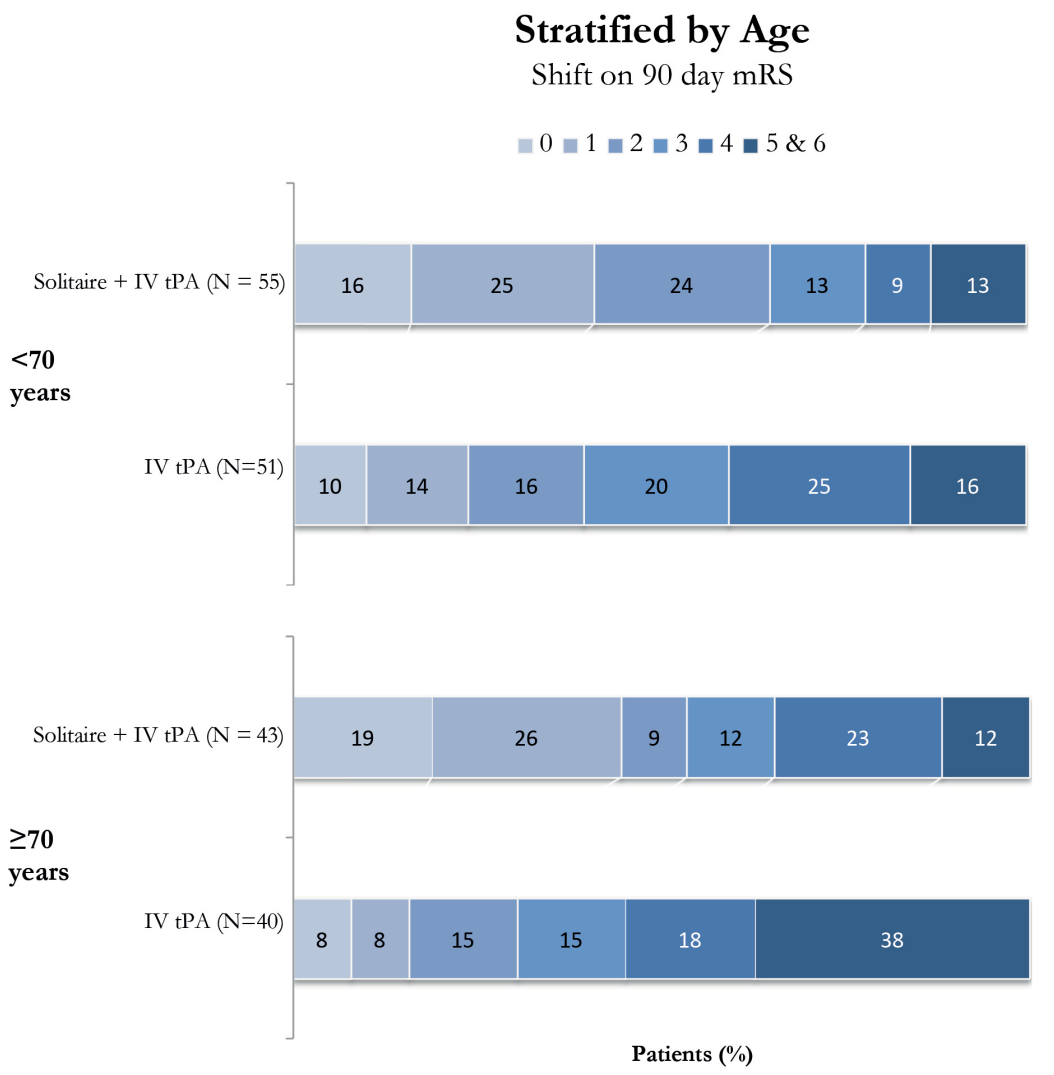


Figure S4c. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patients Stratified by Stroke Deficit Severity (NIHSS Score). There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.68, Breslow-Day test).

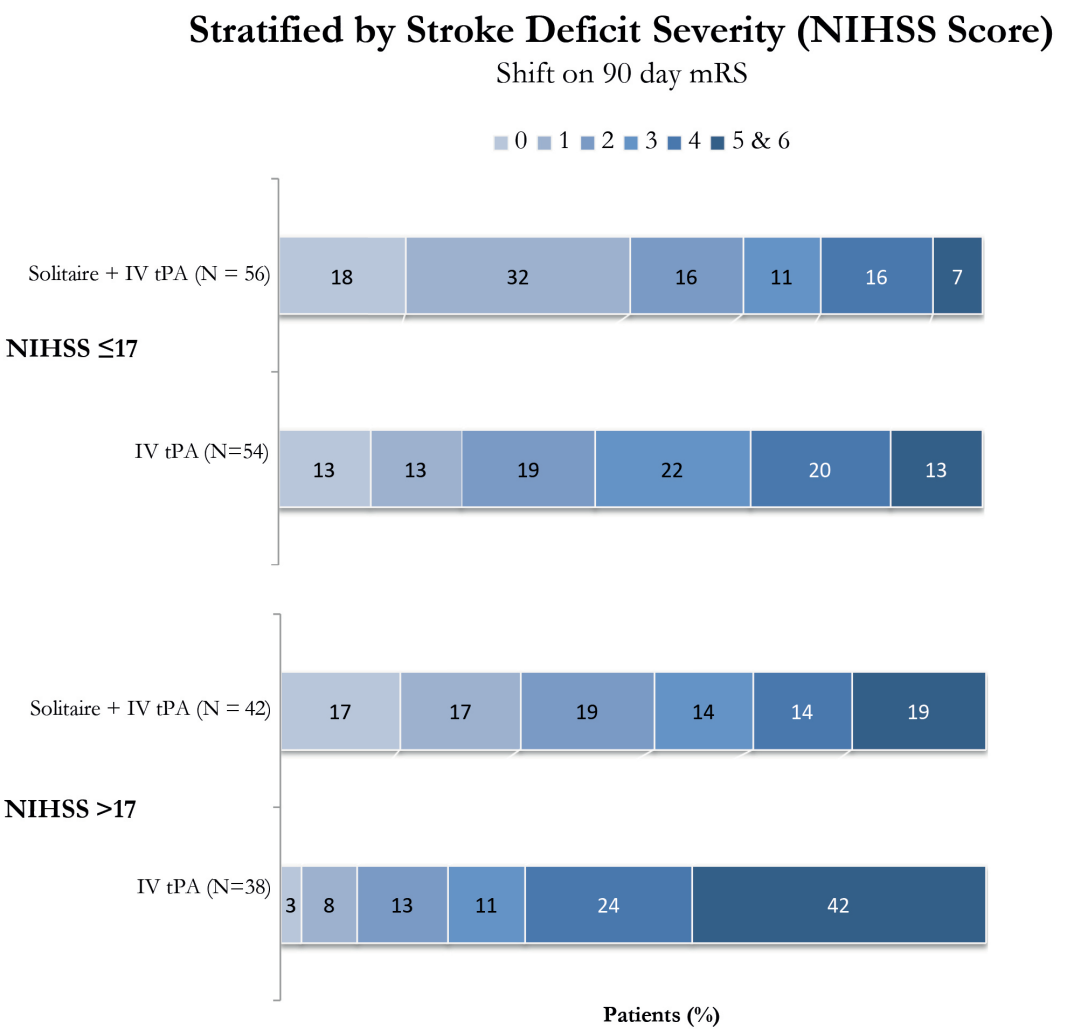


Figure S4d. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patient: Stratified by Occlusion Location. There is no evidence of heterogeneity of treatment effect between the largest subgroup, M1 occlusions, and the other subgroups ($p_{interaction}$=0.29, Breslow-Day test).

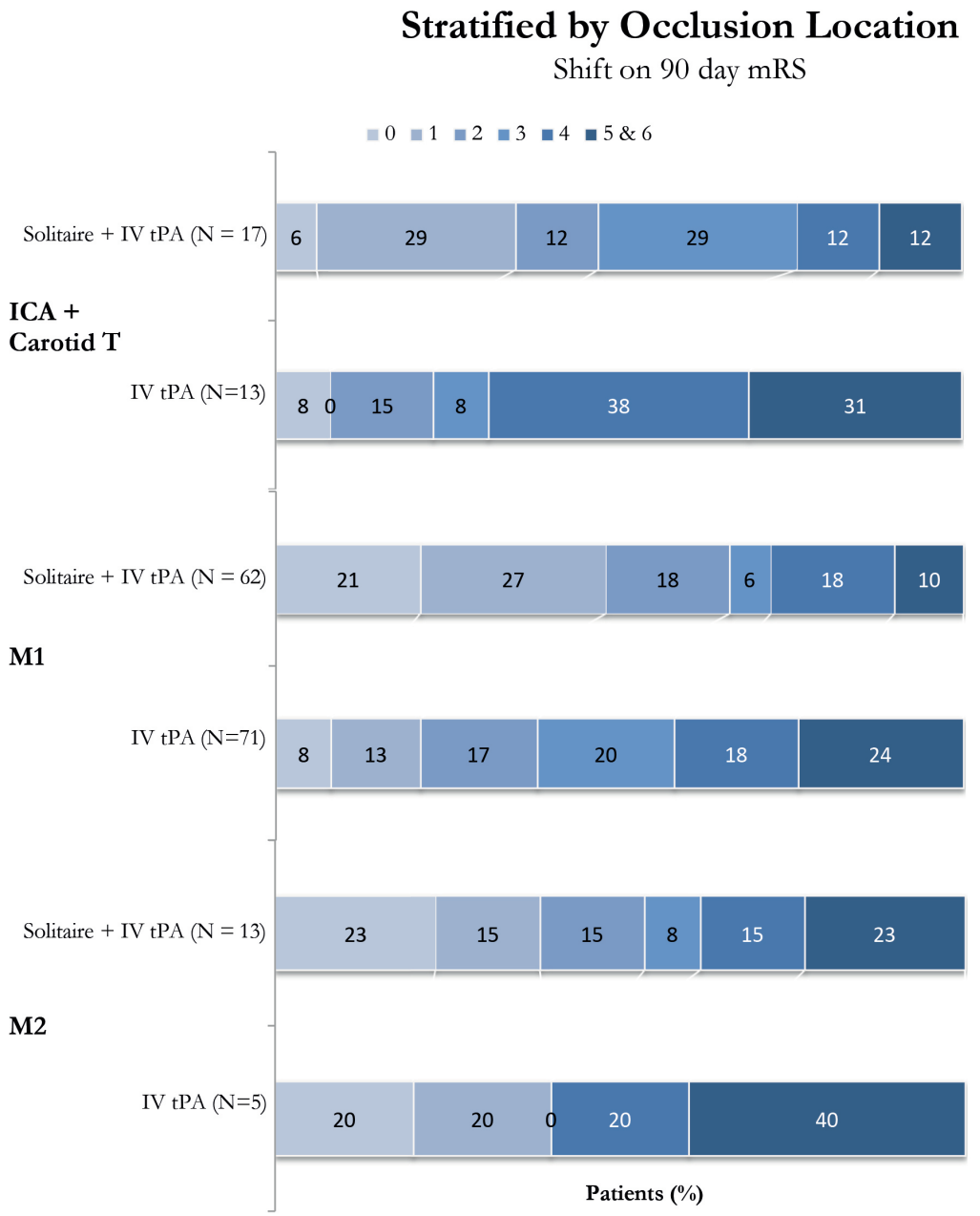


Figure S4e. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patients Stratified by Geographic Location. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.48, Breslow-Day test).

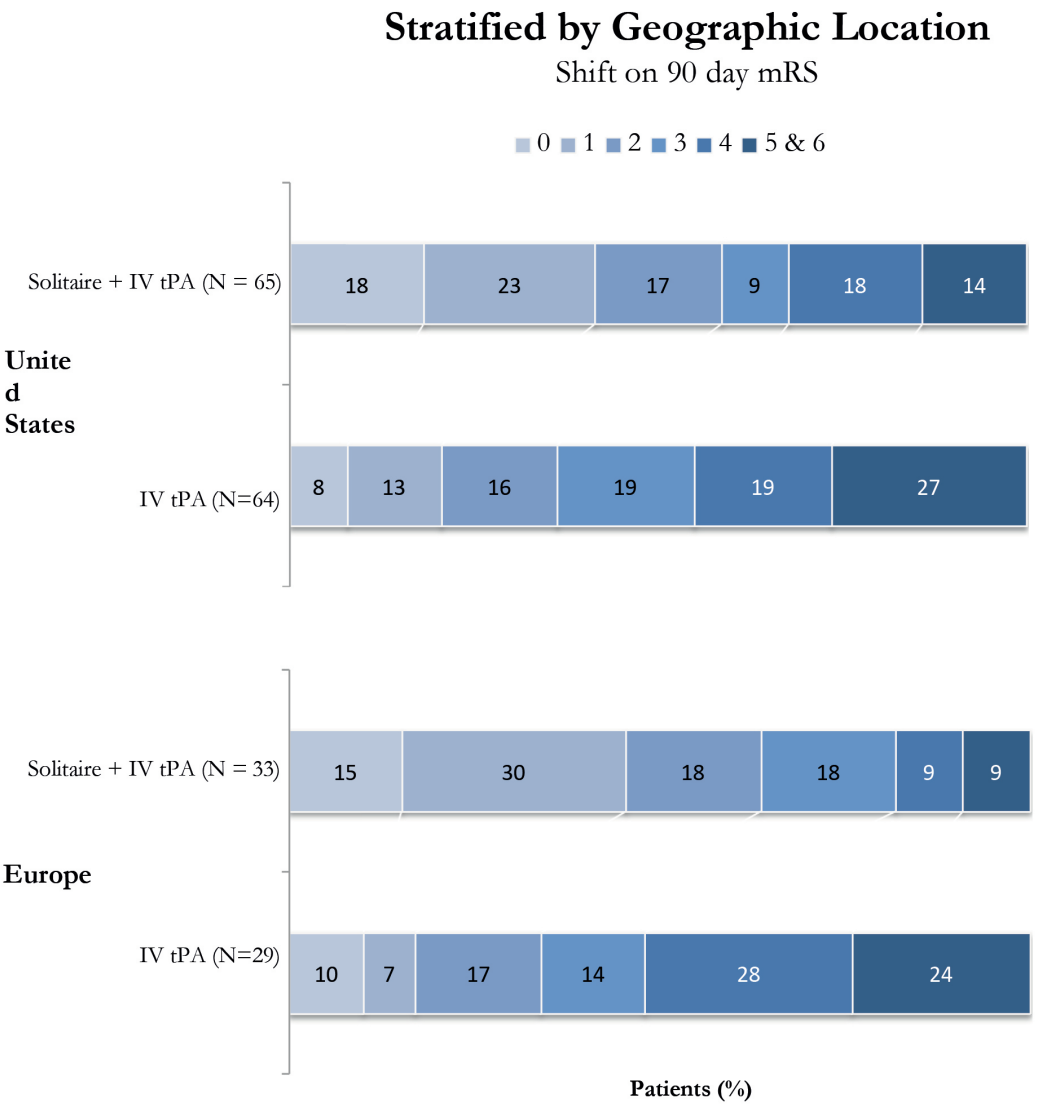


Figure S4f. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patients Stratified by Baseline ASPECTS Score. The cutpoint of 6-7 vs 8-10 was prespecified and selected as several studies have suggested better prognosis among patients with scores of 8 or higher than 6-7. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.64, Breslow-Day test).

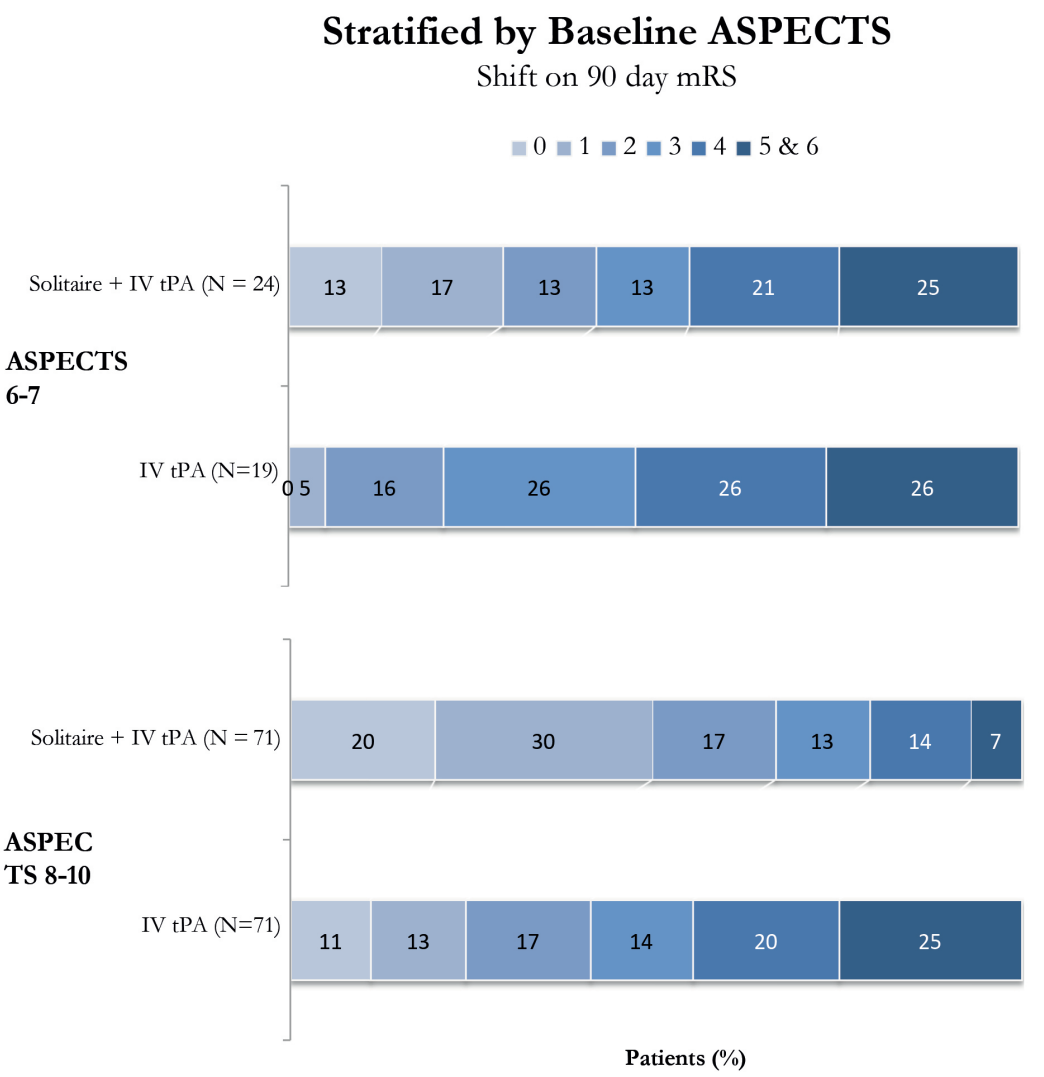


Figure S4g. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patients Stratified by Site of IV tPA Start. Among patients receiving IV tPA at outside hospitals, tPA to groin puncture interval was 160 mins (IQR 134 – 195) and onset to groin puncture interval was 275 mins (IQR 245-334). Among patients receving IV tPA at study hospitals, tPA to groin puncture interval was 58 mins (IQR 39 - 80) and onset to groin puncture interval was 179.5 mins (IQR 147-238). There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.42, Breslow-Day test).

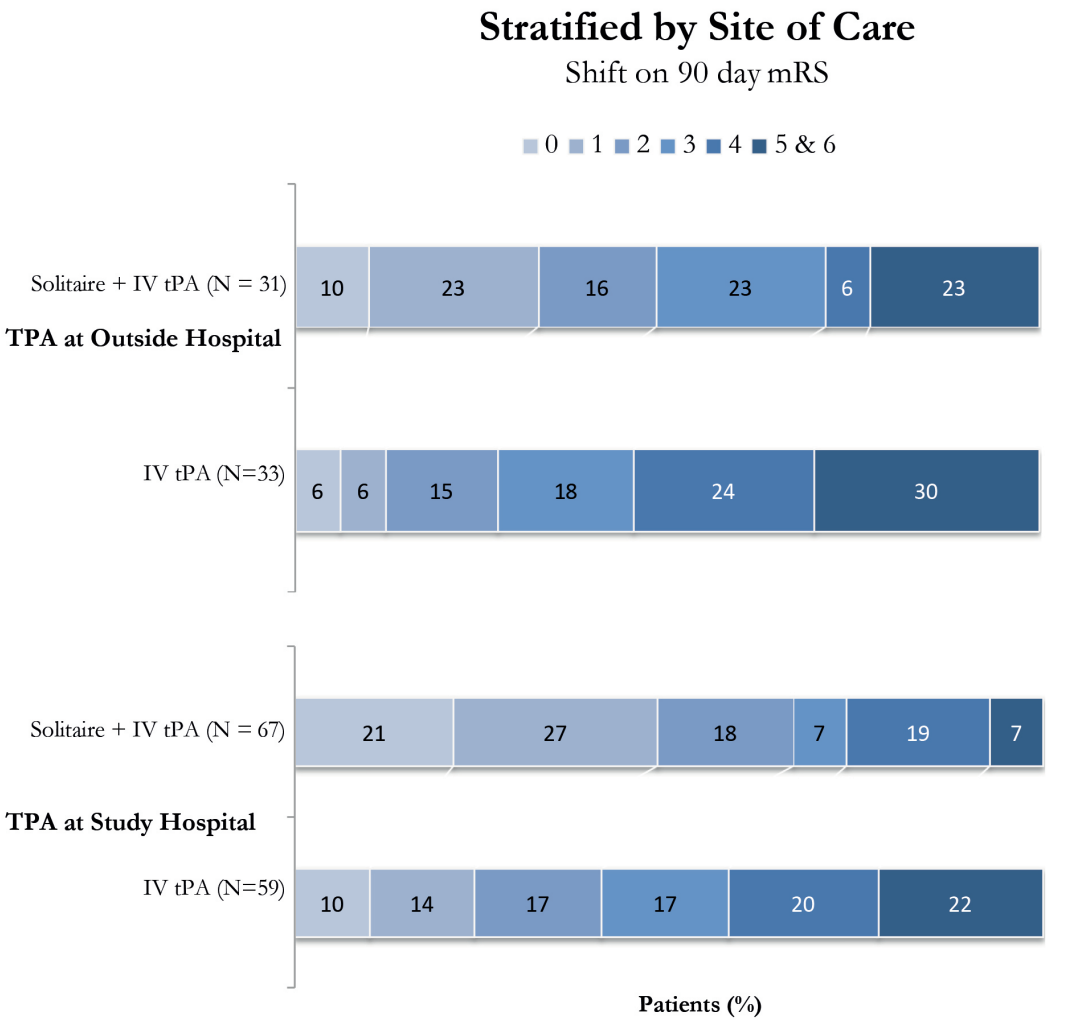
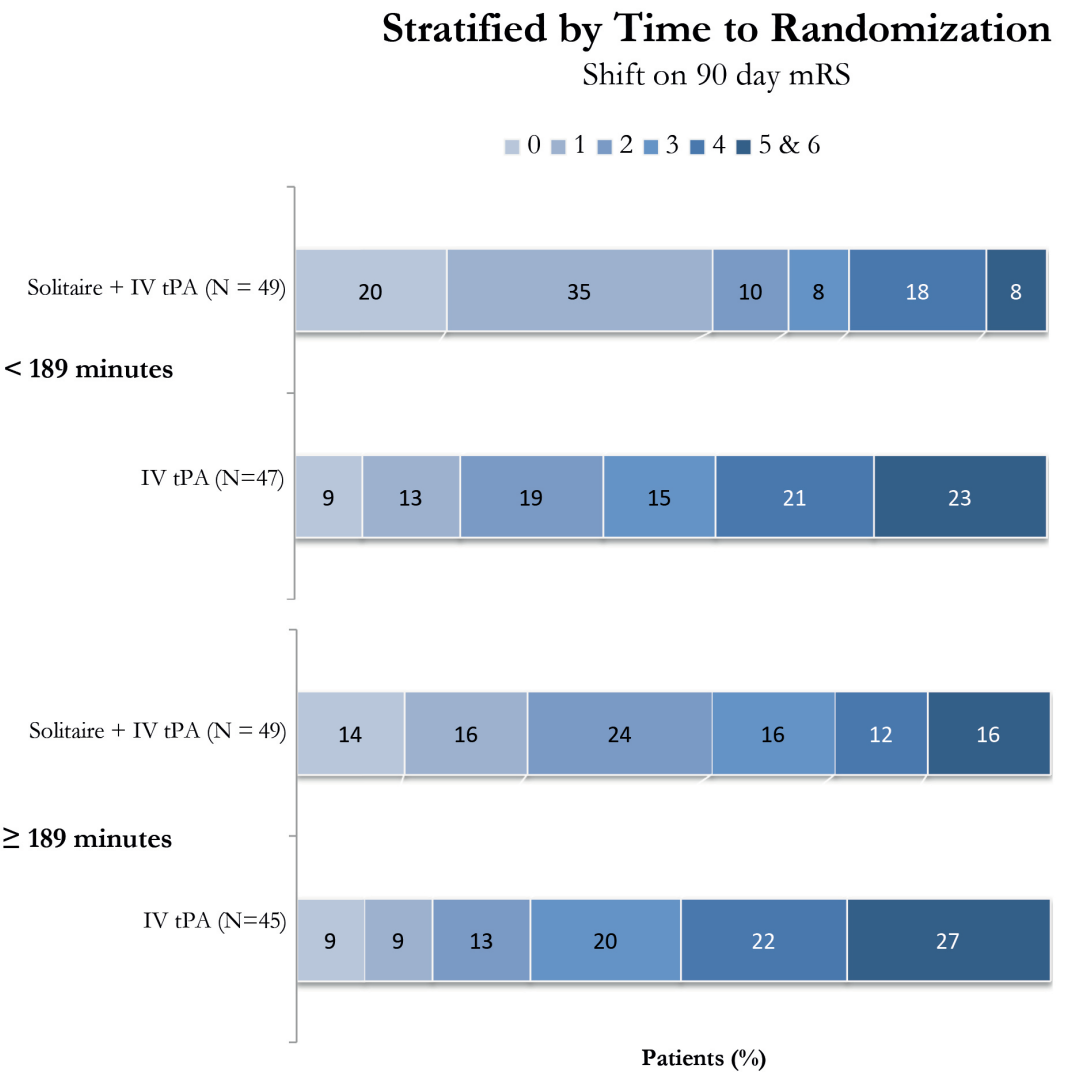


Figure S4h. Distribution of Modified Rankin Scores at 90 Days in the Two Treatment Arms in Patient: Stratified by Time to Randomization. The median value was prespecified as the cutpoint for analysis, and was found to be 189 minutes. There is no evidence of heterogeneity of treatment effect between these subgroups ($p_{interaction}$=0.56, Breslow-Day test).



CHAPTER 2.3

Endovascular Thrombectomy After Large-Vessel Ischaemic Stroke: A Meta-Analysis Of Individual Patient Data From Five Randomised Trials

Based upon:
Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials
Mayank Goyal, Bijoy K Menon, Wim H van Zwam, Diederik W J Dippel, Peter J Mitchell, Andrew M Demchuk, Antoni Dávalos, Charles B L M Majoie, Aad van der Lugt, Maria A de Miquel, Geoffrey A Donnan, Yvo B W E M Roos, Alain Bonafe, Reza Jahan, Hans-Christoph Diener, Lucie A van den Berg, Elad I Levy, Olvert A Berkhemer, Vitor M Pereira, Jeremy Rempel, Mònica Millán, Stephen M Davis, Daniel Roy, John Thornton, Luis San Román, Marc Ribó, Debbie Beumer, Bruce Stouch, Scott Brown, Bruce C V Campbell, Robert J van Oostenbrugge, Jeffrey L Saver, Michael D Hill, Tudor G Jovin, for the HERMES collaborators
Lancet. 2016 Apr 23;387(10029):1723-31

ABSTRACT

Background

In 2015, five randomised trials showed efficacy of endovascular thrombectomy over standard medical care in patients with acute ischaemic stroke caused by occlusion of arteries of the proximal anterior circulation. In this meta-analysis we, the trial investigators, aimed to pool individual patient data from these trials to address remaining questions about whether the therapy is effcacious across the diverse populations included.

Methods

We formed the HERMES collaboration to pool patient-level data from five trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA) done between December, 2010, and December, 2014. In these trials, patients with acute ischaemic stroke caused by occlusion of the proximal anterior artery circulation were randomly assigned to receive either endovascular thrombectomy within 12 h of symptom onset or standard care (control), with a primary outcome of reduced disability on the modified Rankin Scale (mRS) at 90 days. By direct access to the study databases, we extracted individual patient data that we used to assess the primary outcome of reduced disability on mRS at 90 days in the pooled population and examine heterogeneity of this treatment effect across prespecified subgroups. To account for between-trial variance we used mixed-effects modelling with random effects for parameters of interest. We then used mixed-effects ordinal logistic regression models to calculate common odds ratios (cOR) for the primary outcome in the whole population (shift analysis) and in subgroups after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale score), site of occlusion (internal carotid artery vs M1 segment of middle cerebral artery vs M2 segment of middle cerebral artery), intravenous alteplase (yes vs no), baseline Alberta Stroke Program Early CT score, and time from stroke onset to randomisation.

Results

We analysed individual data for 1287 patients (634 assigned to endovascular thrombectomy, 653 assigned to control). Endovascular thrombectomy led to significantly reduced disability at 90 days compared with control (adjusted cOR 2·49, 95% CI 1·76-3·53; p<0·0001). The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on mRS for one patient was 2·6. Subgroup analysis of the primary endpoint showed no heterogeneity of treatment effect across prespecified subgroups for reduced disability (pinteraction=0·43). Effect sizes favouring endovascular thrombectomy over control were present in several strata of special interest, including in

patients aged 80 years or older (cOR 3·68, 95% CI 1·95-6·92), those randomised more than 300 min after symptom onset (1·76, 1·05-2·97), and those not eligible for intravenous alteplase (2·43, 1·30-4·55). Mortality at 90 days and risk of parenchymal haematoma and symptomatic intracranial haemorrhage did not differ between populations.

Conclusion

Endovascular thrombectomy is of benefit to most patients with acute ischaemic stroke caused by occlusion of the proximal anterior circulation, irrespective of patient characteristics or geographical location. These findings will have global implications on structuring systems of care to provide timely treatment to patients with acute ischaemic stroke due to large vessel occlusion.

Funding

Medtronic.

Endovascular thrombectomy for acute ischaemic stroke has evolved substantially; however, only after the 2015 publication of five clinical trials[1-5] has this procedure been accepted as the standard of care for patients with proximal anterior circulation occlusions.[6] Uncertainties remain about the benefit of endovascular thrombectomy in patient groups under-represented in these individual trials, including those who presented to treatment late, are elderly, have mild deficits, and are not eligible for intravenous alteplase.[6] Moreover, because these trials were individually moderate in size, data pooling can provide more precise estimates of treatment effects. As investigators from the MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, and EXTEND IA trials, we seek to address these and other questions about the risks and benefits of modern endovascular therapy by analysing pooled individual patient data for thrombectomy after acute ischaemic stroke.

RESEARCH IN CONTEXT

Evidence Before The Study

Evidence to support endovascular therapy for stroke has previously been poor because randomised trials have used thrombectomy devices of low efficacy, insufficiently robust imaging selection criteria, and had long delays from hospital presentation to reperfusion. Five individual trials published in 2015 established that thrombectomy, when done with newer generation devices (mainly stent retrievers), more stringent imaging selection criteria, and more efficient workflow, significantly reduces disability rates after acute ischaemic stroke caused by proximal occlusion of large vessels in the anterior circulation. Because most of these studies were stopped prematurely, they were underpowered to provide convincing evidence of efficacy across some of the subgroups of great relevance to clinical practice. We did an extensive literature search of major online databases including PubMed and Embase for papers published from Jan 1, 2010, to Dec 23, 2015, and did not identify any other published randomised endovascular stroke studies that used modern thrombectomy devices. Study level meta-analyses have been reported but most included patients enrolled without definitive proof of vessel occlusion and who were treated with less effective reperfusion technology.

Furthermore, study-level meta-analyses are considered less informative than patient-level meta-analytical approaches due to their inability to adjust for confounding baseline variables, which leads to less precise estimates of treatment effect. To our knowledge no patient-level meta-analyses have been reported.

Added Value Of This Study

In this individual patient meta-analysis of trials published in 2015, we provide additional relevant facts that will enable clinicians to better understand the degree of precision of adjusted effect size estimates, safety outcome estimates, and estimates by clinical subgroups. We show clinical benefits for thrombectomy across a wide range of age and initial stroke severity and for patients eligible and ineligible for intravenous alteplase. Smaller amounts of other baseline variables such as degree of early ischaemic changes on baseline CT or time to treatment were reported and therefore the observed effects should be interpreted within the context of the populations included.

Implications Of All The Available Evidence

The consistent results across different patient populations suggest that benefit from thrombectomy is generalisable to a broad range of patients with large-vessel ischaemic stroke. By providing a more precise treatment effect estimate than each individual trial, our findings allow cost-effectiveness of this intervention at society level to be calculated with higher precision. Our study provides clear evidence that in clinical practice, endovascular therapy for stroke should not be withheld on the basis of advanced age, moderately extensive early ischaemic changes on baseline CT, and moderate or severe clinical deficit.

METHODS

Study Inclusion And Procedures

We searched major online databases including Medline and PubMed to identify controlled trials in endovascular stroke published between Jan 1, 2010, and Dec 23, 2015, that used vessel imaging to identify patients with anterior circulation ischaemic stroke and assessed treatment with modern neurothrombectomy devices. Five trials fit these criteria: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND IA.[1-5] These trials differed from all previously published trials of endovascular therapy in that the protocols emphasised fast treatment, had CT (or in some patients magnetic resonance) imaging criteria to include only patients with target large vessel occlusions who are most likely

to benefit from endovascular therapy, and used second-generation neurothrombectomy devices, which have better recanalisation rates and lower complication rates than first-generation devices and techniques.[7,8] In all five studies, patients with acute ischaemic stroke were randomly assigned to receive endovascular neurothrombectomy treatment plus usual care or usual care alone (appendix p1). All patients were treated with standard-dosing (0·9 mg per kg bodyweight) intravenous alteplase, if eligible, before randomisation.

We established a collaborative group to pool patient-level data from these trials: the Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke *Trials* (HERMES) collaboration. Differences from the TREAT meta-analysis protocol[9] include sampling frame and the primary research question.

The study statisticians from each trial extracted the patient-level data by direct access to the study databases. Independent statisticians (BS, SB) collated all data from the individual trials and cross-checked them against previous publications.

Outcomes

The prespecified primary outcome in this meta-analysis was the degree of disability on the modified Rankin Scale (mRS) at 90 days. The score on mRS ranges from normal (0) to death (6). In statistical modelling of the full modified Rankin scale, we merged scores of 5 (severe disability) and 6 (death) into a single category. Prespecified secondary outcomes were proportion of patients with functional independence (mRS 0-2) at 90 days; stroke severity as measured with the National Institutes of Health Stroke Scale (NIHSS) at 24 h after stroke onset; proportion of patients with NIHSS score 0-2 at 24 h; proportion of patients with major early neurological recovery at 24 h, defined as a reduction in NIHSS score from baseline of at least 8 points or reaching 0-1; and change in NIHSS score from baseline to 24 h. Technical efficacy was assessed through the degree of revascularisation at the end of the endovascular procedure, defined using the modified Thrombolysis in Cerebral Infarction (mTICI) scale score of 2b or 3-corresponding to reperfusion of at least 50% of the affected vascular territory. Safety outcomes were the proportion of patients with symptomatic intracranial haemorrhage (as defined by each trial), neuroradiological parenchymal haematoma type 2 (blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days, and mortality within 90 days.

Statistical Analysis

Details of the statistical analysis plan are available in the appendix (pp 12-15). To account for between-trial differences, we used mixed-effects modelling with fixed effects for parameters of interest such as treatment assignment and random effects for trial and treatment within trial. This model structure was used for all statistical analysis a priori, per the statistical analysis plan. With this approach, treatment effects for each trial (t_1, t_2, etc) are not assumed to be deterministically equal, but rather drawn from a common distribution centred on the overall effect across trials. This structure is captured by including "trial" and the interaction term "trial*treatment" as random effects variables in all mixed models. We report the overall treatment effect and all other effects using this model, which ensures that between-trial variance is incorporated in estimation for all parameters, their standard errors, and associated CIs.

For primary analyses we used mixed-effects ordinal logistic regression to answer the following research question: "Do patients with acute ischaemic stroke and proximal anterior circulation occlusions have reduced disability at 90 days with additional endovascular mechanical thrombectomy compared with standard care (including intravenous alteplase in eligible patients)?" For analyses of the full mRS, we report unadjusted and adjusted treatment effects using common odds ratios (cORs), which are derived from ordinal logistic regression and indicate the odds that the intervention would lead to improvement of 1 or more points on the mRS in a shift analysis. In the adjusted analyses we account for the following prespecified covariates: age, sex, baseline stroke severity (NIHSS score), site of occlusion (internal carotid artery *vs* M1 segment of middle cerebral artery *vs* M2 segment of middle cerebral artery), intravenous alteplase (yes vs no), baseline Alberta Stroke Program Early CT Score (ASPECTS), and time from stroke onset to randomisation. Missing data for baseline covariates are reported as percentages and dealt with using prespecified rules (appendix p15). We report overall treatment effect as number needed to treat by calculating the geometric mean of the values derived by the algorithmic joint outcome table method and the permutation test.[10,11]

For secondary analyses, we report rate ratios for prespecified efficacy and safety outcomes (unadjusted and adjusted for the above prespecified covariates) along with 95% CIs calculated with either mixed effects logistic or linear regression as appropriate.

We tested heterogeneity of treatment effect by prespecified clinically relevant variables on the primary outcome (mRS score distribution at 90 days) and two secondary outcomes (mRS score 0-2 at 90 days and death at 90 days) using a multiplicative interaction term (treatment*prespecified variable) and mixed methods modelling. Prespecified variables were age, sex, baseline stroke severity on NIHSS, time from symptom onset to randomisation, baseline ASPECTS, baseline site of thrombi, concomitant ipsilateral carotid artery occlusion or carotid artery stenosis, and whether a patient received (ie, was eligible for) alteplase. We report graphically using forest plots for stratum-specific treatment effects along with the p value for the interaction term. We reported main effects in the text if we found no statistically signifi cant interaction. All secondary analyses are reported as unadjusted and adjusted effects (adjusted for the same prespecifi ed covariates as in primary analyses). Wherever appropriate, treatment eff ects are also reported as rate ratios. For graphical depiction of the effect of variation in age and presenting stroke severity on clinical outcome at 90 days based on treatment type, we estimated the mRS and the mRS transformed into utility scores (using standardised weightings) with adjusted mixed-methods linear regression (adjusted for the above prespecifi ed covariates).[12] We did all statistical analyses with SAS version 9.2 and drew fi gures with Stata/MP version 14.0 and R software.

Role of the funding source

The funding source was Medtronic through an unrestricted grant to the University of Calgary. Medtronic had no role in design, conduct, analysis, or reporting of this study. The corresponding author had full access to all the data. The steering committee had responsibility for the decision to submit for publication.

RESULTS

	Intervention population (n=634)	Control population (n=653)
Demographic characteristics		
Median age (years)	68 (57–77)	68 (59–76)*
Men	330 (52%)	352 (54%)
Women	304 (48%)	301 (46%)
Past medical history		
Hypertension	352 (56%)	388 (59%)
Diabetes mellitus	82 (13%)	88 (13%)
Atrial fibrillation	209 (33%)	215 (33%)
Smoking (recent or current)	194 (31%)	210 (32%)
Clinical characteristics		
Baseline NIHSS score	17 (14–20))†	17 (13–21)‡
Baseline blood glucose (mmol/L)	6·6 (5·9–7·8)§	6·7 (5·9–7·8)¶
Imaging characteristics		
ASPECTS on baseline CT	9 (7–10)§	9 (8–10)¶
Intracranial occlusion location		
Internal carotid artery	133 (21%)	144 (22%)
M1 segment middle cerebral artery	439 (69%)	452 (69%)
M2 segment middle cerebral artery	51 (8%)	44 (7%)
Other	11 (2%)	13 (2%)
Treatment details and process times		
Treatment with intravenous alteplase	526 (83%)	569 (87%)
Treatment with intravenous alteplase documented within 180 min	442 (70%)	462 (71%)
Process times (min)		
Onset to randomisation	195·5 (142–260)‖	196 (142–270)*
Onset to intravenous alteplase	100 (75–133)**	100 (74–140)††
Onset to reperfusion	285 (210–362)	NA

Data are median (IQR), n (%), or mean (SD). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. *n=650. †n=631. ‡n=648. §n=620. ¶n=644. ‖n=632. **n=598. ††n=618.

Table 1: Baseline characteristics in the pooled data

Study Inclusion And Procedures

By pooling data from the five trials, we obtained data for 1287 participants; 634 assigned to endovascular thrombectomy (intervention population) and 653 assigned to standard medical treatment (control population). Baseline characteristics were largely balanced be-

tween the populations (table 1), but slightly fewer patients in the intervention group were treated with intravenous alteplase before randomisation (p=0·04). The most common location of the target occlusion was the M1 segment of the middle cerebral artery, followed by the intracranial internal carotid artery. The median time from onset to the randomised decision to pursue or not pursue endovascular reperfusion was 3 h 16 min (IQR 2 h 22 min to 4 h 27 min)

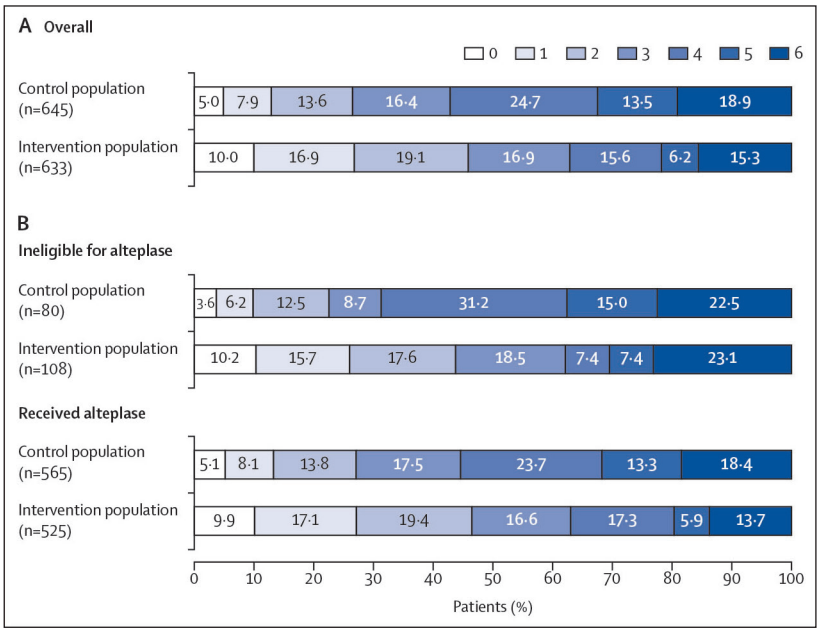


Figure 1. Scores on the modifi ed Rankin Scale at 90 days

Distribution of scores at 90 days in the intervention and control groups in the overall trial population (A) and for patients treated with, or ineligible for, intravenous alteplase (B). Distributions for other subgroups shown in appendix pp 5-11.

Figure 1 shows distribution of mRS scores by treatment population at 90 days. For the primary outcome, pooled data showed reduced chance of disability at 90 days in patients assigned to thrombectomy versus those assigned to control (adjusted cOR 2·49, 95% CI 1·76-3·53; p<0·0001; table 1). The number needed to treat for one patient to have reduced disability of at least 1 point on mRS was 2·6.

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
mRS score reduction (shift analysis; primary outcome)*	..	..	..	..	2·26* (1·67–3·06); p<0·0001	..	2·49* (1·76–3·53); p<0·0001
mRS score 0–1 at 90 days	26·9% (170/633)	12·9% (83/645)	14·0	2·00 (1·54–2·60); p<0·0001	2·49 (1·84–3·35); p<0·0001	2·06 (1·59–2·69); p<0·0001	2·72 (1·99–3·71); p<0·0001
mRS score 0–2 at 90 days	46·0% (291/633)	26·5% (171/645)	19·5	1·7 (1·41–2·05); p<0·0001	2·35 (1·85–2·98); p<0·0001	1·73 (1·43–2·09); p<0·0001	2·71 (2·07–3·55); p<0·0001
NIHSS score 0–2 at 24 h	21·0% (129/615)	8·3% (52/630)	12·7	2·47 (1·79–3·41); p<0·0001	2·91 (2·06–4·12); p<0·0001	2·66 (1·92–3·67); p<0·0001	3·77 (2·49–5·71); p<0·0001
Early neurological recovery at 24 h	50·2% (309/616)	21·2% (134/633)	29·0	2·34 (1·91–2·87); p<0·0001	4·04 (2·75–5·93); p<0·0001	2·34 (1·91–2·87); p<0·0001	4·36 (3·03–6·27); p<0·0001

Data show the proportion of patients with outcome (n/N), unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. *Common odds ratio indicating the odds of improvement of 1 point on the mRS.

***Table 2*: Efficacy outcomes from the pooled data**

The proportion of patients with an mRS score 0-2 at 90 days was higher in the endovascular thrombectomy population than in the control population (table 2) and more patients in the intervention population achieved major neurological recovery (table 2). Of 570 patients assigned to thrombectomy who had persistent and accessible occlusions at the time of catheterisation, 402 (71%) had successful revascularisation (mTICI score 2b or 3). NIHSS score was significantly higher after 24 h and showed more improvement between baseline and 24 h after treatment in patients assigned to thrombectomy (table 3). Mortality at 90 days and risk of parenchymal haematoma type 2 and symptomatic intracranial haemorrhage did not differ between populations (table 4).

	Intervention population (n=615)	Control population (n=630)	Absolute difference (%)	β coefficient (95% CI)	Adjusted β coefficient (95% CI)
NIHSS at 24 h					
Mean score	10·4 (8·7)	14·2 (7·8)	3·8	3·6 (2·5–4·7); p<0·0001	3·8 (2·7–5·0); p<0·0001
Median score	8 (3 to 16)	15 (9 to 19)	..	..	..
Change in NIHSS score from baseline to 24 h					
Mean change	−6·4 (8·2)	−2·6 (6·6)	3·8	4·3 (2·7–5·9); p<0·0001	3·9 (2·7–5·1); p<0·0001
Median change	−7 (−12 to −1)*	−2 (−6 to 1)	..	..	..

Data in parentheses are SD or IQR, unless otherwise stated. NIHSS=National Institutes of Health Stroke Scale. *n=613.

***Table 3*: NIHSS score**

	Intervention population	Control population	Risk difference (%)	Rate ratio (95% CI)	Odds ratio (95% CI)	Adjusted rate ratio (95% CI)	Adjusted odds ratio (95% CI)
Symptomatic intracranial haemorrhage	4·4% (28/634)	4·3% (28/653)	0·1	1·06 (0·63–1·80); p=0·82	1·07 (0·62–1·83); p=0·81	1·07 (0·62–1·80); p=0·81	1·07 (0·62–1·84); p=0·81
Parenchymal haematoma type 2	5·1% (32/629)	5·3% (34/641)	−0·2	0·99 (0·61–1·61); p=0·97	0·99 (0·60–1·63); p=0·97	1·04 (0·64–1·69); p=0·88	1·04 (0·63–1·72); p=0·88
Mortality	15·3% (97/633)	18·9% (122/646)	−3·6	0·82 (0·63–1·07); p=0·15	0·77 (0·54–1·10); p=0·16	0·82 (0·62–1·08); p=0·15	0·73 (0·47–1·13); p=0·16

Data show the proportion of patients with outcome (n/N), unless otherwise stated.

Table 4: **Safety outcomes at 90 days**

For subgroup analysis of mRS distribution shift at 90 days, there was no evidence of heterogeneity of treatment effect across any of the prespecifi ed variables: age, sex, NIHSS, site of intracranial occlusion, intravenous alteplase received or ineligible, ASPECTS, time from onset to randomisation, and presence of tandem cervical carotid occlusion (fi gure 1, appendix pp 5-11). The direction of effect favoured endovascular treatment across all strata, although the adjusted cORs for treatment were not significant for patients younger than 50 years, those with a low ASPECTS or NIHSS score, and in those with an M2 segment thrombus (fi gure 2). Effects favouring the intervention were significant in several subgroups of special interest, including patients older than 80 years, those randomised more than 300 min after symptom onset, and in those not receiving intravenous alteplase (figure 2).

We also noted no evidence of heterogeneity of treatment effect across the prespecified subgroups for achievement of functional independence (mRS 0-2) at 90 days (appendix p2). However, patients randomised after 300 min and patients with tandem lesions also did not show significant benefit on functional independence after thrombectomy. No heterogeneity of treatment effect was noted for mortality ($p_{interaction} = 0 \cdot 33$) but rate ratios were rarely significant in any of the subgroups. Patients older than 80 years assigned to thrombectomy had a slightly reduced risk of death (41 [45%] of 91 patients died *vs* 30 [28%] of 107 assigned to control; adjusted rate ratio 0 · 60, 95% CI 0 · 36-0 · 99; appendix p3). Older age and higher baseline NIHSS score were positively correlated with high mRS score at 90 days in both the treatment and control groups (figure 3). Utility weighted mRS scores by age and NIHSS score show worse clinical outcome with older age and higher

NIHSS score, but the difference between intervention and control groups remains constant, indicating a consistent treatment effect over the entire range (appendix p4).

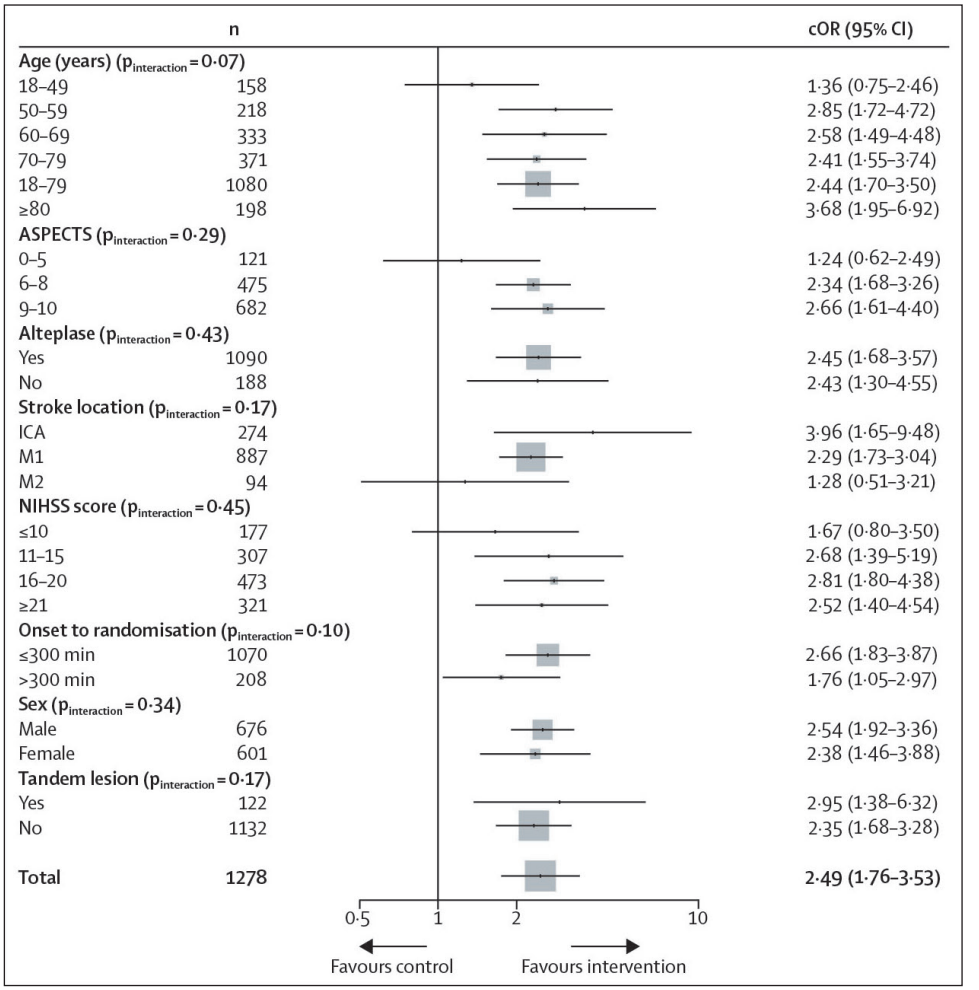


Figure 2. Forest plot showing adjusted treatment eff ect for mRS at 90 days in prespecifi ed subgroups with p values for heterogeneity across subgroups

cOR=common odds ratio. mRS=modified Rankin Scale. ASPECTS=Alberta Stroke Program Early CT score. ICA=internal carotid artery. M1=M1 segment of middle cerebral artery. M2=M2 segment of middle cerebral artery. NIHSS=National Institutes of Health Stroke Scale.

DISCUSSION

In this pooled analysis of patient-level data we show that modern endovascular thrombectomy added to best medical therapy more than doubles the odds of a higher mRS score compared with best medical therapy alone in patients with acute ischaemic stroke due to anterior circulation large vessel occlusion. This analysis confirms benefit of endovascular thrombectomy across a range of subgroups, including in groups of interest such as the elderly, patients not receiving intravenous alteplase, and patients who present later than 300 min from stroke symptom onset. The degree of benefit conferred by endovascular thrombectomy is substantial: for every 100 patients treated, 38 will have a less disabled outcome than with best medical management, and 20 more will achieve functional independence (mRS 0-2) as a result of treatment. The rates of symptomatic intracranial haemorrhage and radiological intracerebral haematoma (parenchymal haematoma type 2) are no higher with endovascular thrombectomy than with best medical therapy alone and mortality risk did not significantly differ between groups (table 4).

Our analysis distinguishes itself from study-level meta-analyses[13-17] by using individual patient data. By permitting adjustment for prognostic variables at the level of individual participants, patient-level pooled analyses provide a more powerful and reliable method of addressing questions that have not been satisfactorily resolved by individual trials.[18] Another strength of this analysis is that it includes only trials that incorporated key elements of current clinical practice, including universal requirement for proven large artery occlusion; timely treatment; and use of second-generation, more effective, devices (mainly stent retrievers). Most of the included trials also emphasised workflow to reduce time to reperfusion, compared with previous trials,[19,20] and several excluded patients with large regions of irreversibly injured brain at initial imaging.

Most (five of every six) patients enrolled across all five trials were eligible for and received intravenous alteplase. The benefit of endovascular thrombectomy in alteplase-treated patients shown in every individual trial analysed is reinforced by our pooled analysis comprising 1090 alteplase-treated patients. By contrast, previous trials individually did not have adequate power to reliably assess the benefit of endovascular therapy in alteplase-ineligible patients. Our pooled analysis of 188 alteplase-ineligible patients showed substantial

benefit in this subgroup (figure 2). This finding does not mean that alteplase should be withheld before thrombectomy in alteplase-eligible patients. Rather, endovascular reperfusion should be pursued for large anterior vessel occlusions, irrespective of eligibility for alteplase.

Our study provides evidence of consistent benefit for endovascular treatment on disability across all age groups, including in octogenarians. Our results suggest that there is no reason to withhold thrombectomy solely on the basis of age. Although age does not modify the treatment effect, it remains a strong independent predictor of final outcome (figure 3A, appendix p4).

Our analysis confirms benefit from endovascular thrombectomy for patients with occlusions of the intracranial arterial circulation segment, with or without concomitant (tandem) occlusions of the extracranial internal carotid artery, indicating that patients with tandem occlusions should not be excluded from treatment (figure 2, appendix p11). However, the heterogeneity of treatment methods given with respect to the proximal extracranial carotid occlusion in this group of patients (no revascularisation of the proximal lesion vs angioplasty vs stenting) does not allow for any conclusions about the optimum treatment approach for patients with tandem occlusions. This strategy remains to be refined through future studies.

The question of benefit with more distally located occlusions in the M2 middle cerebral artery segment is only partially addressed by our analysis. Three of the five trials restricted enrolment to patients with more proximal occlusions and the remaining two enrolled only a few patients with distal occlusions. Although we noted no statistical heterogeneity in treatment effect, our analysis does not have power to fully confirm benefit or harm in this patient subgroup. Furthermore, most of the patients with M2 occlusions included in this analysis were misclassified as having M1 occlusion at the time of enrolment, having subsequently been adjudicated by the core lab as M2 occlusion. These adjusted patients are probably a disproportionate sample of proximal and large M2 occlusions. These off-target enrolments highlight the challenge associated with poor standardisation in distinguishing between M1 and M2 segment stroke. Patients with basilar artery occlusion were not included in these studies. A randomised trial is now assessing the effect of endovascular thrombectomy in this patient group (NCT01717755).[21]

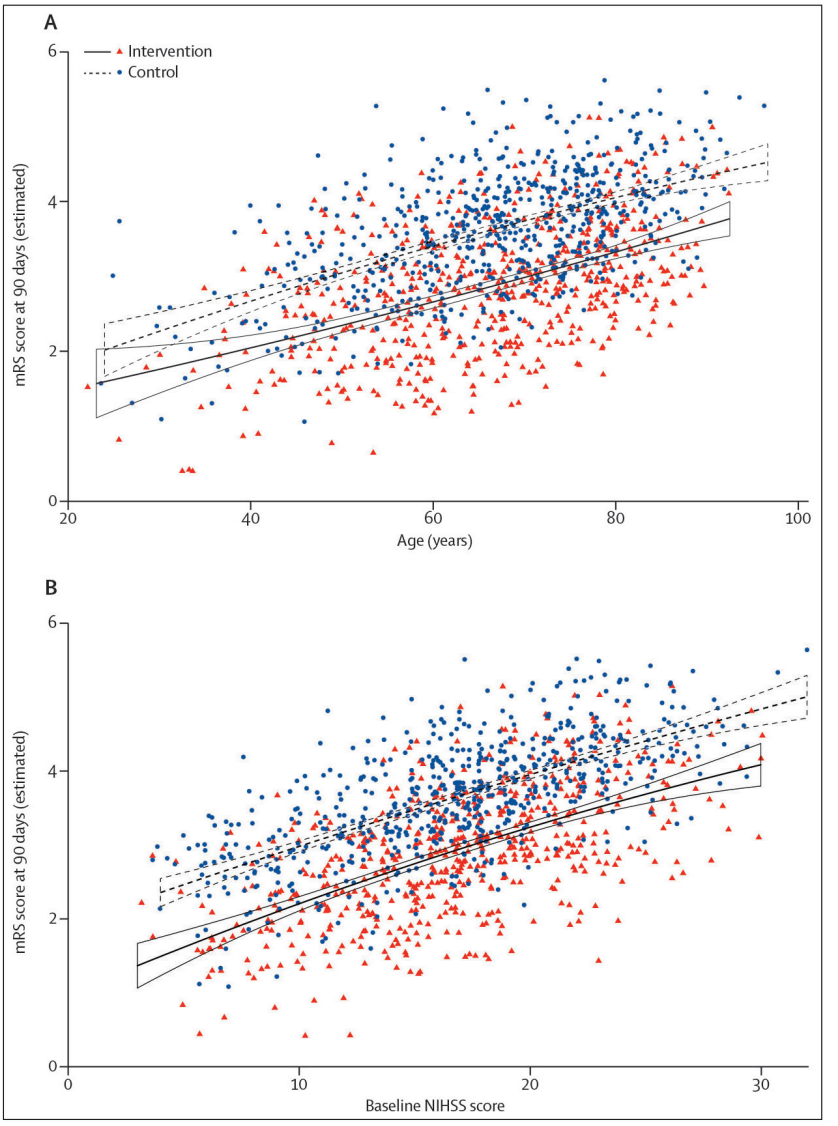


Figure 3. mRS score at 90 days estimated with a mixed methods linear regression versus age (A) and baseline NIHSS (B)

Data are stratified by intervention versus control. Models adjust for covariates (age, sex, baseline stroke severity, site of occlusion, intravenous alteplase [yes vs no], Alberta Stroke Program Early CT Score, and time from onset to randomisation). mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale

Contrary to previous studies that have identified patients with most severe strokes (baseline NIHSS score ≥20) as deriving most benefit from embolectomy,[22] our analysis shows a similar effect on disability across the entire NIHSS severity range. However, few patients with minor strokes were available for analysis. In clinical practice, treatment of patients with mild strokes and confirmed large vessel occlusion should be determined based on specific clinical and radiological features of the individual case, bearing in mind the risk of subsequent clinical deterioration with best medical therapy in patients with large vessel occlusion.[23]

The extent of pretreatment infarction on baseline imaging has been recognised as a critical determinant of clinical outcome in patients treated with reperfusion therapies.[24] For that reason, most studies have excluded from enrolment patients who present with signs of a large infarct on baseline brain imaging. Different trials have assessed this variable with methods of different degrees of sophistication but baseline ASPECTS[25] is an element common to all trials. Our analysis suggests that although lower baseline ASPECTS (more extensive irreversible injury) is strongly associated with lower rates of favourable outcomes, similar benefit is conferred in patients with high baseline ASPECTS (9-10) and those with moderate baseline ASPECTS (6-8). Because most trials excluded patients with an ASPECTS of 5 or lower, the effect of endovascular thrombectomy in this category of patients could not be established by our analysis. In this subgroup the treatment effect on functional outcome was not significant (cOR 1 · 24, 95% CI 0 · 62-2 · 49) and further clarification is needed from future studies. Clinically, an important distinction should be made between low ASPECTS as an indicator of a very poor prognosis and any possible treatment effect of reperfusion. If the prognosis is extremely poor, even a small treatment effect might not represent a useful intervention.

Intervention benefited patients randomised later than 300 min (and generally less than 420 min) from stroke symptom onset. This generally corresponds to start of the endovascular procedure less than 8 h from symptom onset. Definitive proof of benefit in imaging-selected patients treated beyond 6 h remains to be established and is being addressed by ongoing trials (NCT02142283, NCT02586415).

Stent retrievers were the main device used across all five trials and treatment benefit with endovascular thrombectomy is most robust with this technology. Thus, stent retrievers

constitute the benchmark against which future thrombectomy approaches should be measured. Among patients with persistent occlusions at catheterisation, 71% had reperfusion to at least half of the affected vascular territory. Although considerably better than the results with older technology,[7,8] further increases in the rate of successful and complete reperfusion and reduced procedural time are needed, justifying ongoing efforts to improve technological aspects of endovascular thrombectomy.

A strength of this study was that, although the individual trial populations were similar in many respects, they varied in some entry criteria and in diversity of the patient population with respect to geography and ethnic origin (appendix p1). These differences allowed us to explore and confirm consistent benefit across wide ranges of age, baseline stroke severity, and additional patient characteristics. The consistency of results across all five trials suggests that our findings are generalisable to a broad range of patients with large vessel ischaemic stroke.

Our meta-analysis had some limitations. The five trials were done at experienced, comprehensive stroke centres;[1-5] registry studies in a larger group of hospitals are needed to confirm applicability to less experienced centres. Across all five trials, procedural, imaging, and clinical outcome measures (mTICI, ASPECTS, mRS, etc) were all ascertained in a blinded manner, but using different core labs and operationalised approaches (appendix p1). Although the sample size was large (n=1287), the ability to provide adjusted treatment effect estimates for all subgroups analysed was limited by the number of people in each group. Although multiple comparisons inflate type I error, the analyses for the primary outcome were all significant at an α level of $0 \cdot 0001$ (table 2) or non-significant without adjustment for multiplicity, as in table 4. Hence, the resulting statistical inferences would be the same even with techniques adjusting for multiple comparisons. Subgroup analyses, for which the full sample size was by definition not used, remain potentially subject to type I error due to multiplicity of testing; however, no evidence of interaction effects was found (appendix). Finally, the potential for bias was minimised by the pre-specification of analysis objectives and methods, and the variance in resulting estimates was modelled appropriately by the inclusion of random effects in the statistical models.

Some patient populations, particularly those with large infarcts at baseline, those with posterior circulation occlusions, those presenting beyond 12 h, and those with substantial

disability (mRS score ≥2) before stroke were excluded from all the analysed trials. Our results cannot be extrapolated to these patient populations. Finally, since the meta-analysis included some trials that were stopped early, the possibility exists of over-estimation of treatment effect. Establishing broad applicability will need careful systematic collection of registry data.

In conclusion, endovascular thrombectomy reduces disability for patients with large vessel anterior circulation ischaemic stroke. Benefits are seen across a wide range of age and initial stroke severity, and apply to patients irrespective of eligibility for intravenous alteplase.

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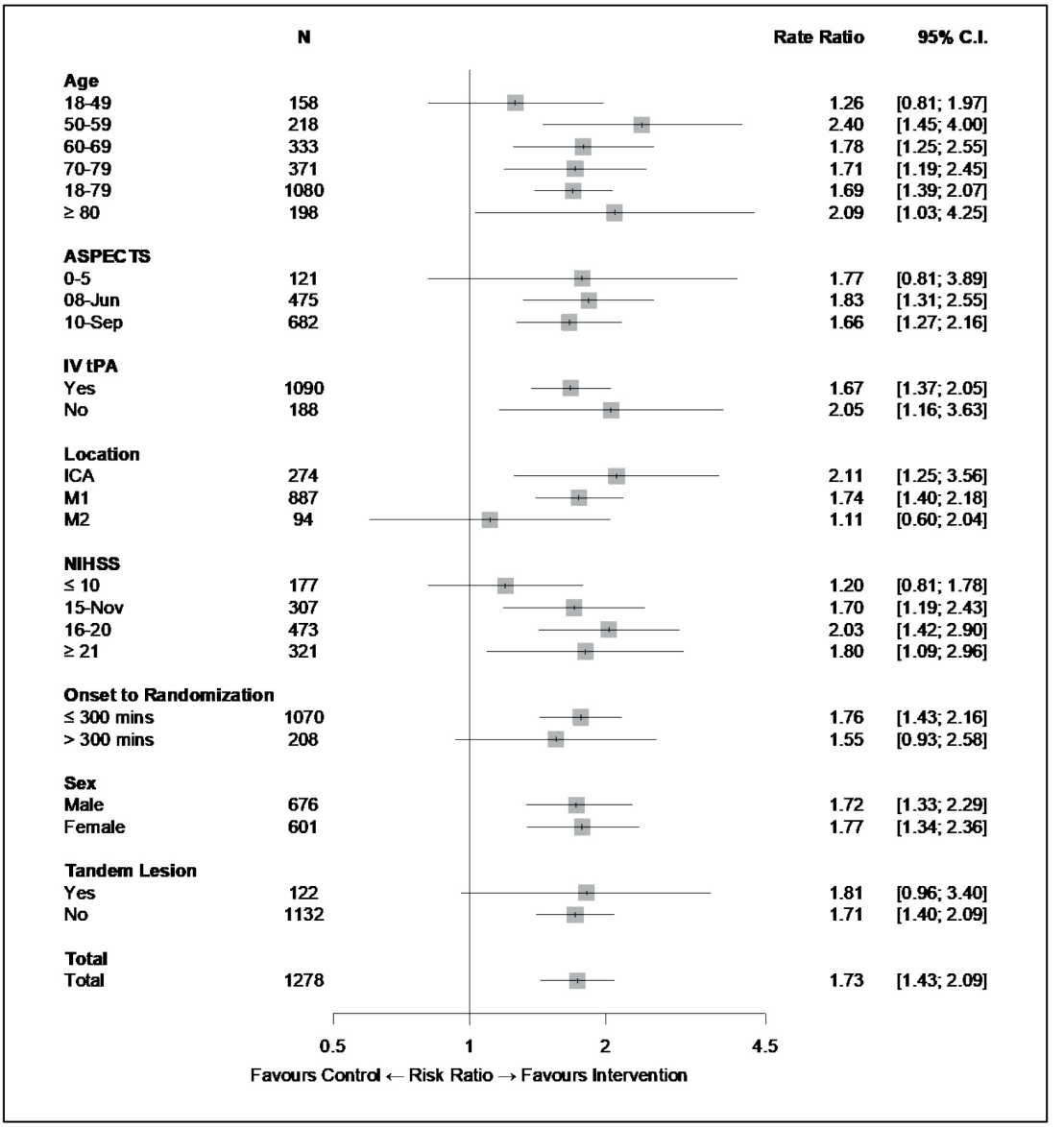
Supplementary Appendix

Supplementary Table 1: Qualitative assessment of between trial differences in population, sampling frame and operational definitions of Interventional and Control Groups.

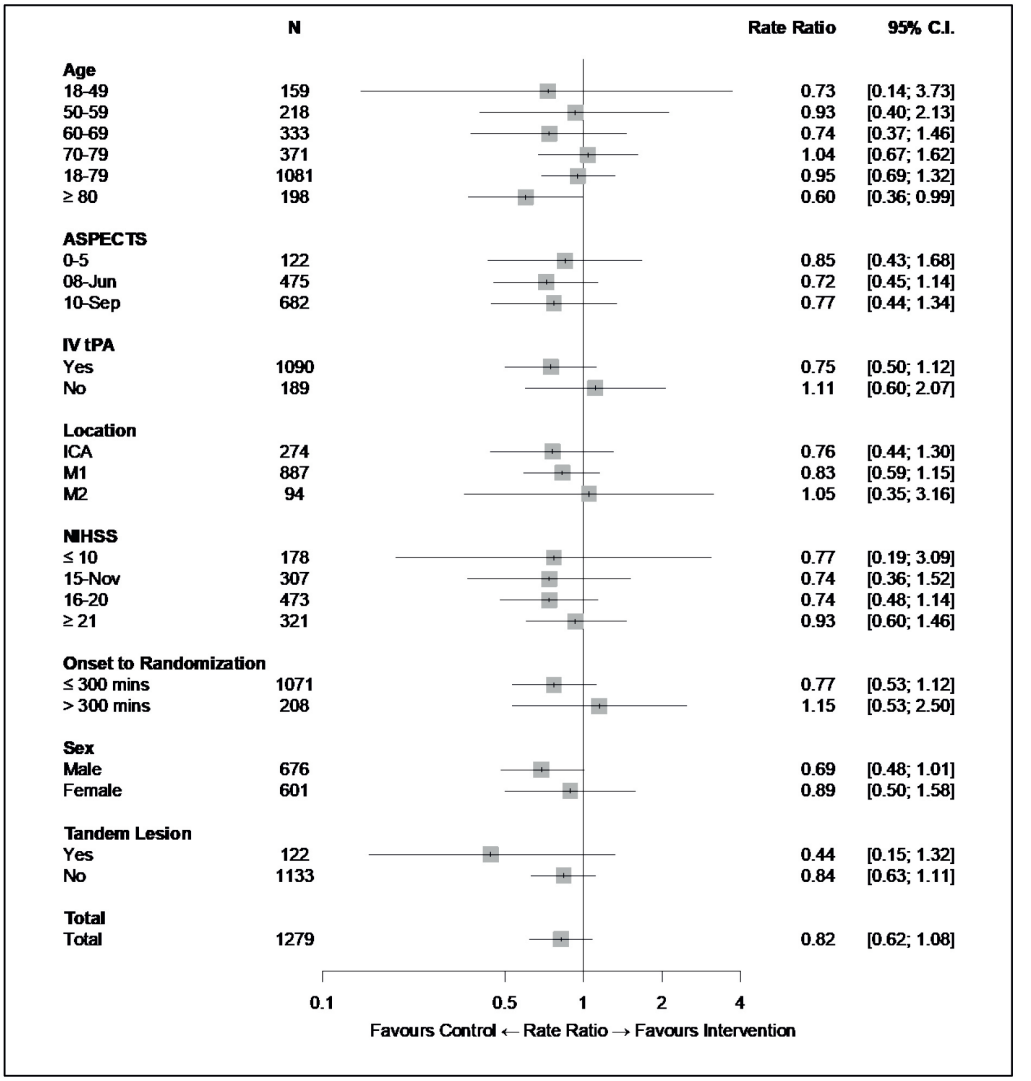
	MR CLEAN	ESCAPE	EXTEND IA	SWIFT PRIME	REVASCAT
			Population		
Continent	Europe	North America, Europe, East Asia	Australia/New Zealand	North America and Europe	Europe
Country	Netherlands	Multiple	Two	Multiple	Spain
			Sampling Frame		
Imaging Criteria					
Modality	NCCT/CTA	NCCT/CTA *CTP optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA/CTP *MRI optional	NCCT/CTA *CTP optional
Occlusion Site	ICA M1 M2	ICA M1	ICA M1 M2	ICA M1	ICA M1
Core	N/A	ASPECTS 6-10 Good Collaterals	CTP mismatch and ischemic core <70mL	CTP and NCCT ASPECTS criteria (modified protocol)	ASPECTS 6-10
Clinical Criteria					
Age (years)	≥18	≥18	≥18	18-85 (later amended to 18-80)	18-80 (later amended to allow 81-85 if ASPECTS>8)
Baseline Stroke Severity	N/A	NIHSS >=6	N/A	NIHSS	NIHSS >=6
Time to randomization	6 hours	12 hours	6 hours	6 hours	8 hours
Definition of SICH					
			Control Group		
	Standard care	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients	Standard care
			Intervention Group		
Wait for response to IV alteplase	No	No	No	No	Yes
Pre-specified time metrics	No	Yes	No	Yes	Yes
Type of Devices	Any	Any	Solitaire	Solitaire	Solitaire

NCCT – Non contrast CT, CTA – CT angiography, CTP – CT Perfusion, MRI –Magnetic Resonance Imaging, ICA –Internal Carotid Artery, MCA – Middle Cerebral Artery ASPECTS - Alberta Stroke Program Early CT Score, PH – Parenchymal Hemorrhage, SAH – Subarachnoid hemorrhage, IVH – Intra-ventricular Hemorrhage, NIHSS – National Institute of Health Stroke Scale, IV - intravenous

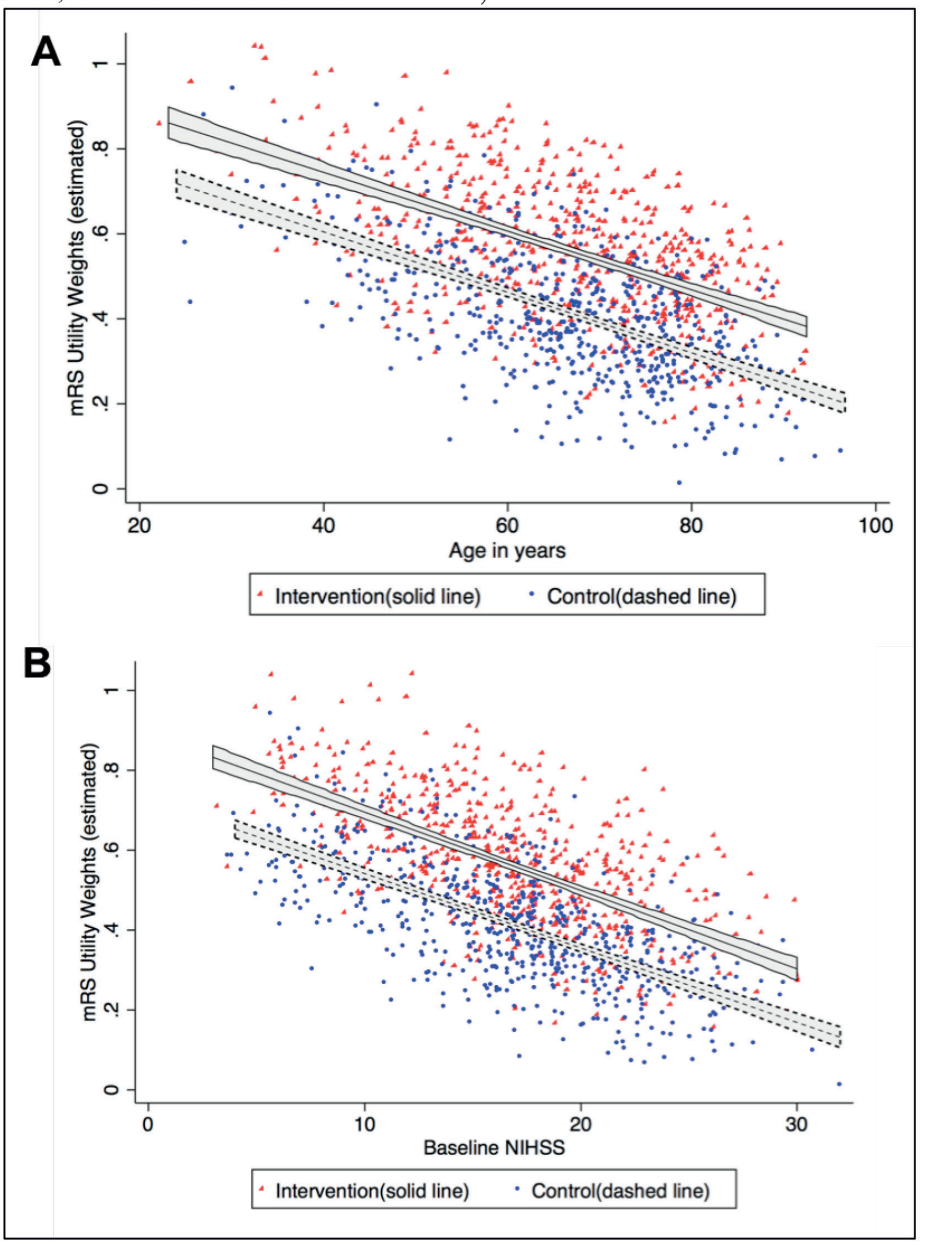
Supplementary Figure 1: Forest plot showing adjusted treatment effect for secondary outcome (mRS 0-2) in pre-specified sub-groups.



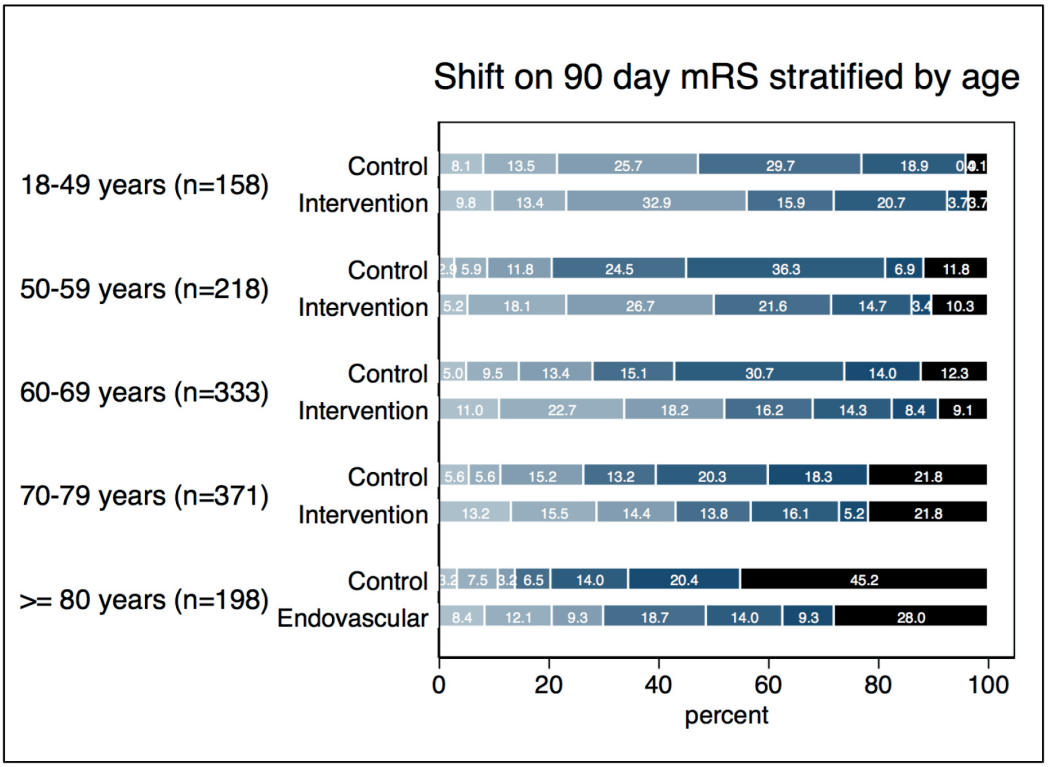
Supplementary Figure 2: Forest plot showing adjusted treatment effect for mortality (within 90 days) in pre-specified sub-groups.



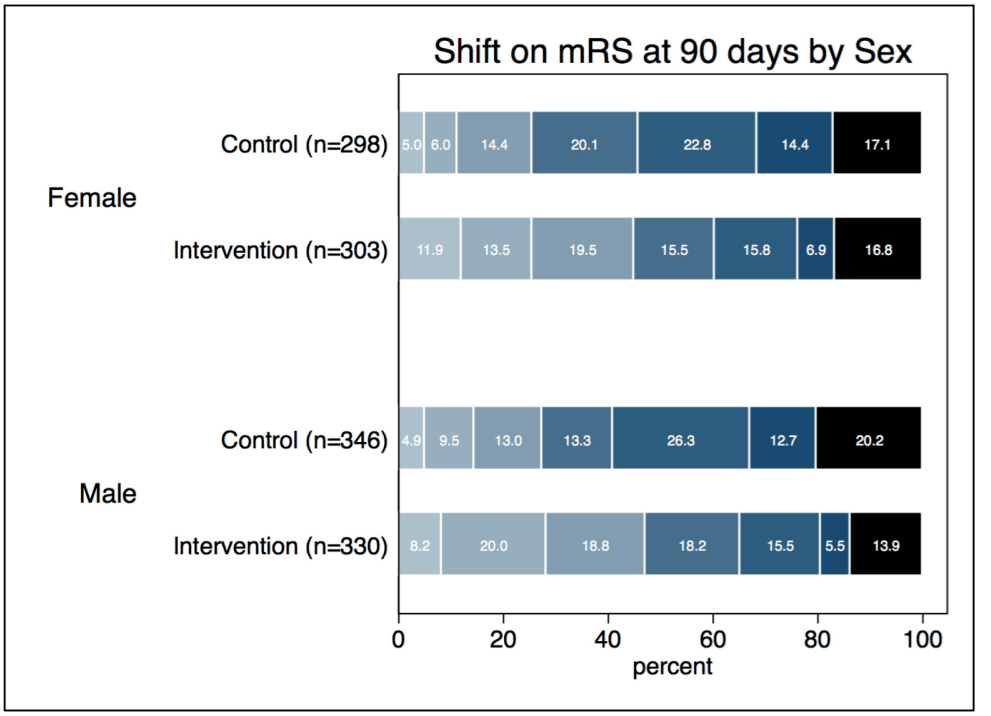
Supplementary Figure 3: Graphs showing utility weighted modified Rankin Scale at 90 days estimated using a mixed methods linear regression vs. age (panel A) and baseline NIHSS (panel B). Data is stratified by intervention vs. control group. Models adjust for co-variates (age, sex, baseline stroke severity, site of occlusion, IV tPA (yes/no), ASPECTS score, and time from onset to randomization).



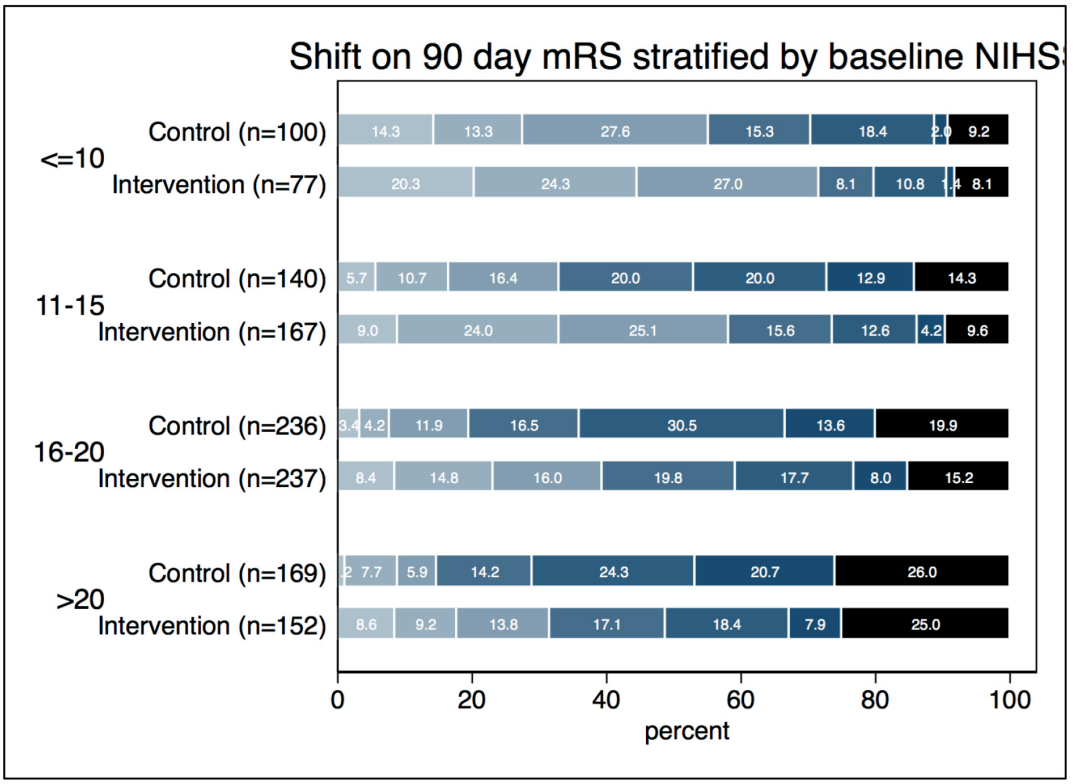
Supplementary Figure 4: Distribution of mRS at 90 days in the intervention and control groups according to age. (p = 0.07 for interaction).



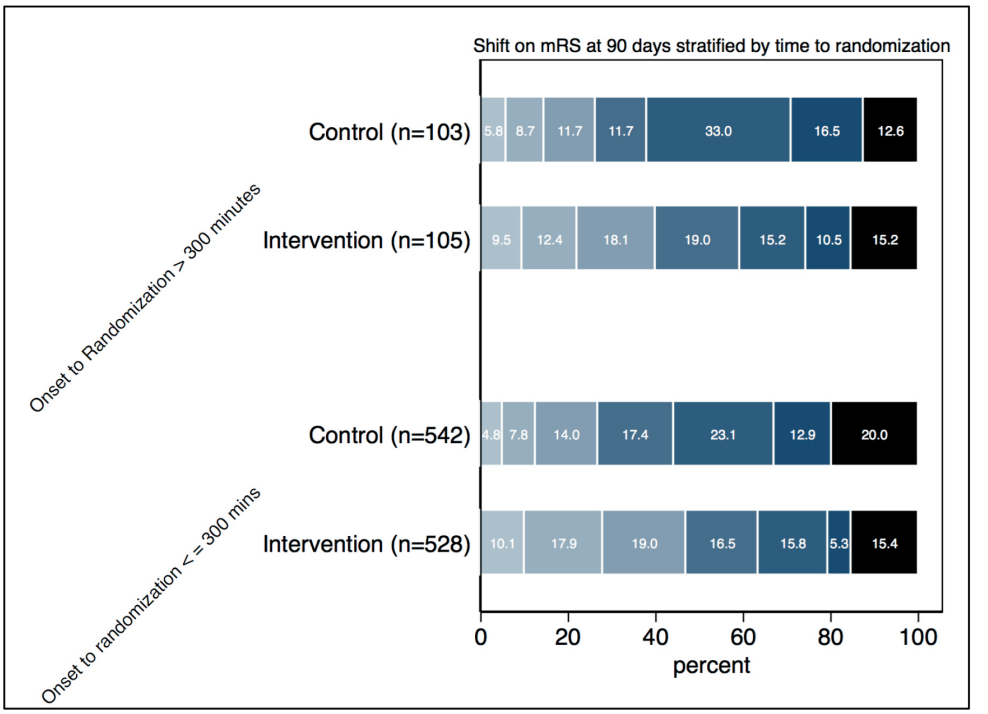
Supplementary Figure 5: Distribution of mRS at 90 days in the intervention and control groups according to sex. (p = 0.36 for interaction).



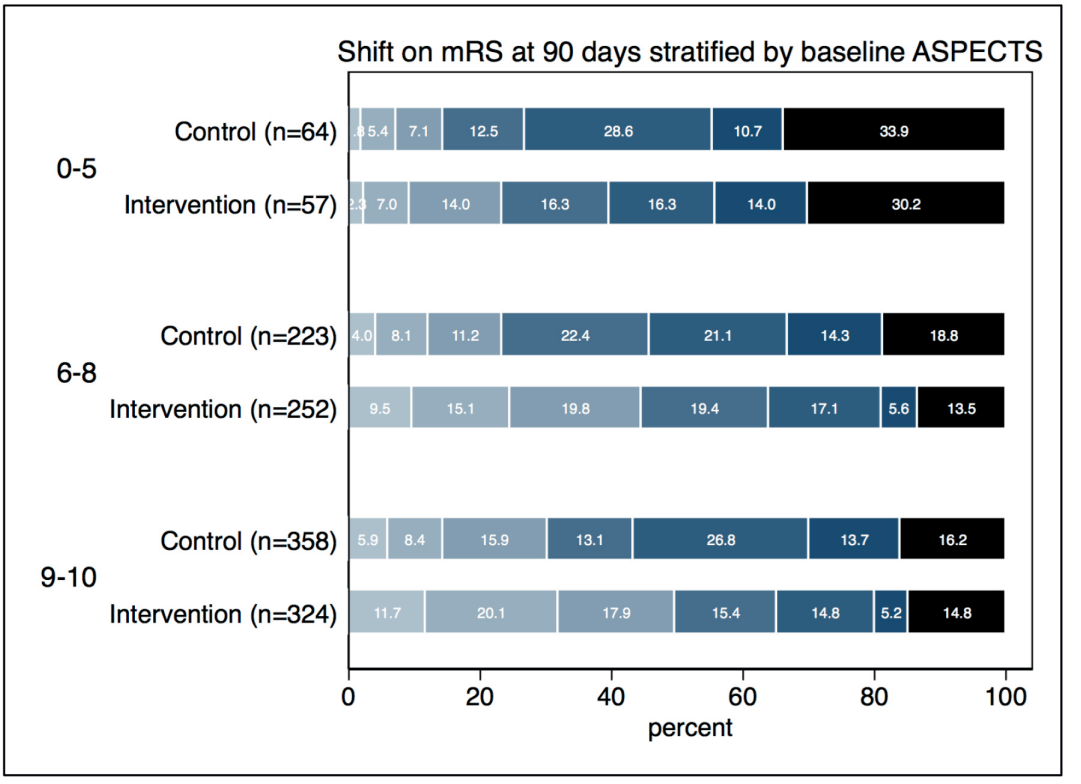
Supplementary Figure 6: Distribution of mRS at 90 days in the intervention and control groups according to baseline stroke severity measured by NIHSS. (p = 0.47 for interaction).



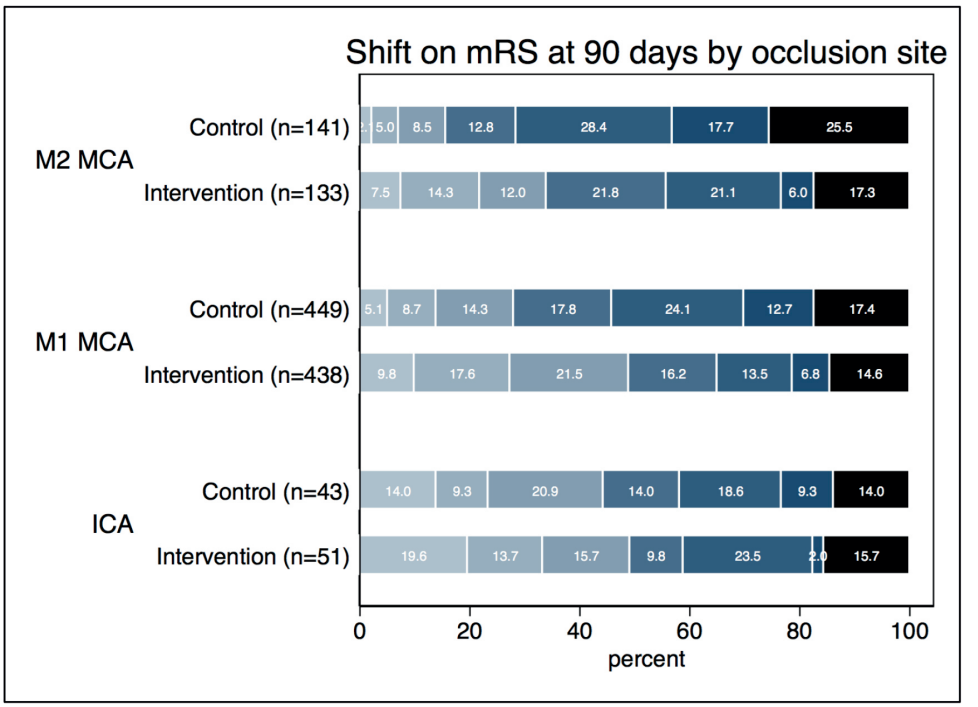
Supplementary Figure 7: Distribution of mRS at 90 days in the intervention and control groups according to time from stroke symptom onset to randomization. (p = 0.13 for interaction).



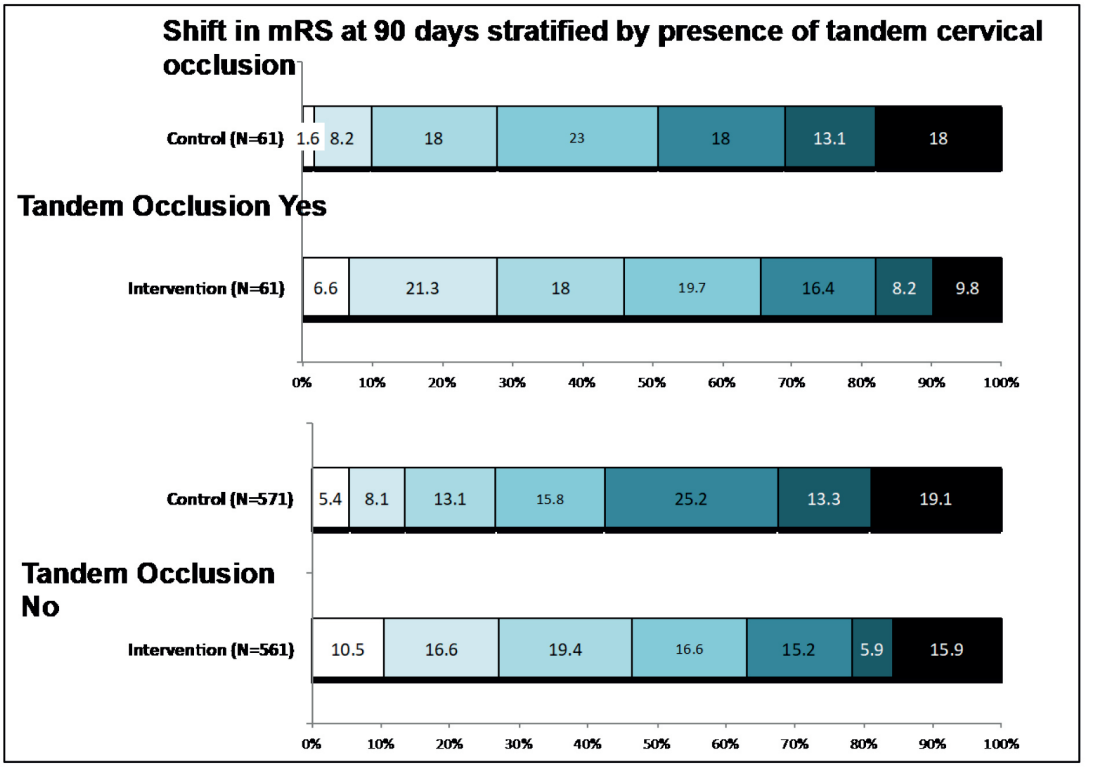
Supplementary Figure 8: Distribution of mRS at 90 days in the intervention and control groups according to baseline non-contrast CT ASPECTS. (p = 0.49 for interaction).



Supplementary Figure 9: Distribution of mRS at 90 days in the intervention and control groups according to site of baseline artery occlusion. (p = 0.35 for interaction).



Supplementary Figure 10: Distribution of mRS at 90 days in the intervention and control groups according to presence or absence of tandem occlusion. (p = 0.49 for interaction).



CHAPTER 3

Importance Of Workflow In Acute Ischemic Stroke

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CHAPTER 3.1

Evaluation Of Interval Times From Onset To Reperfusion In Patients Undergoing Endovascular Therapy In The Interventional Management Of Stroke III Trial

Based upon:

Evaluation of Interval Times From Onset to Reperfusion in Patients Undergoing Endovascular Therapy in the Interventional Management of Stroke III Trial

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ABSTRACT

Background

Meaningful delays occurred in the Interventional Management of Stroke (IMS) III trial. Analysis of the work flow will identify factors contributing to the in-hospital delays.

Methods and Results

In the endovascular arm of the IMS III trial, the following time intervals were calculated: stroke onset to emergency department arrival; emergency department to computed tomography (CT); CT to intravenous tissue plasminogen activator start; intravenous tissue plasminogen activator start to randomization; randomization to groin puncture; groin puncture to thrombus identification; thrombus identification to start of endovascular therapy; and start of endovascular therapy to reperfusion. The effects of enrollment time, CT angiography use, interhospital transfers, and intubation on work flow were evaluated. Delays occurred notably in the time intervals from intravenous tissue plasminogen activator initiation to groin puncture (median 84 minutes) and start of endovascular therapy to reperfusion (median 85 minutes). The CT to groin puncture time was significantly shorter during working hours than after. Times from emergency department to reperfusion and groin puncture to reperfusion decreased over the trial period. Patients with CT angiography had shorter emergency department to reperfusion and onset to reperfusion times. Transfer of patients resulted in a longer onset to reperfusion time compared with those treated in the same center. Age, sex, National Institutes of Health Stroke Scale score, and intubation did not affect delays.

Conclusion

Important delays were identified before reperfusion in the IMS III trial. Delays decreased as the trial progressed. Use of CT angiography and endovascular treatment in the same center were associated with time savings. These data may help in optimizing work flow in current and future endovascular trials.

Clinical Trial Registration

URL: http://www.clinicaltrials.gov. Unique identifier: NCT00359424. (*Circulation*. 2014;130:265-272.)

The outcome of acute ischemic stroke therapies is time dependent.[1,2] Early restoration of blood flow to ischemic brain tissue increases the potential of mitigating the ischemic insult and restoring the normal function of the affected brain.[3,4] In a meta-analysis of randomized trials of intravenous tissue plasminogen activator (tPA) within 6 hours from onset, patients treated with intravenous tPA within 3 hours achieved the greatest treatment benefit.[5] Evidence from intra-arterial cohorts has shown similar results with evidence of improved recovery and lower mortality in patients who achieved short onset to reperfusion times.[6]

The recent introduction of stentrievers resulted in higher rates of successful reperfusion, with procedure times reduced by more than half compared with prior techniques.[7] For reperfusion therapies, attention to minimizing time to reperfusion via work flow improvement, targeting the various steps from emergency department (ED) arrival to microcatheter delivery at the thrombus interface, is paramount.[8] Although some studies demonstrate the feasibility of shortening ED to intravenous tPA needle time to as short as 20 minutes,[9,10] studies on work flow in stroke patients treated with endovascular therapies are scarce.

Multiple factors may contribute to considerable delays before endovascular reperfusion is achieved. Coordinating endovascular therapy is more complex given the resource requirement before treatment, variability in vascular access, and intensive nature of the procedures.[11] With the multiple issues that require attention in the acute stroke setting, delays often go unrecognized by stroke team members, and potential strategies to reduce time to reperfusion may be overlooked.

To improve the various processes and to appropriately allocate resources, an understanding of the flow of patients through the hospital system from arrival to ED, the time loss associated with acquiring additional imaging, and the time of various components within the angiography suite until final reperfusion will be useful. In this study, we examine the patients in the endovascular arm of the Interventional Management of Stroke (IMS) III trial not only to evaluate the system processes but also to identify the factors that ultimately contribute to delays in achieving reperfusion.

METHODS

Trial Design

The IMS III trial was an National Institutes of Health-funded, phase III, randomized, multicenter, open-label clinical trial designed to determine whether a combined approach with endovascular therapy after intravenous tPA is superior to standard intravenous therapy alone when initiated within 3 hours of acute stroke onset in moderate to severe strokes, as determined by a modified Rankin Scale score of 0 to 2 at 90 days. Patients were randomized in a 2:1 ratio, with more patients assigned to the endovascular arm.

The IMS III Trial enrolled 656 patients before enrollment was halted for futility in May 2012 on the basis of a recommendation by the Data and Safety Monitoring Board. The details of the study methods and results have been published.12,13

Of the 434 patients randomized to the endovascular arm, 16 patients were inpatients at the time of their strokes and were excluded from the work flow analysis. In the remaining 418 patients, the following time intervals were calculated: (1) stroke onset to ED arrival;

(2) ED arrival to computed tomography (CT) start; (3) CT to start of intravenous tPA bolus; (4) intravenous tPA bolus to randomization;

(5) randomization to groin puncture; (6) groin puncture to thrombus identification; (7) thrombus identification to start of endovascular therapy; and (8) start of endovascular therapy to reperfusion. Among those imaged with CT angiography (CTA), the CT to CTA times and CTA to start of intravenous tPA bolus times were also assessed.

The time of thrombus identification is defined as the time of the angiographic run that shows the intracranial occlusion. The time of start of endovascular therapy is the time of start of intra-arterial tPA bolus (via Micro-Sonic SV infusion system [EKOS] or a standard microcatheter), or the start time of balloon occlusion (if Merci retriever [Concentric Medical] was the primary intra-arterial device), or the start time of thrombus aspiration (if

Penumbra system [Penumbra] was the primary intra-arterial device), or the time of first deployment of the device (if Solitaire FR [Covidien] was the primary intra-arterial device). The reperfusion time is the time of the last angiographic image.

The impacts of patient transfer, baseline CTA performance (yes versus no), intubation within 7 hours of onset (yes versus no), and time of randomization (working hours [Monday through Friday, 8 am to 5 pm] versus outside these hours) on the overall work flow time were evaluated. Patient transfer type was classified into those who received intravenous tPA and then transferred to another facility for endovascular therapy ("drip and ship"); those who were transferred to the endovascular facility before intravenous tPA initiation ("ship and drip"); and those who presented and treated within the same center ("mother-ship"). In addition, changes in times from ED to reperfusion and from groin puncture to reperfusion over the entire study period were assessed.

All times are reported as medians (with interquartile range [IQR]). The Kruskal-Wallis test was used to compare the median times, with adjustment for multiple comparisons by the Bonferroni method where applicable. To investigate factors associated with delays, univariable and multivariable linear regression models were constructed with both ED to reperfusion time and onset to reperfusion time individually as outcomes. Potential predictors include age, baseline National Institutes of Health Stroke Scale score stratum (≤19 versus ≥20), sex, warfarin use, quartiles of enrollment, randomization during working hours, transfer type, baseline use of CTA, and intubation status. The model for ED to reperfusion time was fit only within patients treated in the mother-ship paradigm and thus excluded transfer type as a predictor. Similarly, the impact of CTA conduct, patient transport, and enrollment time on favorable outcome (modified Rankin Scale score ≤2) was assessed in univariable and multivariable logistic regression models. Model assumptions and goodness of fit were assessed and found to be valid. Analyses were performed with the use of SAS 9.3 software. A 2-tailed significance level of 0.05 was used.

Informed consent was obtained from all participants (or their legal representatives) before enrollment. The study was approved by the institutional review committee of the participating centers.

RESULTS

The clinical characteristics and outcomes of these patients were published previously.[12] The specified time intervals are shown in Table 1. The median time from onset to ED arrival was 50 minutes (IQR 34). Before the start of the endovascular procedure, the longest time interval was from intravenous tPA initiation to groin puncture (85 minutes; IQR 41). During the endovascular procedure, the longest time interval was from start of endovascular therapy until the last angiographic image was acquired (85 minutes; IQR 74). There was a weak negative correlation between the time from onset to ED arrival with the puncture to reperfusion time and between the time interval from ED arrival to baseline CT with the CT to puncture time.

Table 1. Various Time Intervals in the Endovascular Arm of the Interventional Management of Stroke III Trial

	Time Interval, min	
	Median	IQR
Stroke onset to ED arrival (n=418)	50	34
ED arrival to CT start (n=413)	19	15
CT to start of IV tPA bolus (n=412)	42	30
CT to start of IV tPA (patients with CTA, n=206)	39	27
CT to CTA (n=206)	6	7
CTA to start of IV tPA bolus (n=207)	31	24
CT to start of IV tPA bolus (patients without CTA, n=206)	47	28
IV tPA bolus to randomization (n=417)	24	25
Randomization to groin puncture (n=408)	62	38
Groin puncture to thrombus identification (n=327)	15	15
Thrombus identification to start of endovascular therapy (n=310)	20.5	24
Start of endovascular therapy to reperfusion (n=312)	85	74
IV tPA bolus to groin puncture (n=407)	85	41
IV tPA bolus to endovascular therapy initiation (n=314)	125.5	46

CT indicates computed tomography; CTA, computed tomographic angiography; ED, emergency department; IQR, interquartile range; IV, intravenous; and tPA, tissue plasminogen activator.

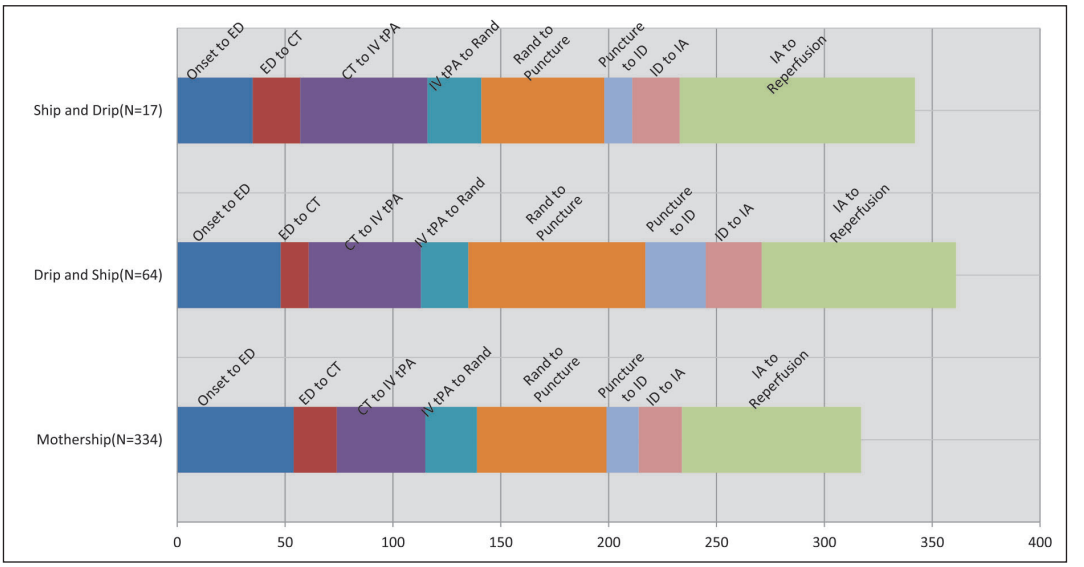

Figure 1.

Various time intervals in patients treated within the same institution (mother-ship) vs those who were transferred from another before (ship and drip) or after (drip and ship) intravenous tissue plasminogen activator (IV tPA) therapy. CTA indicates computed tomographic angiography; ED, emergency department; IA, start of endovascular therapy; ID, thrombus identification; Puncture, groin puncture; and Rand, randomization.

Delays Attributable to Interhospital Patient Transfer

Time from intravenous tPA bolus to groin puncture was affected by transfer status (Figure 1 and Table 2). This difference appears to be driven largely by the time from randomization to puncture because the time from intravenous bolus to randomization is not different according to transfer type. Patients who were treated in the drip and ship paradigm had a significantly longer time from intravenous tPA to puncture than the patients randomized and treated in the same facility ($P<0.0001$ for both the intravenous tPA bolus to puncture and randomization to puncture time intervals). There was no difference in the time from intravenous to puncture in patients who were treated in the ship and drip paradigm compared with those who were randomized and treated in the same facility ($P>0.2$ for both time intervals).

Table 2. Time Intervals According to Treatment Location

	Mother-Ship (n=334)		Drip and Ship (n=64)		Ship and Drip (n=17)	
	Time Interval, min					
	Median	IQR	Median	IQR	Median	IQR
IV tPA bolus to randomization	24	25	22	32	25	27
Randomization to groin puncture*	60	35	82†	34	57	52
IV tPA bolus to groin puncture*	83	37	105†	47	65	57

IQR indicates interquartile range; IV, intravenous; and tPA, tissue plasminogen activator.

*For Kruskal-Wallis test: $P<0.0001$.

†Compared with mother-ship only: $P<0.0001$.

The odds of a good clinical outcome (modified Rankin Scale score ≤2) for subjects treated under the drip and ship paradigm are less than the odds for subjects treated under the mother-ship paradigm (odds ratio, 0.56; 95% confidence interval, 0.31-0.99; $P=0.045$). However, this association was not significant after adjustment for baseline CTA, age, baseline National Institutes of Health Stroke Scale score, baseline Alberta Stroke Program Early CT score, and reperfusion status. Given the small number of patients in the ship and drip model, a comparative outcome analysis of this group was not performed.

Use of CTA

The use of CTA before randomization was not mandatory. However, a total of 207 patients (49.5%) in the endovascular arm had baseline CTA performed. The median time from baseline CT to CTA was 6 minutes (IQR 7). The use of CTA did not cause delays in intravenous tPA bolus initiation. The median time from CT to intravenous tPA bolus in those who underwent CTA (39 minutes) was significantly shorter than in those who did not undergo CTA (47 minutes; Figure 2). Patients who underwent CTA or magnetic resonance angiography had a slightly higher proportion of proximal occlusions compared with those who underwent CT alone, with internal carotid artery or M1 occlusions found

in 66.9% in the CTA/magnetic resonance angiography group versus 61.0% in the CT alone group (P>0.05).

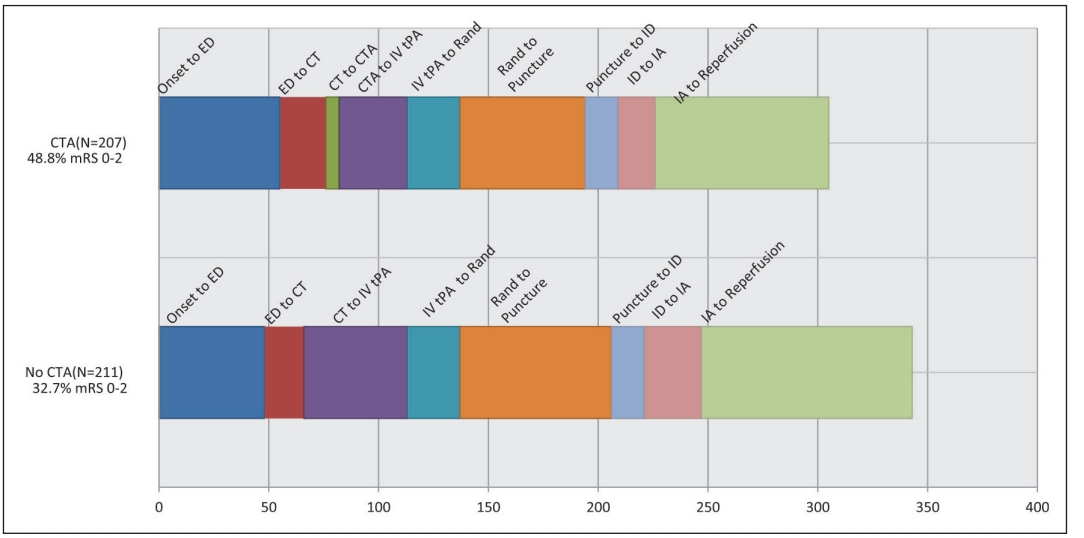

Figure 2.

Time intervals in patients investigated by computed tomography (CT) and computed tomographic angiography (CTA) vs CT alone. ED indicates emergency department; IA, start of endovascular therapy; ID, thrombus identification; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; Puncture, groin puncture; and Rand, randomization.

Transfer patients were less likely to have a baseline CTA and experienced a longer time from randomization to puncture. To minimize the impact of this potential confounding, the effect of baseline CTA use on favorable outcome was analyzed only under the mother-ship paradigm (Figure 3). The odds of favorable outcome among subjects with a baseline CTA were 2.1 times the odds for subjects with CT alone (95% confidence interval, 1.1-3.8) after adjustment for age, baseline National Institutes of Health Stroke Scale score stratum, baseline Alberta Stroke Program Early CT score, site of occlusion, and successful reperfusion (defined as thrombolysis in cerebral infarction score 2b to 3).

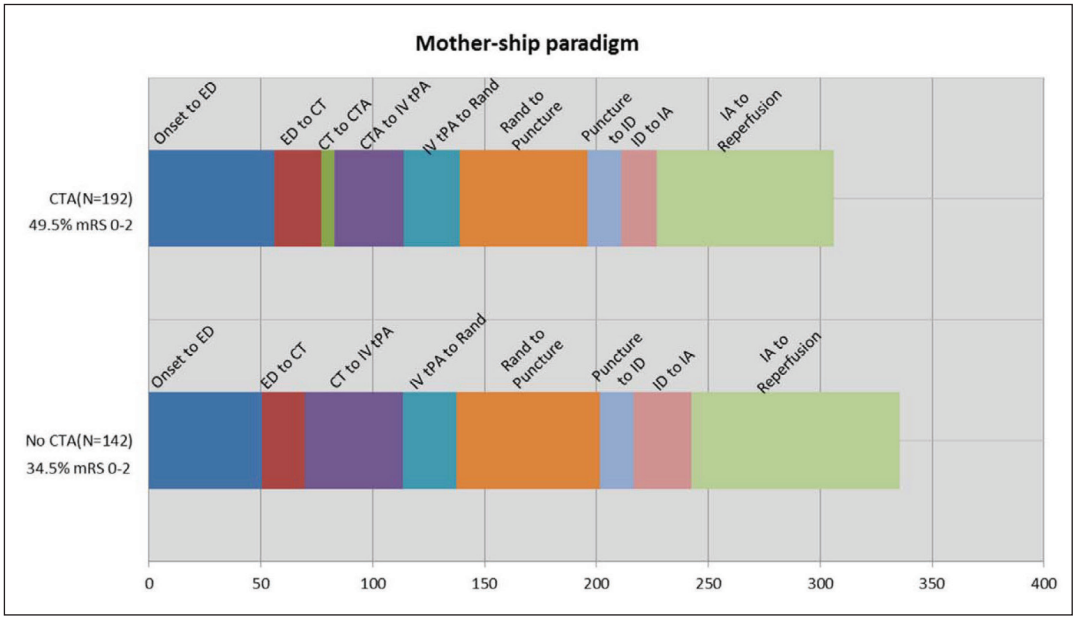

Figure 3.

Time intervals in patients investigated by computed tomography (CT) and computed tomographic angiography (CTA) vs CT alone in the mother-ship paradigm only. ED indicates emergency department; IA, start of endovascular therapy; ID, thrombus identification; IV tPA, intravenous tissue plasminogen activator; mRS, modified Rankin Scale; Puncture, groin puncture; and Rand, randomization.

Intubation

The overall work flow time did not vary significantly according to intubation utilization (Table I in the online-only Data Supplement). The median time from randomization to groin puncture was 60 minutes for those who did not require intubation (n=251 patients) compared with 66 minutes for those who were intubated according to the routine practice of that institution for endovascular therapy (n=73 patients) and 68 minutes for those who required intubation for medical reasons (n=67 patients).

Delays Attributable to Procedural Timing

Randomization occurred during working hours (Monday through Friday, 8 am to 5 pm)

in 207 patients versus 211 patients randomized outside these hours (Figure 4). The ED to imaging time during working hours was 20 minutes (IQR 15 minutes) compared with 19 minutes in those treated outside these hours (IQR 15 minutes; *P*=0.20). The time from CT to groin puncture during working hours (119 minutes; IQR 49 minutes) was shorter than the 141 minutes for those presenting after these hours (IQR 54 minutes; P<0.0001). In those who were randomized during daytime (8 am to 9 pm), the time from CT to groin puncture was 127 minutes (n=341; IQR 51 minutes) compared with 142 minutes during nighttime (n=63; IQR 60 minutes; *P*=0.0012).

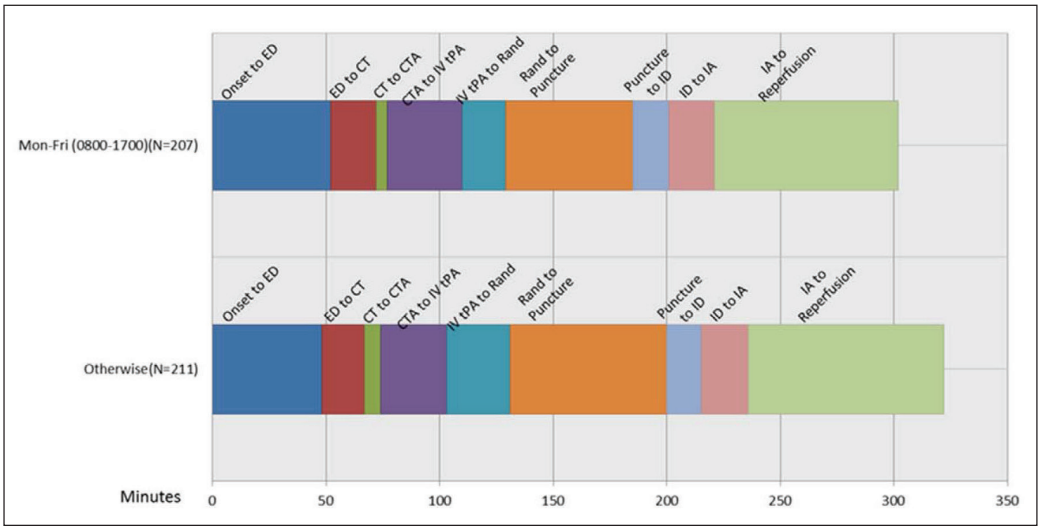

Figure 4.

Time intervals in patients who underwent endovascular procedures during working hours (Monday through Friday, 8 am to 5 pm) compared with patients treated outside these hours. CT indicates computed tomography; CTA, computed tomographic angiography; ED, emergency department; IA, start of endovascular therapy; ID, thrombus identification; IV tPA, intravenous tPA; Puncture, groin puncture; and Rand, randomization.

Work Flow Changes During the Enrollment Period

There was significant improvement in the time from ED arrival to reperfusion as well as the time from groin puncture to reperfusion during the course of the trial (Figure 5). During the first quartile of enrollment, the median time from ED arrival to reperfusion

was 316 minutes compared with 246 minutes in the last quartile (P<0.0001). Similarly, the time from groin puncture to reperfusion decreased from 145 minutes during the first quartile of enrollment to 120 minutes in the last quartile (*P*=0.0005).

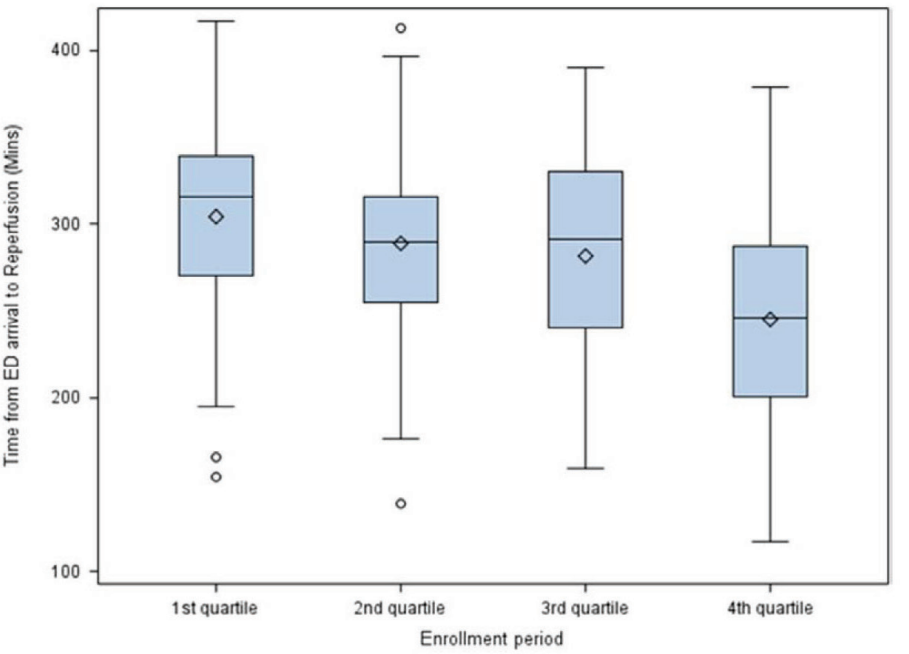

Figure 5.

Change in time from emergency department (ED) arrival until reperfusion by enrollment quartile.

Predictors of Delays in ED Arrival to Reperfusion and Onset to Reperfusion Times

A multivariable linear regression model was fitted to identify predictors of time from ED arrival to reperfusion in 261 patients without missing data who were treated in the same facility (mother-ship). Significant predictors were the use of CTA, procedural timing, and timing of enrollment during the course of the trial. Patients who underwent CTA had ≈20 minutes shorter ED to reperfusion times compared with those who did not have CTA (*P*=0.008). Similarly, patients who were randomized during working hours had 15 minutes shorter ED to reperfusion time compared with those who were randomized

outside these hours (P=0.03). Finally, patients who were enrolled during the last quartile of the study had 46 minutes shorter ED to reperfusion time compared with patients who were enrolled during the first quartile of the study (P<0.0001). The ED to reperfusion times for patients enrolled in the second and third quartiles were not significantly different from those enrolled during the first quartile.

We also investigated factors that affected the onset to reperfusion times. Subjects with baseline CTA had 17 minutes shorter onset to reperfusion times compared with patients who did not have baseline CTA (P=0.016). Compared with patients who were enrolled during the first quartile of the study, patients who were enrolled during the last quartile had 42 minutes shorter onset to reperfusion time (P<0.0001). However, there was not a significant difference in the onset to reperfusion time between patients enrolled during the second or third quartiles and those enrolled in the first. Finally, patients treated in the drip and ship paradigm had 21 minutes longer onset to reperfusion time compared with those treated in the same center (P=0.039). There was insufficient evidence to demonstrate a longer onset to reperfusion time (mean 22 minutes) in those treated in the ship and drip paradigm compared with those treated in the same center (P=0.16); however, there are only 17 patients in this ship and drip category, resulting in limited power for this test. In these 2 models, age, sex, baseline National Institutes of Health Stroke Scale score, and intubation status were not shown to have significant impact on time delays.

DISCUSSION

In acute ischemic stroke therapy with intravenous tPA, ED to needle time within 60 minutes has become an important benchmark in evaluating the efficiency of the work flow for delivering intravenous tPA and measuring the quality of stroke centers. Despite the evidence behind intravenous tPA and the resources allocated to meeting this target, only a quarter of intravenous tPA-treated patients met this time metric in "Get With the Guidelines."[14] Multiple target times have been proposed for endovascular therapy, including, for example, picture-to-puncture[15] and puncture-to-reperfusion times. Certain time metrics capture delays at specific stages of the treatment continuum (eg, delays in patients' transport are captured by the picture-to-puncture time). However, there is no consensus

on a single time metric that would capture the elements unique to those treated with the combined approach of intravenous tPA plus endovascular therapy. Such time metric is increasingly needed to better understand these delays and to provide a target that all centers should aspire to achieve.[16]

The importance of a fast onset to treatment time in acute ischemic stroke cannot be overemphasized. Considerable delays were encountered in starting endovascular therapy in the IMS III trial. Although 63.4% of the patients presented to the ED within 60 minutes, delays occurred from the start of intravenous tPA infusion to randomization, followed by further delays during the endovascular procedures until reperfusion was achieved. With the known strong correlation between time and stroke outcome, such delays are expected to produce lower than anticipated outcomes with endovascular therapy.[17] Although the time from ED arrival to endovascular reperfusion improved during the course of the trial, significant variability in the times within each enrollment quartile may have prevented these shorter times from reflecting on the overall trial results.

Some of the delays encountered during the endovascular procedures may be device related. The current first-choice endovascular device stentrievers were used in only few patients in the endovascular arm, which may have affected both the success and speed of reperfusion. With the increasing use of stentrievers and the progressively short puncture-to-reperfusion times reported, endovascular procedures are already shorter and yield higher rates of successful reperfusion.[7,18,19]

Our data did not show a longer time to intravenous tPA administration when baseline CTA imaging was performed. When added to the other valuable information gained from CTA regarding the exact occlusion site and the vascular bed anatomy, CTA becomes an instrumental tool that will result in a net saving of time from onset to reperfusion.[20] In addition to outlining the anatomic and pathological aspects of the aortic arch and carotid system to aid in planning the endovascular procedure, CTA also serves to localize the exact site of occlusion. It is not uncommon for a thalamic stroke attributable to posterior cerebral artery occlusion to mimic a middle cerebral artery occlusion or for a clinical right anterior cerebral artery occlusion to require endovascular access from the left carotid system when both anterior cerebral arteries originate from the left side (azygous variant). Moreover, CTA helps in planning the use of appropriate catheters and

other tools and obviates the need for a complete angiogram and hence may serve to save procedural time. However, the association of CTA use with shorter time to reperfusion has other potential explanations. Routine CTA use is expected in large-volume centers where protocols for intravenous tPA use are practiced routinely with subsequent efficient and timely execution. In addition, the interpretation of CTA is anticipated to be faster in centers in which this imaging modality is used routinely. We did not measure the time required for CTA interpretation because of numerous practical and perceived difficulties. However, CTA has the advantage of being readily available on acquisition with no need for postprocessing. Moreover, interpretation of CTA images could take place in parallel with other treatment steps without delaying the overall work flow. Our data did not show a significantly longer time to groin puncture in patients who were intubated for the endovascular procedure. However, the time required for intubation may become a factor in patients treated with stentrievers, in which case short imaging to reperfusion times are achievable.[4] In addition, we did not investigate the effects of general anesthesia on stroke outcome in these patients.[21]

Significant delays were noted from intravenous tPA administration to groin puncture in the IMS III study. There are many potential reasons for delays in this time interval. One component might be delays encountered during patient transport after intravenous tPA is initiated. Patients who received intravenous tPA in the drip and ship paradigm had longer times from tPA to groin puncture compared with those transported without receiving intravenous tPA. Although intravenous tPA therapy should be initiated as soon as possible in all eligible patients, this finding highlights the need for protocols to guide the care of patients planned for transport for endovascular stroke therapy to minimize any delays introduced by tPA administration before transportation. Prehospital assessment and triage of the most severe stroke patients directly to comprehensive stroke centers that are experienced in endovascular therapy is another potential mechanism to decrease delays. To measure delays encountered during patient transfer, the American Heart Association defined a time metric (door-in/door-out) for patients with acute coronary syndrome to capture the time interval from admission to the outside hospital to ambulance departure toward the treatment center.[22] When this metric was achieved in ≤30 minutes, faster treatment times and lower mortality were described. To account for delays encountered in the endovascular drip and ship approach, investigators devised the picture-to-puncture time metric to capture delays occurring from the time of baseline CT scan until groin puncture

is done.[15] Patients with a picture-to-puncture time >90 minutes had a significantly lower likelihood of independent functional recovery at 90 days. This stresses the importance of coordinated, protocol-driven steps for the expedited transport and treatment of such patients, particularly when imaging needs to be repeated before the endovascular procedure.

Delays from intravenous tPA administration to randomization were encountered in patients treated with endovascular therapy in the same center. Some of these delays can be attributed to the time spent screening the patient for the trial, obtainment of informed consent, and the randomization process. Such delays are well documented and occur despite best efforts.[23] Deferral of consent, surrogate consent, or shortened consent forms have been proposed to shorten this time interval. Furthermore, the time required for the assembly of the interventional team, for intubation (in centers routinely performing these procedures under general anesthesia), and for preparing the endovascular devices can result in significant delays. Alerting the endovascular team as soon as possible, having an angiography tray ready for use, and using the same catheter/device setup for all endovascular stroke cases are measures that can be considered to decrease these delays. Comprehensive stroke centers with high patient volume might be more accustomed to these practices compared with centers with relatively low patient volume.

Patients treated after hours and on weekends had longer CT to groin puncture times compared with those treated in working or daytime hours. Worse in-hospital outcomes have been reported in stroke patients admitted during weekends compared with regular working hours.[24,25] However, some studies suggest that comprehensive stroke centers seem to avoid this effect.[26] Although our analysis did not account for outcomes, such delays likely affected outcomes. One of the proposed solutions for weekend delays is to cross-train x-ray or CT technologists to assist in angiography suite coverage during these times.[27] This requires that the other members of the interventional team are also readily available. This could be addressed by establishing a group alert paging system that links members of the stroke and interventional teams to provide enough time to travel to the hospital as intravenous tPA is being administered.[28]

This study has limitations. An inherent bias exists that people tend to function better when they are being watched or recorded. This may cause the times recorded in the setting of a trial to look better than real-life times. However, any time saved because of this

bias is likely counteracted by times lost in obtaining trial consent. Our data and analysis of factors affecting work flow are restricted to the variables available in the study. Other variables that may influence time delay are not available for analysis, such as individual centers' case volume and catchment area. We performed exploratory analyses to assess the impact of some of the factors we studied on outcomes. These post hoc analyses do not account for many important baseline differences that could explain any outcome difference. Therefore, the results of the outcome analyses should be viewed in the context of these important limitations, and we hope that they will serve to stimulate further research in this subject.

CONCLUSIONS

In the endovascular arm of the IMS III trial, there were significant delays from start of intravenous tPA to groin puncture. Improvement in work flow times were noted as the trial advanced. The use of CTA correlated with an overall shorter time to reperfusion and was associated with better clinical out-comes than in patients who underwent CT alone. Use of intubation did not result in additional delays. Endovascular treatment outside of working hours resulted in additional delays. These data may help in designing, optimizing, and documenting work flow in current and future endovascular trials.

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CLINICAL PERSPECTIVE

The significance of time in hyperacute ischemic stroke behooves the medical team to guarantee rapid work flow until reperfusion is achieved. The numerous and delicate steps involved require well-planned protocols to ensure the safe and smooth transition of patients from one stage to the next. The recent Interventional Management of Stroke (IMS) III randomized, controlled trial is the largest study to date to examine the efficacy of endovascular therapy against the standard treatment of intravenous tissue plasminogen activator. The IMS III study also offers valuable insights into the importance of work flow in ensuring timely reperfusion. In this article, the work flow of patients enrolled in the endovascular arm of IMS III is divided into different time intervals and analyzed to provide a better understanding of the sources and magnitude of delay. These findings will also inform current and future endovascular trials to accomplish an optimized work flow for their patients and thus faster reperfusion. Furthermore, study-level meta-analyses are considered less informative than patient-level meta-analytical approaches due to their inability to adjust for confounding baseline variables, which leads to less precise estimates of treatment effect. To our knowledge no patient-level meta-analyses have been reported.

Supplementary Appendix

Supplemental Table 1. Various times interval according to the status and indication for intubation.

Time Interval (Minutes)	Not Intubated		Intubated			
			Routine Practice		Medical Intubated	
	Median (%)	IQR	Median (%)	IQR	Median (%)	IQR
Stroke Onset to ED Arrival	50 (64.8)	34	50 (18.2)	35	50 (17.0)	32
ED Arrival to Baseline CT	20 (64.6)	14	19 (18.2)	18	19 (17.2)	15
ED Arrival to Baseline CTA	29 (61.9)	16	29 (21.8)	24	27 (16.3)	18
Baseline CT to CTA	6 (61.7)	7	6 (21.9)	7	7 (16.4)	7
Baseline CTA to IV Bolus	31 (61.9)	22	32 (21.8)	26	28 (16.3)	23
IV Bolus to Randomization	25 (64.8)	24	17 (18.3)	23	25 (17)	24
Randomization to Groin Puncture	60 (64.2)	38	66 (18.7)	34	68 (17.1)	41
IV Bolus to Groin Puncture	85 (64.1)	41	83 (18.7)	34	83 (17.2)	55
Groin Puncture to Thrombus ID	15 (60.8)	15	18 (20.4)	16	15 (18.8)	13
Thrombus ID to IA Therapy	20 (60.1)	26	20 (20.5)	21	22 (19.5)	20
IA Start to Reperfusion	85 (59.7)	74	89 (20.7)	51	85 (19.4)	79
IV Bolus to IA Therapy	126 (59.8)	47	126 (20.9)	54	121 (19.3)	45

CHAPTER 3.2

Analysis Of Workflow And Time To Treatment On Thrombectomy Outcome In The Endovascular Treatment For Small Core And Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized Controlled Trial

Based upon:

Analysis of Workflow and Time to Treatment on Thrombectomy Outcome in the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) Randomized, Controlled Trial

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ABSTRACT

Background

The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial used innovative imaging and aggressive target time metrics to demonstrate the benefit of endovascular treatment in patients with acute ischemic stroke. We analyze the impact of time on clinical outcome and the effect of patient, hospital, and health system characteristics on workflow within the trial.

Methods and Results

Relationship between outcome (modified Rankin Scale) and interval times was modeled by using logistic regression. Association between time intervals (stroke onset to arrival in endovascular-capable hospital, to qualifying computed tomography, to groin puncture, and to reperfusion) and patient, hospital, and health system characteristics were modeled by using negative binomial regression. Every 30-minute increase in computed tomography-to-reperfusion time reduced the probability of achieving a functionally independent outcome (90-day modified Rankin Scale 0-2) by 8.3% (P=0.006). Symptom onset-to-imaging time was not associated with outcome (P>0.05). Onset-to-endovascular hospital arrival time was 42% (34 minutes) longer among patients receiving intravenous alteplase at the referring hospital (drip and ship) versus direct transfer (mothership). Computed tomography-to-groin puncture time was 15% (8 minutes) shorter among patients presenting during work hours versus off hours, 41% (24 minutes) shorter in drip-ship patients versus mothership, and 43% (22 minutes) longer when general anesthesia was administered. The use of a balloon guide catheter during endovascular procedures shortened puncture-to-reperfusion time by 21% (8 minutes).

Conclusions

Imaging-to-reperfusion time is a significant predictor of outcome in the ESCAPE trial. Inefficiencies in triaging, off-hour presentation, intravenous alteplase administration, use of general anesthesia, and endovascular techniques offer major opportunities for improvement in workflow.

Clinical Trial Registration-URL: http://www.clinicaltrials.gov. Unique identifier: NCT01778335. (*Circulation*. 2016;133:2279-2286. DOI: 10.1161/CIRCULATIONAHA.115.019983.)

The Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial provided evidence of the benefit of endovascular treatment in patients with moderate to severe ischemic stroke.1 The trial was based on the premise that patients with large-vessel occlusion of the anterior circulation with small to moderate infarct core and moderate to good collaterals identified on computed tomography (CT)-based imaging would benefit most from endovascular treatment if reperfusion was achieved quickly after imaging.[1,2] In the ESCAPE trial, brain and neurovascular imaging identified favorable physiology; the clock started ticking from first imaging, the point of clinical decision making.

In these prespecified secondary analyses, we analyze the effect of time from stroke symptom onset to imaging, time from imaging to reperfusion, and time from stroke symptom onset to reperfusion on clinical outcome among patients who received endovascular treatment in the ESCAPE trial. To reduce the inefficiencies in workflow that prolong the delivery of treatment and subsequent reperfusion, the ESCAPE trial used an active quality improvement process that provided site guidance on rapid image acquisition and interpretation, quick transfer to the angiography suite, and fast endovascular techniques. This quality improvement process contributed to the trial achieving highly efficient workflow metrics. Nonetheless, by recognizing that inefficiencies still exist, strategies for further improvement can be formulated. We analyzed patient, hospital, and health system characteristics associated with inefficiencies in workflow, ie, increase in interval times from stroke symptom onset to arrival in the emergency department, to imaging, to treatment administration, and to reperfusion.

METHODS

The ESCAPE trial (clinicaltrials.gov NCT01778335) was an investigator-initiated multicenter randomized, controlled trial assessing the additional benefit of modern endovascular treatment in comparison with guideline-based standard of care. The trial screened patients fulfilling clinical eligibility criteria if they presented within 12 hours of stroke symptom onset and then included them only if they met neurovascular imaging criteria. The trial enrolled 316 patients from 22 sites across 3 continents between February 2013 and October 2014.[1,3] The drive to optimal workflow began with site selection. Sites were selected only after documentation of efficient workflow demonstrated by 5 cases showing a CT-to-groin puncture time of <60 minutes and CT-to-reperfusion time of <90 minutes. All sites were visited in person. In half of the sites where it was permitted by local research ethics boards or institutional review boards, a deferral of consent process was used. A CT-based imaging paradigm that included noncontrast CT and multiphase CT angiography was designed to allow for quick acquisition and interpretation.[4] The quality improvement process focused on achieving a qualifying CT-to-groin puncture time of ≤60 minutes and a qualifying CT-to-reperfusion time of ≤90 minutes through frequent in-person and Web-based teaching aids.[3] Workflow and imaging data were analyzed weekly and frequent feedback provided to all sites through Web-based teleconferences.[5]

The trial collected data on multiple events in the workflow from stroke symptom onset to reperfusion including time of stroke symptom onset, arrival in the emergency department of the endovascular-capable hospital, baseline imaging, randomization, intravenous tissue plasminogen activator (alteplase) administration, randomization, groin puncture, and reperfusion. Among patients who were referred to the endovascular-capable hospital from another hospital, data were collected on whether intravenous alteplase was administered before

Statistical Analyses

We considered 4 specific interval times: onset to emergency department arrival, emergency department arrival to qualifying CT scan, qualifying CT scan to groin puncture, and groin puncture to reperfusion. When reperfusion was not achieved, the reperfusion time

Table. Interval Times in the Workflow of the ESCAPE Trial

Workflow Time Intervals	N*	Median, min	Interquartile Range
Stroke symptom onset to arrival in emergency department of endovascular-capable hospital	308	107.5	49.5–224
Stroke symptom onset to qualifying CT	311	135	76–244
Stroke symptom onset to randomization	314	174	119–285
Stroke symptom onset to first reperfusion†	145	241	176–359
Arrival in emergency department of endovascular-capable hospital to qualifying CT	311	19	11–29
Qualifying CT to groin puncture†	161	51	39–68
Groin puncture to first reperfusion†	144	30	18–45.5

CT indicates computed tomography.
*Data available after central adjudication of all interval times.
†Endovascular group only

was considered missing and was not imputed. Interval times from stroke symptom onset to first reperfusion are reported using medians and interquartile range (Table). All time intervals have skewed data distributions (nonnormal; Figure 1 in the online-only Data Supplement). A graphical examination of the residuals from linear regression revealed that the assumption of normality of residuals was not tenable for the time interval data, despite attempting a variety of transformations. We therefore investigated the use of generalized linear regression models for modeling the time interval data as discrete count data. Specifically, we examined whether Poisson regression, negative binomial regression, or gamma regression could provide the best fit to the data. Information theory approaches such as likelihood ratio test and Akaike information criterion were used to determine the regression model with the best fit to the data. To assess the relationship between patient, hospital, and health system characteristics as predictors of longer interval times, a negative binomial regression provided the best fit to the data. Therefore incidence rate ratios are reported for predictor variables associated with prolongation in each interval time after adjusting for other prespecified variables (Figure 2).

Logistic regression models were used to estimate the probability of functionally independent outcome (modified Rankin Scale 0-2 at 90 days) based on time from stroke

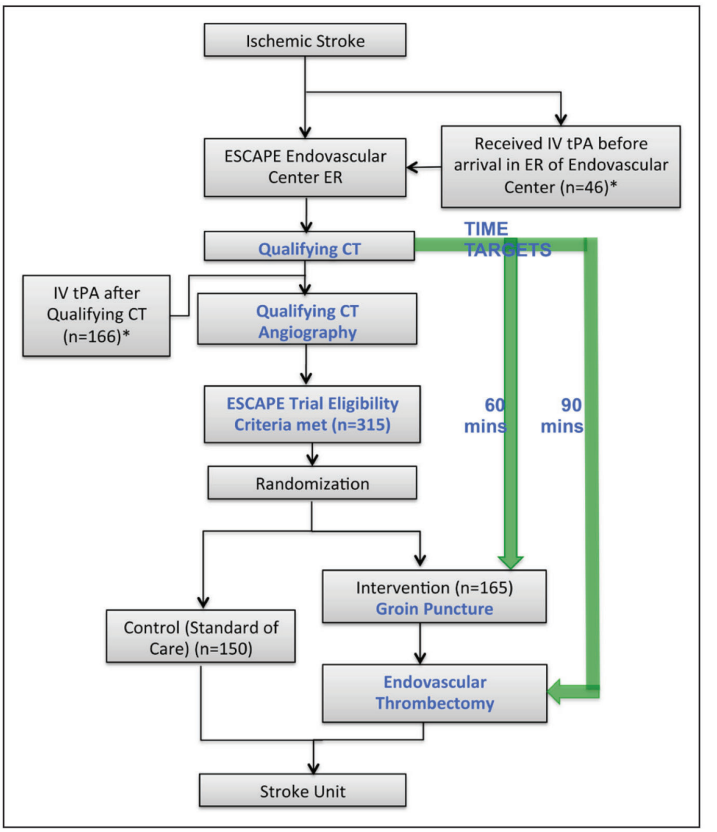

Figure 1.

Flow chart showing workflow in the ESCAPE trial from stroke symptom onset to reperfusion and stroke unit care. CT indicates computed tomography; ER, emergency room; IV, intravenous; and tPA, tissue plasminogen activator.

symptom onset to qualifying CT, stroke symptom onset to first reperfusion, and qualifying CT to reperfusion after adjusting for age, sex, baseline National Institutes of Health Stroke Scale, occlusion site, baseline Alberta Stroke Program Early CT Score (ASPECTS), intravenous alteplase administration (and time from stroke symptom onset to qualifying CT when the predictor time variable was time from qualifying CT to reperfusion). Finally, because the primary outcome of the ESCAPE trial was the common odds ratio (shift analysis), similar analyses were performed for all other cut points on the ordinal modified

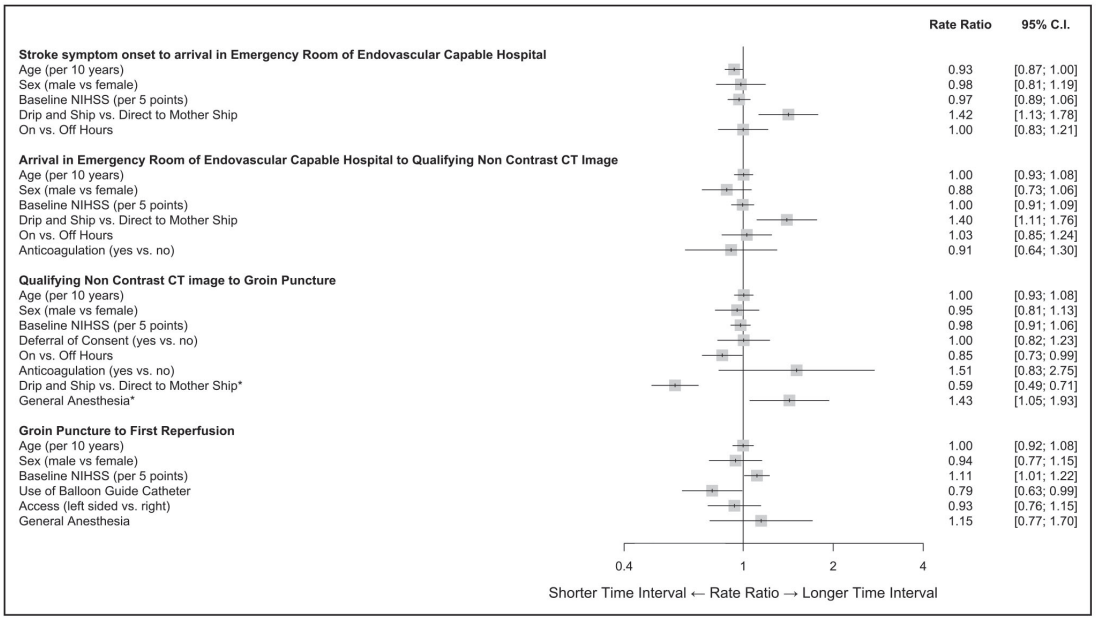

Figure 2.

Forest plots reporting effect sizes (rate ratios) with 95% confidence intervals of prespecified patient, hospital, and health system characteristics associated with delay in prespecified interval times. An incidence rate ratio >1 indicates prolonged interval times and can be interpreted as a relative increase or decrease in time (minutes) in comparison with the base case. For example, general anesthesia was associated with a 1.43 times longer CT-to-groin puncture time interval in comparison with no general anesthesia. CI indicates confidence interval; CT, computed tomography; and NIHSS, National Institutes of Health Stroke Scale.

Rankin Scale at 90 days. Statistical analysis was performed in R version 3.2.1 (R Development Core Team, 2014) and Stata/MP version 14.0 (StataCorp LP). Statistical significance was assessed at $\alpha<0.05$ in all analyses.

RESULTS

Interval times for trial workflow are described in the Table. Predictors of prolonged time intervals are shown in Figure 2. Time from stroke symptom onset to arrival in the emergency department of the endovascular-capable hospital was, on average, 42% (34 minutes) longer among patients who received intravenous alteplase at the referring hospital and were subsequently transferred to the endovascular-capable hospital (drip and ship) in comparison with patients who were directly transferred to the endovascular-capable hospital (direct to mothership). Similarly, time from emergency department arrival to qualifying CT was, on average, 40% (8 minutes) longer intravenous alteplase and endovascular treatment (n=109), time from qualifying CT to groin puncture was, on average, 41% (24 minutes) shorter when intravenous alteplase was administered before emergency department arrival (drip and ship) than when intravenous alteplase was administered after qualifying CT (direct to mothership). Administration of general anesthesia was associated with prolongation of CT-to-groin puncture time by 43% (22 minutes), on average, in comparison with patients who did not receive general anesthesia. The use of a balloon guide catheter as part of the endovascular technique was associated with shortened time from groin puncture to first reperfusion by 21% (8 minutes), on average, whereas a 5-point increase in the baseline National Institutes of Health Stroke Scale (stroke severity) prolonged this time by 11% (2 minutes). Deferral of consent, anticoagulation use before stroke onset, and side of stroke were not associated with differential workflow metrics in the trial.

The relationship between the probability of achieving functionally independent outcome (modified Rankin Scale [mRS] 0-2 at 90 days) and time from stroke symptom onset to qualifying CT, qualifying CT to reperfusion, and stroke symptom onset to reperfusion is shown in Figure 3. Every 30-minute increase in time from qualifying CT to reperfusion is associated with an absolute decrease in the probability of functionally independent outcome (mRS 0-2 at 90 days) by 8.3%, after adjusting for age, sex, baseline National Institutes of Health Stroke Scale, occlusion site, baseline ASPECTS, intravenous alteplase administration, and time from onset to qualifying CT (P=0.006). No statistically significant relationship was noted between stroke symptom onset to qualifying CT time and functionally independent outcome (mRS 0-2 at 90 days) in either arm of the tri-

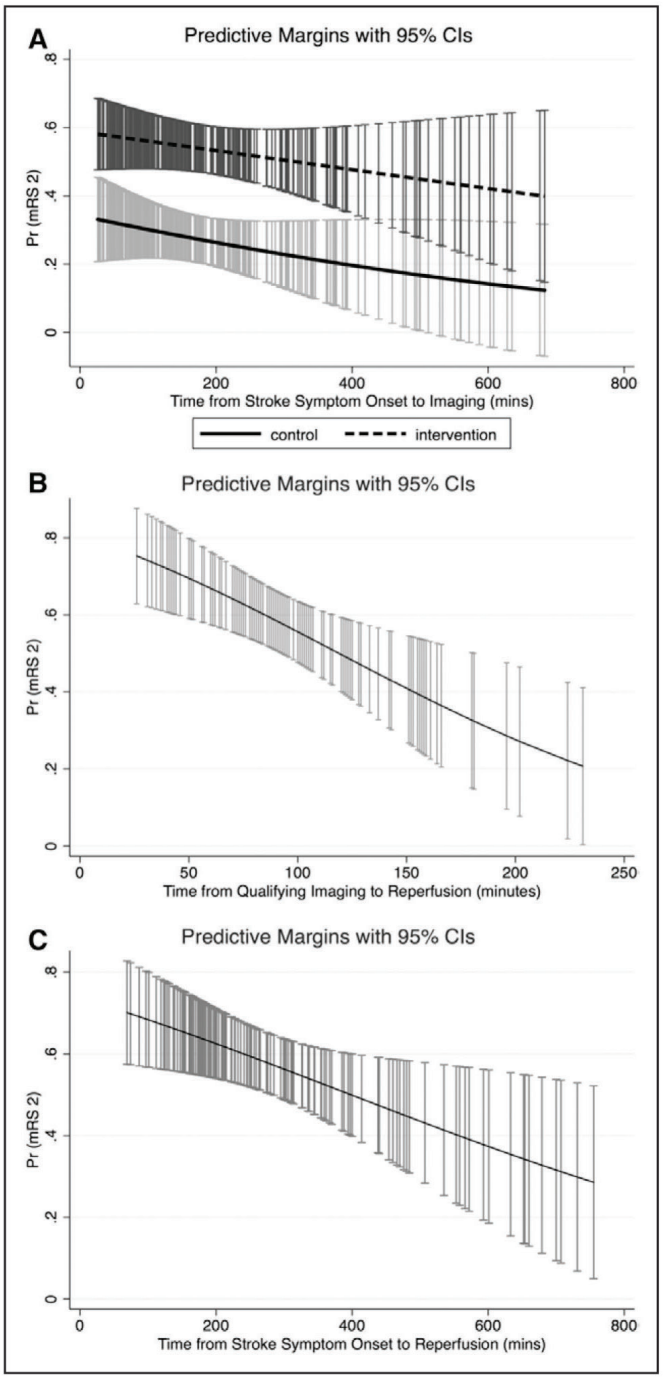

Figure 3.

Estimated probability of achieving functionally independent outcome (modified Rankin Scale [mRS] 0-2) at 90 days by time from stroke symptom onset to qualifying CT (for both intervention and control arm; (A), qualifying CT to first reperfusion (B), and stroke symptom onset to first reperfusion (C) in patients in the ESCAPE trial. A significant relationship between probability of functionally independent outcome and time is noted with imaging to reperfusion time. Every 30-minute increase in time from qualifying CT to reperfusion is associated with an absolute decrease in the probability of functionally independent outcome by 8.3%. A modest relationship is seen between stroke symptom onset to reperfusion time and functionally independent outcome. Every 30-minute increase in time from stroke symptom onset to reperfusion is associated with an absolute decrease in the probability of functionally independent outcome by 1.9%. No relationship is noted between stroke symptom onset to imaging time and outcome in either intervention or control arms of the study. CI indicates confidence interval; and CT, computed tomography.

al (P≥0.05). Test for interaction between stroke symptom onset to qualifying CT time and treatment allocation was nonsignificant (P=0.69; Figure 3). A modest relationship was noted between time from stroke symptom onset to reperfusion and the probability of achieving functionally independent outcome (mRS 0-2 at 90 days; P=0.04). Every 30-minute increase in time from stroke symptom onset to reperfusion is associated with an absolute reduction in the probability of functionally independent outcome (mRS 0-2 at 90 days) by 1.9% (Figure 3).

The relationship between the probability of achieving each mRS cut point and time from stroke symptom onset to qualifying CT, qualifying CT to reperfusion, and stroke symptom onset to reperfusion is shown in Table I in the online-only Data Supplement. The relationship between the probability of achieving functionally independent outcome (mRS 0-2 at 90 days) and time from stroke symptom onset to randomization in either arm of the trial (P≥0.05) is shown in Figure II in the online-only Data Supplement.

DISCUSSION

In the ESCAPE trial, achieving a short imaging-to-reperfusion time significantly improved the chance of achieving a functionally independent outcome. There was no relationship between outcome and stroke symptom onset-to-imaging time, whereas the relationship between outcome and stroke symptom onset to reperfusion was modest. These results support the underlying premise of the trial design, that eligibility for reperfusion therapy in patients with ischemic stroke and proximal anterior circulation occlusion is determined by simple imaging as an instantaneous measure of the brain physiology. Acting rapidly and successfully on that information then predicts the outcome.[1,3]

Our results provide strong supportive evidence for the use of the imaging-to-puncture and imaging-to-reperfusion metrics as performance metrics and benchmarks for administering endovascular therapy.[6,8] The finding that there is no relationship between clinical outcome and time from stroke symptom onset to qualifying CT should not be overinter-

preted. All time delays before imaging matter.[6,10,11] Stroke symptom onset time, however, is often inaccurate. Reasons include the fact that a majority of stroke patients are older and live alone, thereby having unwitnessed symptom onset; many strokes happen when patients are sleeping; many patients have fluctuating symptoms; and, in some cases, the witness is unable to recall the precise time of onset. Stroke symptom onset to imaging or reperfusion time is probably a less accurate measure of stroke physiology than imaging. Moreover, the ESCAPE trial design limited enrollment to patients with small to moderate ischemic core on imaging regardless of the time from stroke symptom onset. Although not captured in the trial, we suspect that the proportion of eligible patients with beneficial physiology on imaging dropped with increasing time from stroke symptom onset to qualifying CT.[12]

Several factors contribute to the speed of treatment. The ESCAPE trial used an intensive quality improvement process focused on quick, reliable imaging and efficient workflow from imaging to reperfusion with targets of qualifying CT-to-groin puncture time of <60 minutes and a CT-to-reperfusion time of <90 minutes. These workflow metrics are the fastest reported in patients with acute disabling ischemic stroke and significantly better than those required by the recent Multi-society Consensus Quality Improvement Guidelines for Intra-arterial therapy.[6,8,13-19] The trial enrollment rate of 1.44 subjects per site per month, among the highest in recent acute stroke trials, at 22 sites on 3 continents attests to the generalizability of the workflow metrics achieved in the trial.[1] Nonetheless, our analysis identified inefficiencies. Among these, transport of patient from first contact to endovascular-capable hospital (drip and ship versus direct to mothership paradigms), patient arriving at endovascular-capable hospital during off hours, intravenous alteplase administration in endovascular-capable hospitals, general anesthesia before endovascular procedure, and not using balloon guide catheters during the endovascular procedure represent opportunities for improvement.[6,9,13]

As in previous studies, we show that workflow was less efficient during off hours.[6,9,13] Although the low number of patients with stroke currently eligible for endovascular treatment might make it challenging to have 24/7 in-house interventional teams, centralized hub-and-spoke models of stroke care, by increasing patient volumes in hub hospitals, could potentially make these changes pragmatically viable. Akin to multiple previous studies, we show that the use of general anesthesia is associated with longer times and pro-

longed work-flow.[6,13,20,21] General anesthesia is often unnecessary for thrombectomy and was used in only 9% of patients in the ESCAPE trial. The endovascular procedure itself is challenging, more so in patients with difficult access to the target thrombus. As shown in previous technical reports, our data suggest that the use of balloon guide catheters may potentially lead to quick and efficient recanalization.[22] Finally, although deferral of consent was used in some patients, this process itself was not measurably associated with improvement in workflow.

Administration of intravenous alteplase is standard of care in patients with acute ischemic stroke presenting within 4.5 hours of symptom onset.[23,24] The ESCAPE trial stressed the need for a parallel workflow in endovascular-capable hospitals aimed at delivering intravenous alteplase to eligible patients without in any way delaying the patient's transport to the angiography suite. Strategies included randomization before international normalized ratio results, because alteplase decision making was independent of ESCAPE randomization, administering alteplase bolus and infusion while the technologist was preparing the patient for CT angiography, and transferring the patient to the angiography suite without waiting for a clinical response to intravenous alteplase. Despite these measures, our analysis reveals that alteplase administration was associated with longer times from qualifying CT to groin puncture, suggesting that workflow may not have been in parallel in many patients.[6] Novel thrombolytic agents such as intravenous tenecteplase, with its potentially faster treatment administration protocol as an intravenous bolus rather than infusion over 60 minutes, may help improve workflow.[25,26] For endovascular-eligible patients identified on imaging, who are also eligible to receive intravenous alteplase, a focus on improving the first imaging-to-groin puncture (picture to puncture) metric should mirror ongoing efforts at improving the door-to-needle metric.[6,8,27]

The longer time from stroke symptom onset to emergency department arrival (at endovascular-capable tertiary hospitals) in the drip-and-ship treatment paradigm (intravenous alteplase before endovascular hospital emergency department arrival) in comparison with the direct to mothership approach is well known.[13,28] Improving interval times is a complex system issue that must take into account geographical distributions and staffing patterns of primary and tertiary hospitals, transport times to these hospitals from first patient contact and with the drip-and-ship paradigm, mandating short (ideally ≤30 minutes) door-in to door-out times.[9,18,29,30] Depending on the extent of centralization of stroke

services, each health system may identify different solutions to minimize the time from first contact to reperfusion.

In conclusion, data from the ESCAPE trial support a refinement of the now well-known onset-to-treatment paradigm for acute stroke treatment. We show that the onset-to-reperfusion time epoch can now be broken up into 2 epochs, ie, time from onset to imaging and from imaging to reperfusion. These time epochs now provide a model for understanding the role of time and imaging selection. The first time epoch may determine who is eligible for therapy. The second time epoch, ie, imaging to reperfusion (treatment), determines who does well from therapy. Speed of treatment can be achieved in dedicated stroke centers with teamwork, parallel workflow, and a focus on quality improvement. Inefficiencies in triaging systems, presentation during off hours, intravenous alteplase administration, use of general anesthesia, and endovascular techniques offer major opportunities for improvement. Endovascular-capable hospitals should identify eligible patients by using quick and reliable imaging techniques and focus on achieving reperfusion as quickly and efficiently as possible.

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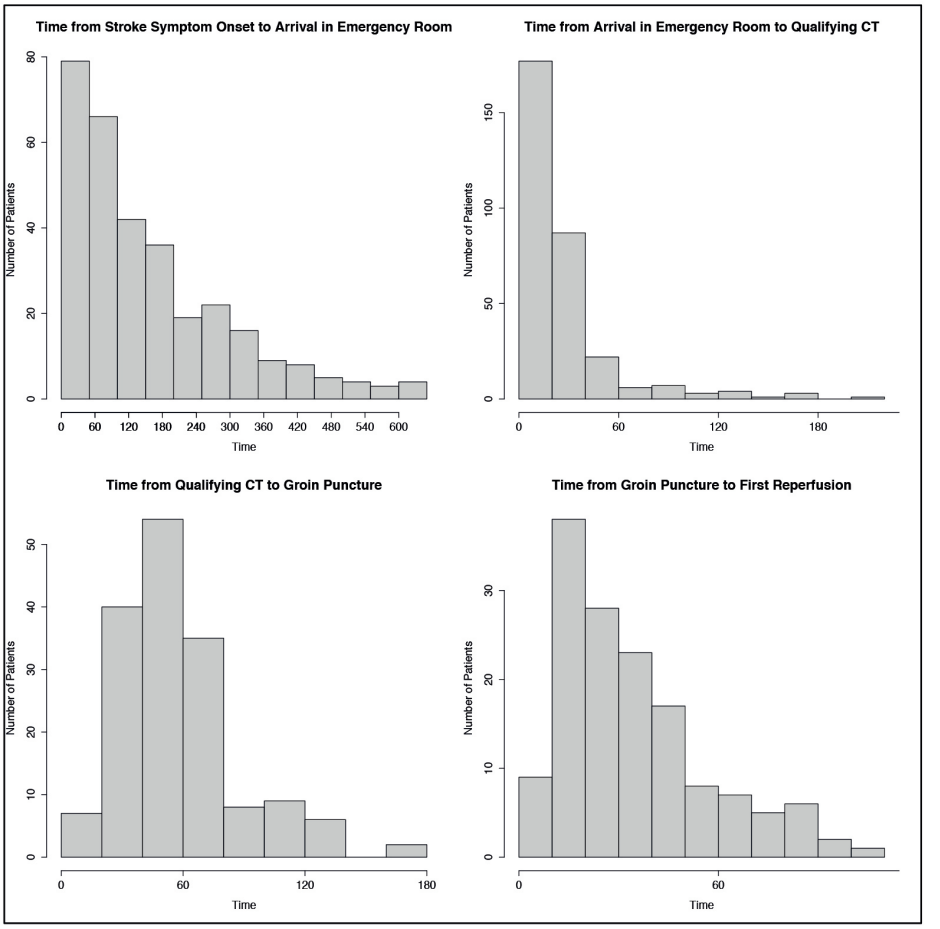
CLINICAL PERSPECTIVE

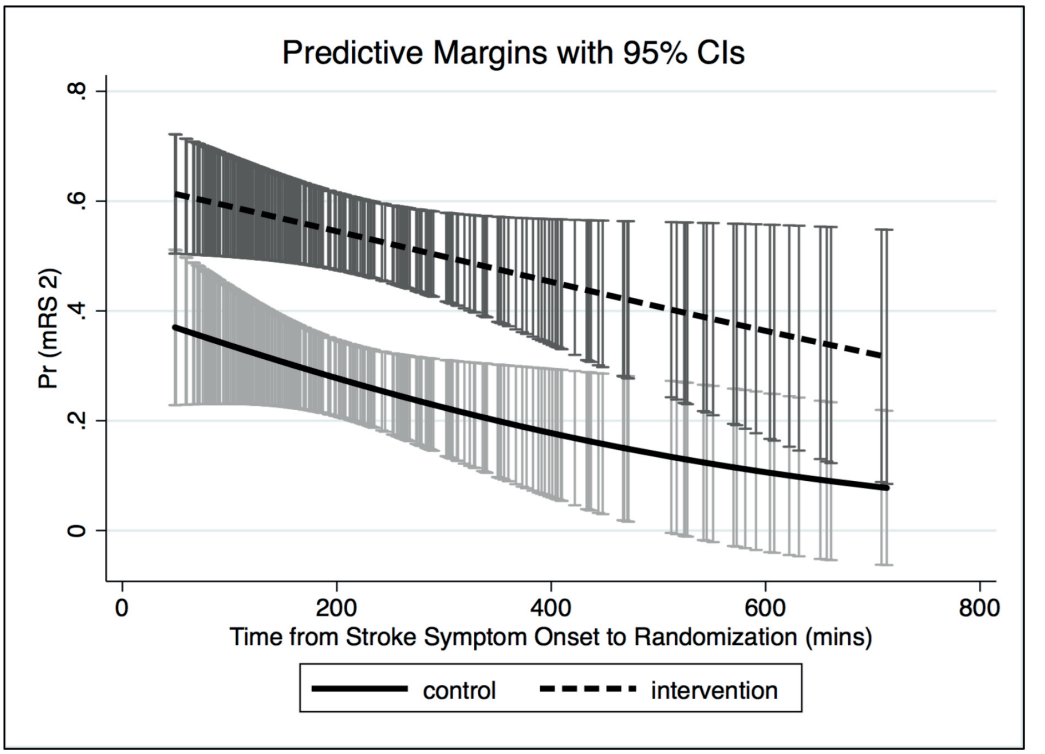
Data from the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial support a refinement of the now well-known onset-to-treatment paradigm for acute stroke treatment. We show that the onset-to-treatment time epoch can now be broken up into 2 epochs, ie, time from onset to imaging and from imaging to reperfusion. These time epochs now provide a highly physiological model for understanding the role of time and imaging selection. The first time epoch, ie, stroke onset to imaging, determines who is eligible for therapy. The second time epoch, ie, imaging to reperfusion (treatment), determines who does well from therapy. The ESCAPE trial reports on data from a new era associated with the use of mechanical stent retrievers and an explicit focus on improving workflow. Although workflow metrics within the trial are the fastest reported to date, we are still able to identify inefficiencies including delay around intravenous alteplase administration, off-hour presentation, general anesthetic use, and specific endovascular techniques that suggest opportunities toward further improvement in workflow and consequently better outcome. The ESCAPE trial data presented here are the first prospective and comprehensive analyses of inefficiencies that continue to exist in the modern acute ischemic stroke treatment workflow. Health systems can focus on transporting patients with disabling symptoms and proximal occlusions as quickly as possible to endovascular-capable hospitals. Physicians in these hospitals can then identify patients with beneficial physiology by using imaging and focus on delivering treatment to these patients quickly and efficiently. A focus on improving imaging-to-groin puncture and imaging-to-reperfusion time metrics should mirror ongoing efforts at improving the door-to-needle time metric in tertiary hospitals.

Supplementary Appendix

Supplemental Figure 1: Skewed distribution of the four pre-specified interval times used in the analysis.



Supplemental Figure 2: Estimated probability of achieving functionally independent outcome [modified Rankin Scale (mRS) 0-2] at 90 days by time from stroke symptom onset to randomization in patients in the control and intervention arm of the ESCAPE trial (adjusted for age, sex, baseline NIHSS, occlusion site, baseline ASPECTS, intravenous alteplase administration). No statistically significant relationship is noted between stroke symptom onset to randomization time and outcome in either arm of the trial (p>=0.05). Test for interaction between stroke symptom onset to randomization time and treatment allocation is non-significant (p=0.63).



Supplemental Table 1: Relationship between probability of achieving each mRS cut-point and time from stroke symptom onset to qualifying CT, qualifying CT to reperfusion and stroke symptom onset to reperfusion (after adjusting for age, sex, baseline NIHSS, occlusion site, baseline ASPECTS and intravenous alteplase administration).

Relationship between Time from Stroke Symptom Onset to Imaging (Intervention arm)			
mRS Cut-point	Odds Ratio (for every 30 min increase in time)	95% CI	p value
0 vs. 1-6	1	0.918-1.089	0.999
0-1 vs. 2-6	1.022	0.960-1.089	0.494
0-2 vs. 3-6	0.964	0.907-1.023	0.232
0-3 vs. 4-6	0.971	0.915-1.031	0.336
0-4 vs. 5-6	0.925	0.864-0.991	0.026
0-5 vs. 6	0.976	0.901-1.057	0.557
Relationship between Time from Qualifying Imaging to Reperfusion (Intervention arm)			
mRS Cut-point	Odds Ratio (for every 30 min increase in time)	95% CI	p value
0 vs. 1-6	0.878	0.606-1.271	0.49
0-1 vs. 2-6	0.774	0.582-1.029	0.078
0-2 vs. 3-6	0.662	0.493-0.890	0.006
0-3 vs. 4-6	0.724	0.534-0.981	0.037
0-4 vs. 5-6	0.908	0.587-1.402	0.662
0-5 vs. 6	1.057	0.572-1.954	0.859
Relationship between Time from Stroke Onset to Reperfusion (Intervention arm)			
mRS Cut-point	Odds Ratio (for every 30 min increase in time)	95% CI	p value
0 vs. 1-6	0.965	0.864-1.077	0.526
0-1 vs. 2-6	0.978	0.899-1.064	0.604
0-2 vs. 3-6	0.912	0.834-0.997	0.044
0-3 vs. 4-6	0.940	0.855-1.032	0.198
0-4 vs. 5-6	0.913	0.812-1.027	0.13
0-5 vs. 6	0.959	0.833-1.105	0.567

CHAPTER 3.3

Analysis Of Workflow And Time To Treatment And The Effects On Outcome In Endovascular Treatment Of Acute Ischemic Stroke: Results From The SWIFT PRIME Randomized Controlled Trial

Based upon:
Analysis of Workflow and Time to Treatment and the effects on Outcome in endovascular Treatment of acute ischemic stroke: Results from the SWIFT PRIME Randomized Controlled Trial
Mayank Goyal, Ashutosh P. Jadhav, Alain Bonafe, Hans Diener, Vitor Mendes Pereira, Elad Levy, Blaise Baxter, Tudor Jovin, Reza Jahan, Bijoy K. Menon, Jeffrey L. Saver, For the SWIFT PRIME investigators
Radiology. 2016 Jun;279(3):888-97.

ABSTRACT

Purpose

To study the relationship between functional independence and time to reperfusion in the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial in patients with disabling acute ischemic stroke who underwent endovascular therapy plus intravenous tissue plasminogen activator (tPA) administration versus tPA administration alone and to investigate variables that affect time spent during discrete steps.

Materials and Methods

Data were analyzed from the SWIFT PRIME trial, a global, multicenter, prospective study in which outcomes were compared in patients treated with intravenous tPA alone or in combination with the Solitaire device (Covidien, Irvine, Calif). Between December 2012 and November 2014, 196 patients were enrolled. The relation between time from (a) symptom onset to reperfusion and (b) imaging to reperfusion and clinical outcome was analyzed, along with patient and health system characteristics that affect discrete steps in patient workflow. Multivariable logistic regression was used to assess relationships between time and outcome; negative binomial regression was used to evaluate effects on workflow. The institutional review board at each site approved the trial. Patients provided written informed consent, or, at select sites, there was an exception from having to acquire explicit informed consent in emergency circumstances.

Results

In the stent retriever arm of the study, symptom onset to reperfusion time of 150 minutes led to 91% estimated probability of functional independence, which decreased by 10% over the next hour and by 20% with every subsequent hour of delay. Time from arrival at the emergency department to arterial access was 90 minutes (interquartile range, 69-120 minutes), and time to reperfusion was 129 minutes (interquartile range, 108-169 minutes). Patients who initially arrived at a referring facility had longer symptom onset to groin puncture times compared with patients who presented directly to the endovascular-capable center (275 vs 179.5 minutes, P, .001).

Conclusion

Fast reperfusion leads to improved functional outcome among patients with acute stroke treated with stent retrievers. Detailed attention to workflow with iterative feedback and aggressive time goals may have contributed to efficient workflow environments.

In acute ischemic stroke, "time is brain." Multiple studies have shown a correlation between early recanalization and functional independence (1,2), but initial endovascular trials failed to show benefit with mechanical clot retrieval (3-5). Analysis of the Interventional Management of Stroke III trial demonstrated that the median time from emergency department (ED) arrival to recanalization was more than 230 minutes (6), indicating that there was substantial scope for improvement in workflow. Establishing target time intervals and providing direct feedback in real time have led to improvements in workflow and outcomes in patients undergoing percutaneous coronary intervention after myocardial infarction (7).

On the basis of these considerations, the Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial was designed to include an intensive program of workflow acceleration. Aggressive time targets were set (eg, qualifying image acquisition to groin puncture of, 70 minutes) to promote faster work-flow (8). In addition, a continuous quality improvement program was conducted with all participating sites during the trial. We sought to understand the relationship between functional independence and time to reperfusion in the SWIFT PRIME trial and investigated variables that affect the time spent during discrete steps.

ADVANCES IN KNOWLEDGE

- Revascularization within 2.5 hours of symptom onset was associated with functional independence (minimal or no disability) in 91% of patients.
- Likelihood of functional independence was 10% higher in patients treated within 2.5 hours compared with patients treated between 2.5 and 3.5 hours after stroke onset.
- Every 60-minute delay after 3.5 hours resulted in a 20% lower likelihood of functional independence.
- Upon arrival to the emergency department, sources of delay from imaging acquisition, delivery of patient to the angiography suite, and reperfusion can all be decreased with streamlined workflow.

IMPLICATIONS FOR PATIENT CARE

- Optimizing outcomes in patients undergoing mechanical thrombectomy requires fast workflow, as rapid recanalization is associated with higher likelihood of functional independence.
- Quality initiatives for monitoring workflow may be warranted to identify and address sources of delay.
- Interfacility transfer times are prolonged and are currently a significant source of delay in the treatment of patients with acute large-vessel occlusive disease.

Abbreviations:

CI = confidence interval
ECC = endovascular-capable center ED = emergency department
IQR = interquartile range
SWIFT PRIME = Solitaire with the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke
tPA = tissue plasminogen activator

MATERIALS and METHODS

SWIFT PRIME was a global, multi-center, randomized, controlled trial conducted to compare the benefit of Solitaire stent retriever (Covidien, Irvine, Calif) thrombectomy added to intravenous tissue plasminogen activator (tPA) administration versus intravenous tPA administration alone. The methods and primary results have been published previously (8,9). In the trial, 196 patients were enrolled (98 in each arm) before termination due to crossing of a predefined effectiveness boundary. The institutional review board at each site approved the trial. Enrolled patients provided written informed consent, or at select sites, there was an exception from having to acquire explicit informed consent in emergency circumstances. For sites within the United States, Health Insurance Portability and Accountability Act guidelines were followed. The trial was funded by Covidien (now Medtronic) and was designed and led by a steering committee that included academic investigators and representatives of the sponsor. The site investigators gathered the data, with monitoring and database maintenance performed by the sponsor. The first and subsequent drafts of the manuscript were written by the first and second authors by incorporating input from all authors. The academic authors had unrestricted access to the data (M.G., A.P.J.), performed the data analysis with the primary and the independent study statisticians, and attest to the integrity of the trial and the completeness and accuracy of the reported data. The trial was monitored by an independent data and safety monitoring board.

Quality Improvement Program

Sites were instructed to fill in a work-flow form (Fig 1) after each patient enrollment that was immediately sent for analysis to the global interventional workflow principal investigator of the study (M.G., see Appendix E1 [online]). Data from the form were used to calculate various time intervals and were used to provide feedback via conference call and e-mail. Other sources of time stamps, such as computed tomographic (CT) images, angiography images, and postprocessed perfusion images, were also used for workflow analysis. It was acknowledged that there would be some degree of inaccuracy in these times, owing to a lack of synchronization across all clocks; however, there is no expectation of directionality of effect (there is no reason clocks would be biased in a particular

COVIDIEN

SWIFT PRIME Patient Workflow Timesheet

Site #		Site Name	
Patient #		Enrollment Date (dd/mm/yy)	

Complete only **one column** per subject.

Patient arrive at treating hospital (Time is hh:mm format)		Transfer patient (Time is hh:mm format)	
Stroke Onset Time:	☐ AM ☐ PM	Stroke Onset Time:	☐ AM ☐ PM
Arrive at ER:	☐ AM ☐ PM	Arrive at initial ER:	☐ AM ☐ PM
CT: Non Contrast CT:	☐ AM ☐ PM	Non Contrast CT at initial ER:	☐ AM ☐ PM
CTA:	☐ AM ☐ PM	CTA at initial ER (if done):	☐ AM ☐ PM
CTP (if done):	☐ AM ☐ PM	IV tPA Administration:	☐ AM ☐ PM
MRI: Diffusion (DWI):	☐ AM ☐ PM	Time leave initial hosp:	☐ AM ☐ PM
MRA:	☐ AM ☐ PM	Arrive at treating hosp:	☐ AM ☐ PM
Perfusion (PWI):	☐ AM ☐ PM	**CT:** Non Contrast CT at treating hosp:	☐ AM ☐ PM
IV tPA Administration:	☐ AM ☐ PM	CTA at treating hosp:	☐ AM ☐ PM
RAPID analysis available (if used):	☐ AM ☐ PM	CTP (if done) at treating hosp:	☐ AM ☐ PM
Time of Consent:	☐ AM ☐ PM	**MRI:** Diffusion (DWI) at treating hosp:	☐ AM ☐ PM
Randomization:	☐ AM ☐ PM	MRA at treating hosp:	☐ AM ☐ PM
Arrive at angio suite:	☐ AM ☐ PM	Perfusion (PWI) at treating hosp:	☐ AM ☐ PM
Groin Puncture Time:	☐ AM ☐ PM	RAPID analysis available (if used):	☐ AM ☐ PM
First DSA run of relevant vessel:	☐ AM ☐ PM	Time of Consent:	☐ AM ☐ PM
First Solitaire Deployment:	☐ AM ☐ PM	Randomization:	☐ AM ☐ PM
First TICI 2B observed:	☐ AM ☐ PM	Arrive at angio suite:	☐ AM ☐ PM
Final DSA run:	☐ AM ☐ PM	Groin Puncture Time:	☐ AM ☐ PM
Sedation type:	☐ Conscious ☐ General Anesthesia	First DSA run of relevant vessel:	☐ AM ☐ PM
If general anesthesia used, select reason:	☐ Hospital standard practice ☐ Patient condition clinically indicated	First Solitaire Deployment:	☐ AM ☐ PM
		First TICI 2B observed:	☐ AM ☐ PM
		Final DSA run:	☐ AM ☐ PM
		Sedation type:	☐ Conscious ☐ General Anesthesia
		If general anesthesia used, select reason:	☐ Hospital standard practice ☐ Patient condition clinically indicated

CTA to groin puncture greater than 70 min? ☐ Yes ☐ No If yes, please indicate reason below:

☐ General Anesthesia	☐ Consenting issue	Other (Specify):
☐ Vessel tortuosity	☐ Imaging interpretation delays	
☐ Staff availability	☐ Groin access	

V3.0_07Apr2014

Figure 1. SWIFT PRIME patient workflow timesheet.

direction). Overall guidance regarding workflow and parallel processing was provided on the basis of previously recommended strategies aimed to improve process (2,10). For sites with excellent workflow, the phone calls were taken as opportunities to learn about local best practices and techniques that could be used to educate staff and improve workflow within sites. Sites with excellent workflow were highlighted in the monthly newsletter to encourage further improvement. The primary metric of workflow efficiency was a target time of qualifying imaging acquisition to groin puncture of less than 70 minutes.

For this current report, the following time intervals were calculated: (a) symptom onset to arrival at the hospital ED that was participating in the trial and was capable of administering endovascular treatment, (b) arrival at the ED to start of imaging, (c) start of imaging to qualifying image acquisition, (d) start of imaging to acquisition of penumbral imaging post-processed maps (whenever this was performed), and (e) start of imaging to start of intravenous tPA administration (only in patients who presented to and were treated within the same center). In the interventional arm, the additional following times were calculated: (a) qualifying image acquisition to groin puncture, (b) groin puncture to first deployment of device, and (c) groin puncture to reperfusion, with reperfusion defined as Thrombolysis in Cerebral Infarction grade 2b or 3. Qualifying image acquisition time was (a) the time of CT perfusion or magnetic resonance (MR) perfusion image acquisition among the first 72 enrolled patients, when perfusion imaging was mandatory for randomization; and (b) the time of CT or MR angiographic image acquisition among subsequent patients when perfusion imaging was encouraged but not mandated. Additional time intervals were also evaluated when relevant, including time from arrival at the ED to randomization, symptom onset to reperfusion, and arrival at the ED to reperfusion.

The probability of functional independence (as defined by a modified Rankin scale score of 0-2 at 90 days) was evaluated as a function of time from symptom onset to reperfusion for the full cohort of patients, in both adjusted and unadjusted analyses. The probability of functional independence was also evaluated as a function of qualifying imaging acquisition to reperfusion (as defined by Thrombolysis in Cerebral Infarction grade 2b or 3 reperfusion). The imaging to reperfusion time analysis was restricted to patients who presented directly to endovascular-capable centers (ECCs), in whom imaging to reperfusion times are a major component of overall treatment speed. In patients who are given intravenous tPA infusion at a primary facility before being transferred to an ECC, extend-

ed time periods at the referring hospital and in interfacility transfer have a dominant effect over imaging to reperfusion times at study hospitals (Fig 2 and Table 1).

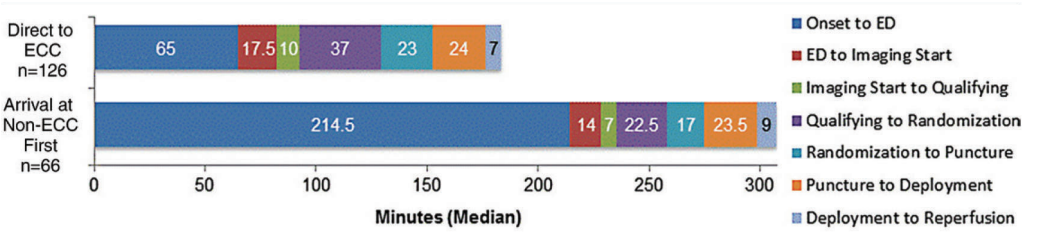


Figure 2.

Graph of time intervals in patients treated within the same institution (an ECC) versus those who were transferred from another facility after receiving intravenous tPA therapy. *Deployment* = device deployment, *puncture* = groin puncture, *qualifying* = qualifying image acquisition

Table 1

Patient Transfer Type

Time Interval	Patient Presented Directly to the ECC Facility (min)	Patient Transferred from a Non-ECC Facility (min)
Qualifying image acquisition to groin puncture	69.5 (48–83)	40 (27–54)
Qualifying image acquisition to device deployment	93 (73–122)	64 (56–94)
Arrival at the ED to groin puncture	107 (83–131)	63 (52–81)
Arrival at the ED to device deployment	137 (112–167)	84.5 (74–119)
Arrival at the ED to reperfusion	149 (121–187.5)	104 (86–137)
Symptom onset to device deployment	203 (173–263)	299 (273–348)

Note.—Data are medians, with IQRs in parentheses.

Analysis of the endovascular intraprocedural workflow was also performed. This included an analysis of groin puncture to first stent retriever deployment and groin puncture to final reperfusion on the basis of (a) degree of tortuosity in the neck vessels (as assessed by experienced neurointerventionists in the core laboratory on the basis of a trichotomized scale-mild, moderate, or severe), reflecting subjective impression of the degree to which vessel tortuosity would cause difficulty in accessing the relevant carotid artery or the intracranial occlusion; (b) right-sided versus left-sided occlusion; and (c) type of guide catheter used, including a balloon guide catheter (a guide catheter with a balloon at its tip that can be inflated to occlude antegrade flow), a distal access catheter (a large-bore pliable catheter that can be advanced to the intracranial circulation), and a routine guide catheter.

Statistical Analyses

Workflow time intervals as cited earlier are reported by using medians and interquartile ranges (IQRs), owing to nonnormality of the data; differences between subgroups were tested by using the Wilcoxon rank sum test. The association between time intervals and baseline characteristics of the patient, mode of arrival at the ECC, and procedural characteristics was evaluated with multivariable negative binomial regression by using a logarithmic link function, and absolute differences in minutes between subgroups were evaluated by using the same models but by using the identity link; goodness of fit was checked by using the Akaike information criterion. Outputs from these analyses include rate ratios and their associated 95% confidence limits. The relationship between time and functional independence was assessed by using standard logistic regression in adjusted and unadjusted analyses.

In the adjusted analyses, the three clinically relevant covariates used as stratification variables at randomization (National Institutes of Health Stroke Scale, age, and occlusion location) and the two baseline characteristics found to be significantly different between randomized groups (presence of cervical carotid artery stenosis and platelet count at baseline) were incorporated. In analyses in which patients from both randomized groups were incorporated, treatment assignment was also included as a stratification variable. Reported P values are two sided, with values less than .05 deemed to indicate a statistically significant difference. Statistical analysis was performed by using R version 3.2.1 software (R Development Core Team, R Foundation, Vienna, Austria).

Table 2

Time Intervals in Patients Treated in the SWIFT PRIME Trial

Time Interval	No. of Patients	Median Time (min)	IQR (min)
Symptom onset to arrival at the ED	192	109.5	54–192.5
Arrival at the ED to start of imaging	192	16	10–23.5
Start of imaging to qualifying image acquisition	184	9	5–19.5
Qualifying image acquisition to randomization	190	30	20–48
Randomization to groin puncture	97	22	12–32
Groin puncture to device deployment	85	24	18–33
Device deployment to reperfusion	78	8	5–23
Arrival at ED to groin puncture	97	90	69–120
Arrival at ED to device deployment	85	119	94–146
Arrival at ED to reperfusion	79	139	108–169

RESULTS

Median interval times for the overall workflow are summarized in Table 2. Qualifying image acquisition to groin puncture was achieved with a median time of 52 minutes; in 61% of patients (59 of 97), the optimal time of less than 70 minutes was achieved, and in 88% of patients (85 of 97), the protocol-specified maximal time of less than 90 minutes was achieved.

Overall Effect of Time on Outcome

In adjusted analysis, the probability of functional independence among patients with stent retrievers was 91% if reperfusion was achieved 150 minutes from symptom onset, which decreased by approximately 10% (absolute) over the next 60 minutes and then 20% (absolute) with every subsequent 60-minute delay (Fig 3a). Findings were similar in unadjusted analysis (Fig E1a [online]). Similarly, rates of functional independence among patients with reperfusion in the stent retriever group declined substantially as the time from qualifying imaging acquisition to reperfusion increased among patients who presented directly to the ECC in adjusted (Fig 3b) and unadjusted (Fig E1b [online]) analyses. A relation

between time from qualifying imaging acquisition to rate of functional independence effect was not present when analysis included patients who were given intravenous tPA infusion at a primary facility before being transferred to an ECC, among whom imaging to reperfusion time was a much smaller fraction of overall symptom onset to reperfusion time (Fig E2 [online]). The odds ratio for functional independence rates in the stent retriever group versus the tPA alone group showed superiority of the stent retriever group, with a nominal down-downward trend over time that did not reach statistical significance (Fig 3c, Fig E1c [online]).

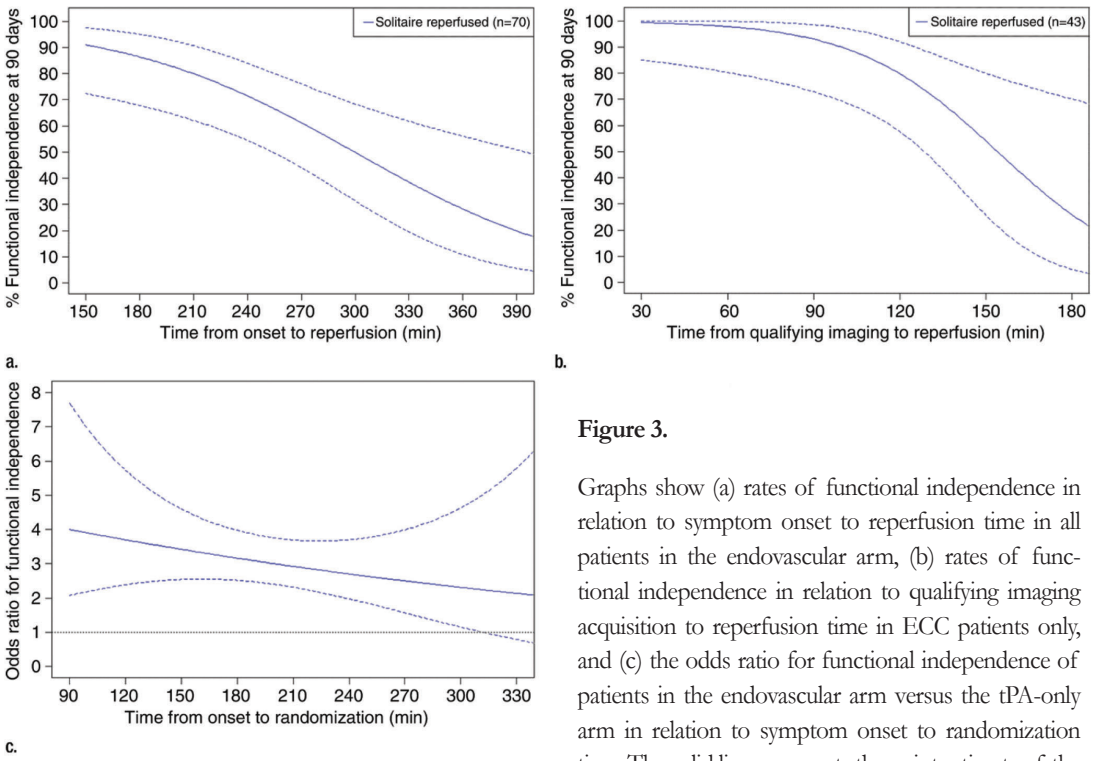


Figure 3.

Graphs show (a) rates of functional independence in relation to symptom onset to reperfusion time in all patients in the endovascular arm, (b) rates of functional independence in relation to qualifying imaging acquisition to reperfusion time in ECC patients only, and (c) the odds ratio for functional independence of patients in the endovascular arm versus the tPA-only arm in relation to symptom onset to randomization time. The solid line represents the point estimate of the odds ratio across time, while the dotted lines collectively represent the 95% CI (upper and lower values) for the odds ratio.

Patient Arrival Route and Timing

During the study period, a total of 196 patients were randomized in SWIFT PRIME, with most patients arriving directly at the ECC versus arriving at a referring facility, where personnel initiated intravenous thrombolysis and subsequently transferred the patient to the study site (126 vs 66 patients, Fig 2a). In multivariable analysis, initial presentation to a referral facility added 129 minutes to when the patient finally arrived at the ECC; this corresponded to a 158% increase in delay in reaching the emergency room of the ECC (Fig 4, Table E1 [online]). In patients who were transferred to the ECC, workflow within the ECC was much faster than when patients presented directly to the ECC; in multivariable analyses, arrival at the ED to imaging time was less (rate ratio, 0.73; 95% confidence interval [CI]: 0.57, 0.92; P = .009; absolute difference, 7 minutes), and time of imaging to groin puncture was less (rate ratio, 0.55; 95% CI: 0.47, 0.65; P, .001; absolute difference, 41 minutes) (Fig 4). Patients who presented during weekday hours (Monday to Friday, 8 am to 5 pm) had a shorter time from arrival in the ED to randomization (rate ratio, 0.81; 95% CI: 0.71, 0.92; P , .001; absolute difference, 17 minutes) versus those who presented during evening, overnight, and weekend hours (Fig 4).

Baseline Imaging

The imaging modality for qualifying imaging acquisition was CT in 83% of patients (161 of 193) and MR imaging in 17% of patients (32 of 193). Over-all, there was no difference in arrival to randomization time according to image modality; however, this analysis was in part confounded by the greater use of MR imaging in patients who were given intravenous tPA infusion at a primary facility before being transferred to an ECC. Still, when analysis was confined to patients who reported directly to the ECC, numerical differences in arrival to randomization time among patients who underwent MR imaging versus CT did not reach statistical significance (median time of 84 minutes for MR imaging vs 76 minutes for CT; P = .17).

While the SWIFT PRIME investigators initially mandated perfusion imaging for patient selection by using automated software, a revision was made to the protocol during the study period that allowed enrollment without perfusion imaging, although perfusion imaging was still encouraged whenever feasible. As a result, a preponderance of patients underwent CT or MR perfusion imaging (81%, 158 of 195). In 126 patients, likely accurate

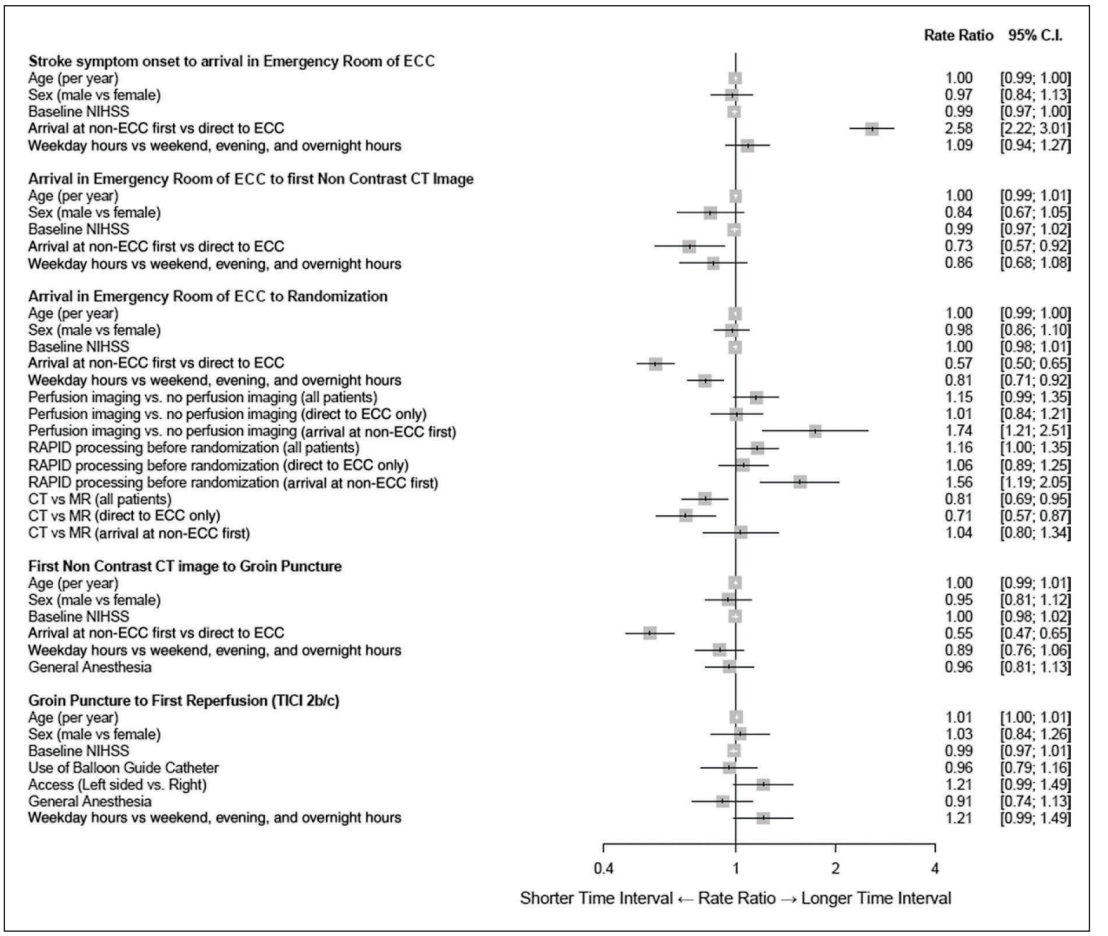


Figure 4.

Graph shows the subgroup analyses for the adjusted effects of patient presentation and process features on work flow. All interval times except first unenhanced CT examination to groin puncture and groin puncture to first reperfusion time were significantly different on the basis of enrollment location when that variable was included in the models. A rate ratio of more than 1 indicates prolonged interval times. NIHSS = National Institutes of Health Stroke Scale, TICI = Thrombolysis in Cerebral Infarction.

times of perfusion map acquisition by using automated software were available. Among patients in whom CT perfusion imaging was used or likely used for randomization, the unenhanced CT to CT angiography acquisition time was 9 minutes (IQR, 4-26 minutes), while the time from unenhanced head CT to successful postprocessing of CT perfusion images by using RAPID software (Ischemaview, Calif) was 22 minutes (IQR, 14-34 minutes). (In patients in whom CT perfusion imaging was used, the time stamp on the postprocessed CT perfusion images was prior to the time stamp of randomization; however, it was not documented whether the perfusion data were actually used [trial eligibility could be met without perfusion data after revision F], and errors in the time stamp were possible [since the clocks were not synchronized]). In multivariable analyses, automated perfusion image processing prior to randomization was associated with longer time from emergency room arrival to randomization at hospitals where patients were transferred to the ECC (19 minutes; 95% CI: 4, 35). However, this difference was not significant in patients who reported directly to an ECC (4 minutes; 95% CI: 212, 21). For rates of independent modified Rankin score of 0-2, outcomes according to different imaging strategies were as follows: (a) automated perfusion image processing mandated for randomization (initial study phase): 54.1% for the stent retriever device (20 of 37 patients) and 28.1% for tPA (nine of 32 patients) (absolute difference, 26.0%; 95% CI: 3.6%, 48.3%; P = .049); (b) automated perfusion image processing likely performed prior to randomization: 61.3% for the stent retriever device (38 of 62 patients) and 38.6% for tPA (22 of 57 patients) (absolute difference, 22.7%; 95% CI: 3.5%, 38.6%; P = .02); (c) no perfusion imaging performed: 60.0% for the stent retriever device (nine of 15 patients) and 27.3% for tPA (six of 22 patients) (absolute difference, 32.7%; 95% CI: 23.9%, 69.3%; P = .09); and (d) automated perfusion imaging process likely not used for randomization (either perfusion imaging not performed or processed only after randomization): 57.9% for the stent retriever device (22 of 38 patients) and 28.6% for tPA (10 of 35 patients) (absolute difference, 29.3%; 95% CI: 4.9%, 53.8%; P = .02).

Procedural Features

Most patients underwent mechanical thrombectomy without general anesthesia (64%, 61 of 96 patients), but the centers that used general anesthesia as part of their routine practice in all patients did not experience workflow delay in the time from arrival at the ED to groin puncture (median, 89 minutes for general anesthesia vs 95.5 minutes for conscious sedation; P = .76; Fig 4). Severe vessel tortuosity and left-sided lesions were found to lead

to longer groin puncture to reperfusion time, although neither difference was statistically significant (median, 38 minutes for left-sided lesions vs 34.5 minutes for right-sided lesions [P = .12]; median, 42 minutes for severe tortuosity vs 38 minutes for nonsevere tortuosity [P = .86]). In both cases, the main delay was in groin access to target lesion engagement (deployment), particularly for left-sided lesions (median, 32.5 minutes for left-sided lesions vs 22 minutes for right-sided lesions; P =.046). Once deployment was achieved, deployment to reperfusion times were comparable. Finally, the use of a guide catheter was not required in this study design, but most cases involved use of the balloon guide catheter or routine catheter. The median times from groin puncture to reperfusion were 35.5 minutes for the balloon guide catheter (n = 51), 49 minutes for the distal a cess catheter (n = 40), and 37.5 minutes (n = 3) for the routine catheter. These variables were, however, not significant in multivariable analysis (Fig 4).

Center Characteristics

Several center-specific characteristics were investigated as potential modifiers of workflow process. Academic affiliation and United States versus European location did not alter workflow.

DISCUSSION

This multicenter trial demonstrated that faster times from stroke symptom onset to endovascular reperfusion and from qualifying imaging to endovascular reperfusion are strongly associated with increased likelihood of functional independence. In SWIFT PRIME, a robust relation between speed of reperfusion and outcome was observed-every 6-minute delay from symptom onset to reperfusion in the stent retriever arm was associated with 1-1.5 fewer functionally independent outcomes at 90 days among every 100 patients treated. When patients underwent reperfusion hyperacutely, within the first 2.5 hours of onset, nearly nine of every 10 achieved an independent outcome. This work adds to a growing body of evidence supporting the importance of "time is brain" in the endovascular treatment of acute ischemic stroke (1,11,12).

The intensive workflow speed focus in SWIFT PRIME succeeded in yielding faster treatment times than in earlier endovascular trials. In the Interventional Management of Stroke III clinical trial, a time of under 90 minutes from intravenous tPA bolus to groin puncture was targeted and achieved, but this time metric may not have been aggressive enough. A detailed analysis of the Interventional Management of Stroke III trial demonstrated particularly long delays from randomization to groin puncture (62 minutes compared with 22 minutes in SWIFT PRIME) and groin puncture to reperfusion (120.5 minutes compared with 32 minutes in SWIFT PRIME). This improvement by 128.5 minutes in the interval from randomization to reperfusion time was likely an important contributor (in addition to other factors, such as the use of newer-generation devices and achieving excellent reperfusion in the endovascular arm) to the higher rate of functional independence in the endovascular treatment arm of the SWIFT PRIME trial. A key component to improved workflow was the parallel nature of care processes in the SWIFT PRIME trial. Notably, the rapid workflow in SWIFT PRIME was consistent across 39 study sites in multiple countries and states across two continents, independent of academic affiliation, suggesting that the workflow efficiencies achieved in the trial are generalizable to multiple hospitals and national health systems.

Workflow was more efficient when patients were candidates to be given intravenous tPA infusion before being transferred to an ECC, which is likely related to the advance notice

provided to the study center, permitting mobilization of the stroke evaluation and intervention teams, clearance of imaging units, and preparation of the catheterization laboratory. Furthermore, consent to receive tPA infusion and delivery of the intravenous tPA itself introduces workflow delays, and the completion of this step in advance likely contributed to improved workflow once the patient arrived at the study hospital (13). However, a major cause for delay among patients who received initial tPA before transfer was the prolonged arrival time from referral hospitals to the ECC. Several factors may have accounted for these delays, such as inefficient mechanisms of triage in the referral center; overall organization of stroke care at the referral center, including interpretation of images and consent and decision making for intravenous tPA administration; and organization of a separate transport team. Transport might be delayed until the 1-hour tPA infusion is complete, unless a specialized critical-care emergency medical services transport team is available. Potential solutions to this challenge include training emergency medical services staff to detect patients who have a high likelihood of having a proximal vessel occlusion so they may bypass the nearest hospital and go directly to an ECC. Selective use of direct routing to ECCs would of course need to be fine-tuned on the basis of local geography, travel times, and available regional resources.

The results in this study highlight the importance of tracking endovascular workflow times and providing feedback to maintain good results in the acute management of stroke. To achieve the outcomes observed in SWIFT PRIME in routine practice, quality improvement target interval times will need to match more closely and preferably exceed the time intervals achieved in the trial. Recent recommendations from the Society of Neurointerventional Surgery support this approach (14). In the SWIFT PRIME trial, time between head CT and successful postprocessing of CT perfusion images was longer than the time between CT and CT angiography source image availability. The use of perfusion imaging did not affect the effectiveness of treatment. The results in patients enrolled without the use of perfusion imaging are consistent with the results of the Endovascular Treatment for Small Core and Anterior *Circulation* Proximal Occlusion with Emphasis on Minimizing CT to Recanalization Times, or ESCAPE, trial (15). Given the data regarding the substantial decrease in functional independence with increase in time to reperfusion, every step in the work-up and treatment of these patients shall need to be weighed against the time spent versus the potential benefit.

There are several limitations to this study. All the participating centers were chosen on the basis of their experience and patient volume. As such, the results may not be generalizable to all centers that offer endovascular treatment for acute stroke. Some of the components of the imaging paradigm used for decision making were not precisely documented but had to be extrapolated from the time stamps. Experienced operators determined the degree of tortuosity on a subjective scale. The scale has not been validated. The quality improvement and feedback process was implemented for the entire duration of the trial. Hence, it is not possible to precisely determine its effect on overall workflow.

In conclusion, detailed analysis of the workflow in the SWIFT PRIME trial provides further data on the importance of time and efficiency in acute ischemic stroke management, likely contributing to the superior clinical outcome observed in the intervention arm of the trial. Aggressive time metrics and frequent feedback likely played a key role in maintaining efficiency. Targets for further improvement include patient triage and transport at referring facilities, efficient imaging paradigms and consent processes, and procedural times in patients with difficult anatomy.

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Supplementary Appendix

Appendix E1

All sites were expected to fill in the workflow form (Fig 1) within 24 hours of enrolling a patient into the study. This was sent to the workflow principal investigator (M.G.) over e-mail. The workflow principal investigator evaluated the workflow for each patient and broadly categorized it as (a) good workflow (no action needed), (b) excellent workflow (congratulate the team, include them in the next newsletter, and, if necessary, organize a conference call with the site to learn the reasons behind their success; these findings were then disseminated to other sites through personal e-mails, conference calls, or newsletters), or (c) poor workflow (global principal investigator [J.L.S.] and workflow principal investigator [M.G.] organized a conference call with the site to understand the reasons for the delays, provided advice and input on how to improve the procedure times, and assessed whether the delay was a one-off case or a systematic problem).

Table E1. Relation of Patient and Care Process Variables with Workflow Times

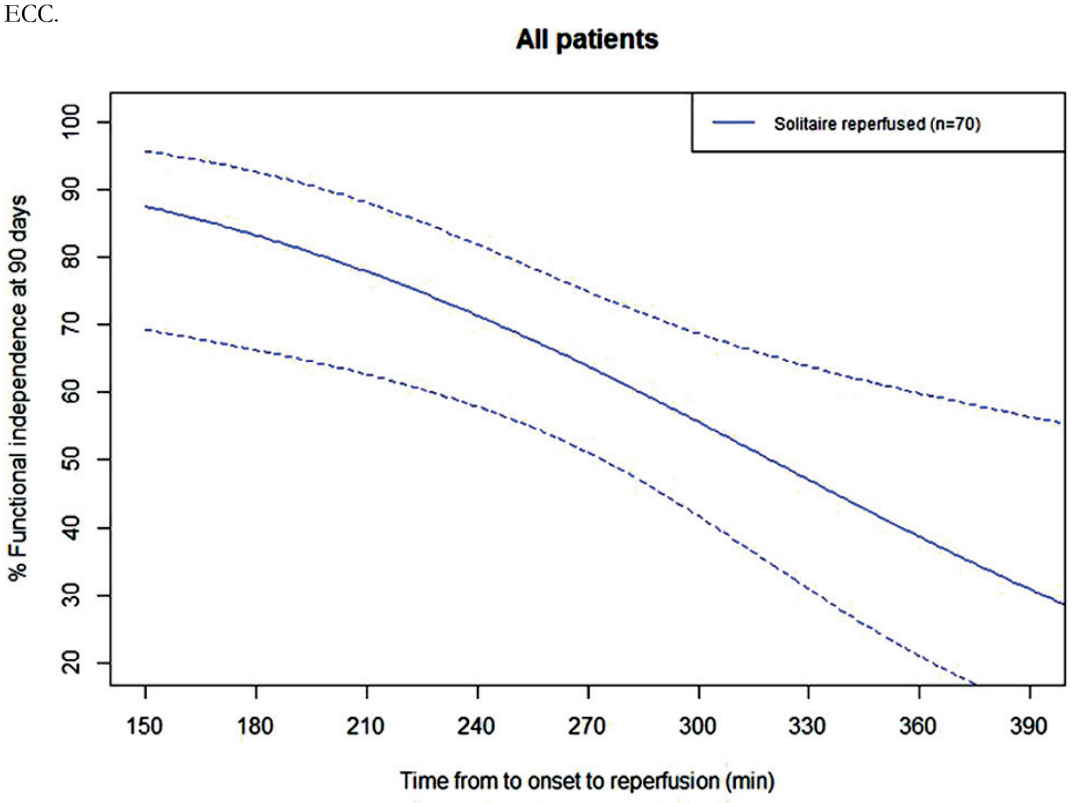
Workflow Interval and Variable	Unadjusted Mean Difference	*P* Value	Adjusted Mean Difference	*P* Value
Stroke symptom onset to arrival in the ECC emergency room				
Age (per 10 y)	1 (–9, 10)	.92	0 (–6, 7)	.97
Sex (male vs female)	–7 (–30, 16)	.57	–2 (–18, 13)	.77
Baseline NIHSS score (per 5 points)	–5 (–18, 7)	.43	–5 (–13, 3)	.22
ECC first vs non-ECC first*	129 (113, 145)	<.001	129 (113, 145)	<.001
Weekday versus weekend and overnight hours	9 (–15, 33)	.45	9 (–6, 25)	.25
Arrival in the ECC emergency room to first unenhanced CT examination				
Age (per 10 years)	1 (–3, 4)	.66	1 (–3, 4)	.74
Sex (male vs female)	–4 (–12, 4)	.28	–4 (–12, 4)	.30
Baseline NIHSS score (per 5 points)	–1 (–5, 3)	.67	–1 (–5, 3)	.63
ECC first vs non-ECC first*	–7 (–15, 1)	.097	–7 (–15, 1)	.098
Weekday versus weekend and overnight hours	–4 (–12, 5)	.39	–3 (–11, 5)	.43
Arrival in the ECC emergency room to randomization				
Age (per 10 y)	–1 (–5, 4)	.78	–1 (–5, 4)	.73
Sex (male vs female)	–3 (–14, 9)	.65	–3 (–13, 7)	.54
Baseline NIHSS score (per 5 points)	0 (–5, 5)	.99	–1 (–6, 5)	.85
ECC first vs non-ECC first*	–37 (–48,-26)	<.001	–37 (–48,-27)	<.001
Weekday vs weekend and overnight hours	–17 (–28,-5)	.005	–17 (–27,-6)	.002
First unenhanced CT examination to groin puncture				
Age (per 10 y)	0 (–3, 3)	.91	0 (–1, 1)	.89
Sex (male vs female)	–6 (–22, 10)	.48	–6 (–21, 9)	.45
Baseline NIHSS score (per 5 points)	1 (–8, 9)	.87	0 (–8, 8)	.95
ECC first vs non-ECC first*	–40 (–55,-25)	<.001	–41 (–56,-25)	<.001
Weekday vs weekend and overnight hours	–6 (–23, 10)	.47	–6 (–22, 9)	.40
General anesthesia	–4 (–21, 12)	.61	–5 (–20, 10)	.50
Groin puncture to first reperfusion (TICI grade 2b or 2c)				
Age (per 10 y)	3 (–1, 6)	.17	2 (–2, 6)	.29
Sex (male vs female)	–1 (–9, 8)	.98	2 (–7, 11)	.72
Baseline NIHSS score (per 5 points)	–2 (–7, 3)	.47	–4 (–9, 1)	.12

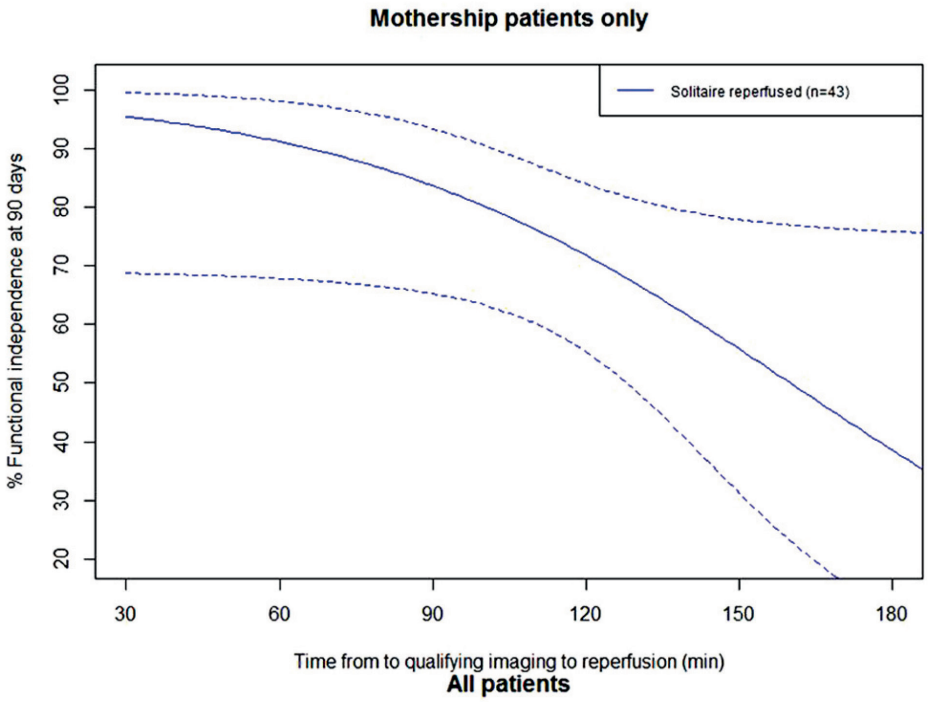
Use of balloon guide catheter	0 (–9, 8)	.97	–1 (–9, 8)	.90
Access (left sided vs right sided)	7 (–2, 15)	.12	10 (1, 19)	.040
General anesthesia	–2 (–11, 7)	.69	–5 (–15, 4)	.29
Weekday versus weekend and overnight hours	5 (–4, 14)	.28	9 (0, 19)	.049

Note.—Numbers in parentheses are 95% CIs. NIHSS = National Institutes of Health Stroke Scale, TICI = Thrombolysis in Cerebral Infarction.

* Indicates patients who were given tPA at a non-ECC before transfer to an ECC.

Figure E1: **(a)** Graph shows the unadjusted rates of functional independence in relation to symptom onset to reperfusion time in patients in the endovascular arm of the study. **(b)** Graph shows the unadjusted rates of functional independence in relation to qualifying imaging acquisition to reperfusion time in patients who presented directly to the ECC. **(c)** Graph shows the unadjusted odds ratio for functional independence in patients in the endovascular arm versus the tPA only arm in relation to symptom onset to randomization time. The solid line represents the point estimate of the odds ratio across time, while the dotted lines collectively represent the 95% CIs (upper and lower values) for the odds ratio. *Mothership* = ECC.




Mothership patients only
Solitaire reperfused (n=43)
% Functional independence at 90 days
20
30
40
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100
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120
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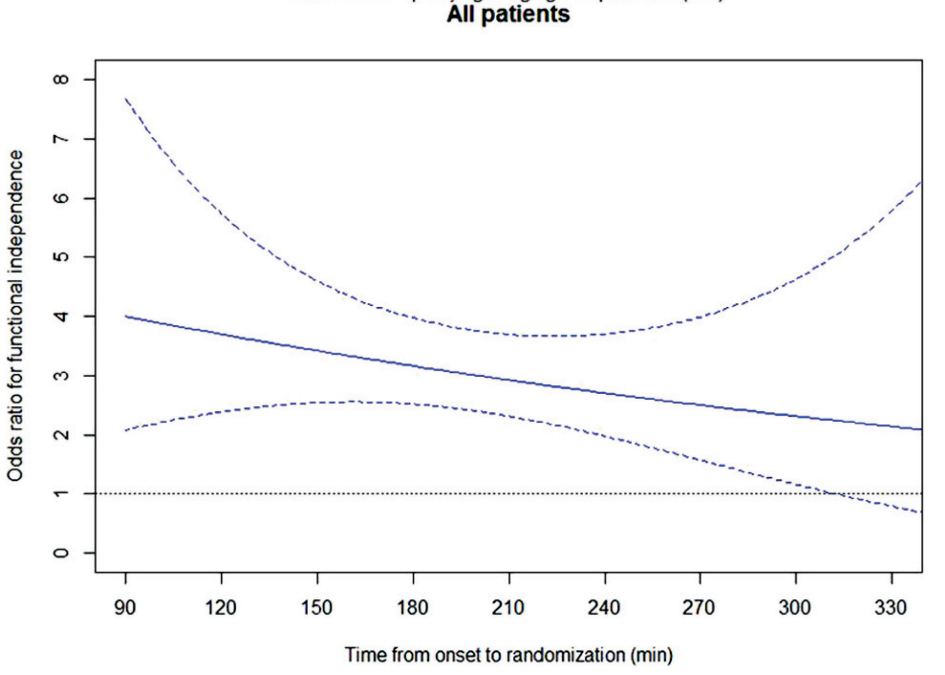
180
Time from to qualifying imaging to reperfusion (min)


All patients
Odds ratio for functional independence
0
1
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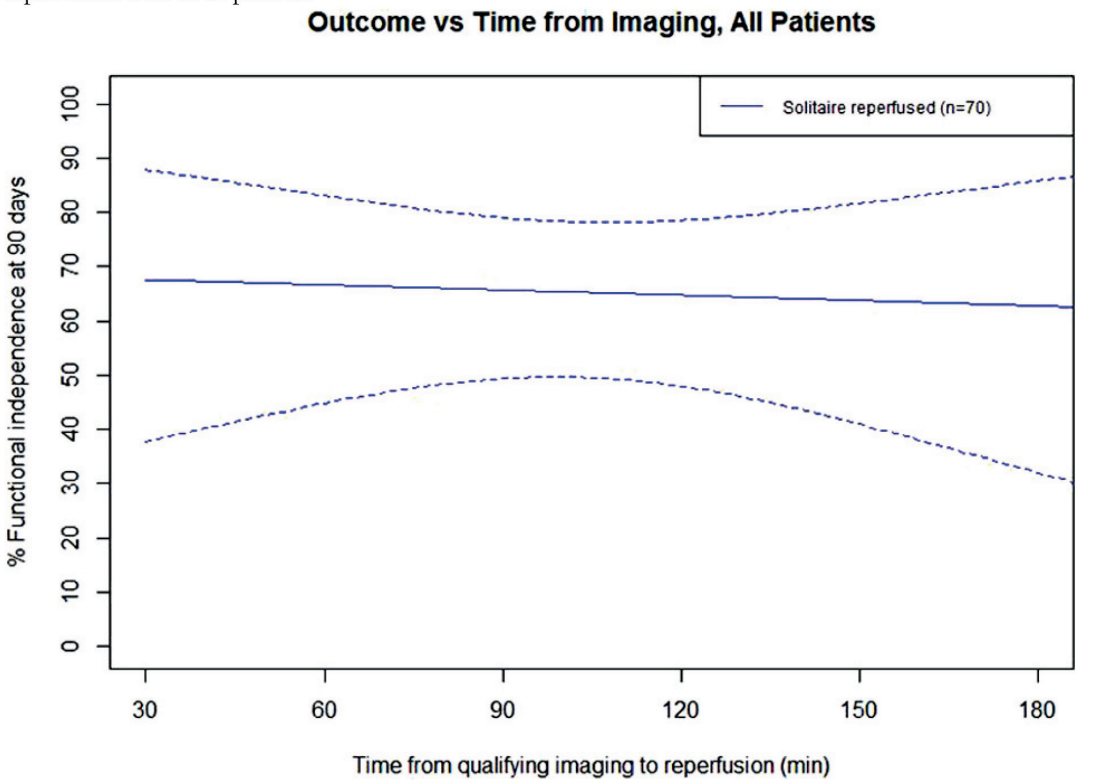
7
8
90
120
150
180
210
240
270
300
330
Time from onset to randomization (min)

Figure E2: Graph shows rates of functional independence in relation to qualifying imaging acquisition to reperfusion time in all patients



CHAPTER 3.4

Time To Treatment With Endovascular Thrombectomy And Outcomes From Ischemic Stroke: A Meta-Analysis

Based upon:
Time to Treatment With Endovascular Thrombectomy and
Outcomes From Ischemic Stroke: A Meta-analysis
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ABSTRACT

Importance

Endovascular thrombectomy with second-generation devices is beneficial for patients with ischemic stroke due to intracranial large-vessel occlusions. Delineation of the association of treatment time with outcomes would help to guide implementation.

Objective

To characterize the period in which endovascular thrombectomy is associated with benefit, and the extent to which treatment delay is related to functional outcomes, mortality, and symptomatic intracranial hemorrhage.

Design, Setting, and Patients

Demographic, clinical, and brain imaging data as well as functional and radiologic outcomes were pooled from randomized phase 3 trials involving stent retrievers or other second-generation devices in a peer-reviewed publication (by July 1, 2016). The identified 5 trials enrolled patients at 89 international sites.

Exposures

Endovascular thrombectomy plus medical therapy vs medical therapy alone; time to treatment.

Main Outcomes and Measures

The primary outcome was degree of disability (mRS range, 0-6; lower scores indicating less disability) at 3 months, analyzed with the common odds ratio (cOR) to detect ordinal shift in the distribution of disability over the range of the mRS; secondary outcomes included functional independence at 3 months, mortality by 3 months, and symptomatic hemorrhagic transformation.

Results

Among all 1287 patients (endovascular thrombectomy + medical therapy [n = 634]; medical therapy alone [n = 653]) enrolled in the 5 trials (mean age, 66.5 years [SD, 13.1]; women, 47.0%), time from symptom onset to randomization was 196 minutes (IQR, 142 to 267). Among the endovascular group, symptom onset to arterial puncture was 238 minutes (IQR, 180 to 302) and symptom onset to reperfusion was 286 minutes (IQR, 215 to 363). At 90 days, the mean mRS score was 2.9 (95% CI, 2.7 to 3.1) in the endovascular group and 3.6 (95% CI, 3.5 to 3.8) in the medical therapy group. The odds

of better disability outcomes at 90 days (mRS scale distribution) with the endovascular group declined with longer time from symptom onset to arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96 to 3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30 to 3.00), ARD, 30.2%; cOR at 8 hours,1.57 (95% CI, 0.86 to 2.88), ARD, 15.7%; retaining statistical significance through 7 hours and 18 minutes. Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76 to 0.93]; ARD, -6.7%) and less functional independence (OR, 0.81 [95% CI, 0.71 to 0.92], ARD, -5.2% [95% CI, -8.3% to -2.1%]), but no change in mortality (OR, 1.12 [95% CI, 0.93 to 1.34]; ARD, 1.5% [95% CI, -0.9% to 4.2%]).

Conclusions And Relevance

In this individual patient data meta-analysis of patients with large-vessel ischemic stroke, earlier treatment with endovascular thrombectomy + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months. Benefit became nonsignificant after 7.3 hours.

Five randomized trials have demonstrated the benefit of second-generation endovascular recanalization therapies (primarily stent retrievers) over medical therapy alone among patients with acute ischemic stroke due to large-vessel occlusions.[1-6] However, uncertainties remain about the benefit and risk of endovascular intervention when undertaken more than 6 hours after symptom onset as well as the degree to which benefit varies with time within the first 6 hours after symptom onset. In addition, evaluation of the workflow speeds achieved in the trials could guide time targets for quality improvement in clinical practice. National guidelines and consensus statements in the United States, Europe, and Canada recommend endovascular recanalization up until 6 hours after symptom onset, but thrombectomy devices are cleared by the US Food and Drug Administration for use up to 8 hours after symptom onset, and the Canadian guidelines additionally recommend thrombectomy for selected patients up to 12 hours after symptom onset.[7-9]

To address these uncertainties regarding temporal aspects of endovascular recanalization therapy, the investigators from the 5 trials agreed to pool their individual patient data for analysis. The objectives of this pooled analysis were to delineate the period in which endovascular thrombectomy is associated with benefit and to investigate the extent to which treatment delay is related to the association of endovascular intervention with functional outcomes, mortality, and symptomatic intracranial hemorrhage, with greater power and precision than achievable in analyses of individual trials.[10-13]

- **cOR** common odds ratio
- **ICA** internal carotid artery
- **IV tPA** intravenous tissue plasminogen activator
- **MCA** middle cerebral artery
- **mRS** modified Rankin Scale
- **mTICI** modified Thrombolysis in Cerebral Infarction

METHODS

Study Design and Inclusion Criteria

A detailed description of the analytic approach is provided in the statistical analysis plan (Supplement 1). The study investigators established the Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke *Trials* (HERMES) collaboration to undertake meta-analysis of pooled individual patient data. The collaboration included all randomized phase 3 trials in which stent retrievers or other second-generation devices were used in the majority of endovascular interventions for treatment of acute ischemic stroke, and for which a peer-reviewed, complete primary results manuscript was published by July 1, 2016. PubMed search and inquiry among collaborators and colleagues was performed to confirm that all eligible trials were included (eTable 1 in Supplement 2).14,15 Comparative design features of the contributing trials have been described.[6] All included trials enrolled patients with ethics approval from the local institutional boards at participating sites. The trials enrolled patients using prospective (4 trials) or prospective and deferred (1 trial) written informed consent from patients or their legally authorized representatives.

KEY POINTS

- **Question** What is the relation between time to treatment and outcome from endovascular mechanical thrombectomy for acute ischemic stroke?
- **Findings** In this meta-analysis of pooled individual patient data from 1287 adults in 5 randomized trials, compared with medical therapy alone, thrombectomy up to 7.3 hours after symptom onset was associated with improved outcomes. Rates of functional independence after thrombectomy were 64% with reperfusion at 3 hours vs 46% with reperfusion at 8 hours.
- **Meaning** In acute ischemic stroke due to large-vessel occlusion, endovascular mechanical thrombectomy should be initiated as soon as possible within the first 7 hours after symptom onset.

Outcomes

Two approaches were used to analyze the association between treatment time and outcomes: (1) the association of time with differences in outcome between treatment strategies was analyzed in an intention-to-treat manner, comparing patients allocated to treatment with endovascular thrombectomy + medical therapy (endovascular group) vs patients allocated to medical therapy alone (medical therapy group); (2) the association between time and outcome with substantial endovascular reperfusion was analyzed in the subset of endovascular group patients with modified Thrombolysis in Cerebral Infarction (mTICI) scale scores of 2b or 3.16

Efficacy outcomes analyzed at 3 months were (1) degree of disability, assessed across 6 levels of the modified Rankin Scale (mRS), with ranks 5 and 6 combined into a single worst outcome rank; (2) functional independence, defined as mRS scores of 0 through 2; and (3) excellent outcome, defined as mRS score of 0 through 1. Safety outcomes evaluated were 90-day mortality, symptomatic intracranial hemorrhage within 36 hours, and radiologic major intracerebral parenchymal hematoma within 36 hours. Symptomatic intracranial hemorrhage was classified according to the definitions of symptomatic intracranial hemorrhage used in each trial. Major parenchymal hematoma was defined as parenchymal hematoma type 2.[17]

Statistical Analysis

A detailed description of the analytic approach is provided in the statistical analysis plan, which was modified from the pre-analysis document to incorporate additional analyses based on the initial findings (eAppendix in Supplement 1). Briefly, probability of each outcome as a function of time was analyzed using mixed-method ordinal logistic regression for ordinal outcomes and mixed-method binary logistic regression for binary outcomes, with trial and trial-by-treatment interaction as random-effects variables. In the main analyses, models were constructed of the linear dependence of the log odds of a particular outcome on allocation to endovascular vs medical therapy groups and time interval (a linear variable). For models including both randomized groups, the interaction of time and treatment assignment was also included. In addition to these linear models, exploratory nonlinear models were constructed of the relations of outcomes with time toreperfusion by analyzing each modified Rankin Scale (mRS) cut point in 6 separate, binary

mixed-method logistic regression models, using a locally weighted scatterplot smoothing (LOWESS) regression technique. The common odds ratio (cOR) of the ordinal shift in the distribution of disability over the range of the mRS was the primary effect measure estimated from these models. The proportion of patients having better outcome by 1 or more disability levels on the mRS (absolute risk difference) was calculated by averaging values derived using the algorithmic joint outcome table and permutation test methods.[18,19]

For binary outcomes, absolute risk differences were calculated as differences of predicted proportions from logistic regression models. Variables included in adjusted analyses were age (a linear variable), sex (binary variable), baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] score), target occlusion location (a 3-level categorical variable-internal carotid artery [ICA], M1 middle cerebral artery [MCA], M2 MCA), entry Alberta Stroke Program Early Computed Tomography Score (ASPECTS; linear variable), and pretreatment intravenous (IV) tissue plasminogen activator (tPA [alteplase]; binary variable). Race/ethnicity was not included both because collection of race data was legally prohibited in some countries where studies were performed and because race/ethnicity is not a known major independent determinant of outcome from large-vessel ischemic stroke.

In all 5 trials, all patients eligible for IV tPA received it; only patients with contraindications to IV tPA did not receive it. Subgroups analyzed included IV tPA-treated vs IV tPA-ineligible patients, target occlusion location, extent of cerebral infarction at entry on the ASPECTS scale, and mode of arrival (direct from out-of-hospital setting to endovascular hospital [direct arrival patients] vs interhospital transfer from outside initial receiving hospital [transfer patients]).

An independent statistician collated, cleaned, and merged the data. A minimum data set was designed by the collaborative authors and retrieved by each study statistician and submitted to the independent statistician. Data definitions were harmonized, and when data queries arose, detailed information was sought from each trials' data center and statistician. Additional data checking (eg, for sequence generation, data consistency, and completeness) was performed by comparing independent analysis of the acquired data to published results and to unpublished summaries provided by the collaborative authors. Final analyses were performed on the collated and merged data set after the above steps.

For comparisons of treatment groups, time intervals analyzed included (1) symptom onset to randomization; (2) symptom onset to expected arterial puncture; (3) arrival at the emergency department door to randomization; and (4) arrival at the emergency department door to expected arterial puncture. Symptom onset time was time the patient was last known to be well. Symptom onset-to-expected arterial puncture time was derived by adding to the symptom onset-to-randomization value for each patient in both the endovascular and medical therapy groups (the study mean for the time from randomization to arterial puncture of the trial in which they participated). Symptom onset-to-expected arterial puncture time was considered the lead analytic time interval, as it is the time interval used in national guidelines for treatment recommendations.[7-9] For analysis of the association with outcome of time of revascularization among the subset endovascular group patients achieving substantial reperfusion (mTICI score of 2b or 3), the primary time interval analyzed was symptom onset to actual substantial reperfusion. Analyses of symptom onset-to-treatment event time intervals always included both direct arrival and transfer patients. Analyses of emer-gency department door-to-treatment event time intervals were confined to direct arrival patients (because transfer patients, having undergone workup at outside facilities, often had paradoxical short emergency department door-to-treatment event and long symptom onset-to-treatment event times.)

All effect size estimates were provided with their 95% CIs; P values were 2-sided with values less than .05 considered statistically significant, without adjustment for multiple comparisons. Statistical analyses were performed in SAS (SAS Institute), version 9.3. Graphical output was obtained from R (R Foundation for Statistical Computing), version 3.2.

RESULTS

The systematic search identified 5 trials enrolling 1287 participants (eTable 1-2 and eFigure 1 in Supplement 2). Data from all patients in all trials were included; across all possible time points and outcomes, data availability was 99.2% (eTable 4 in Supplement 2). Formal assessment of trial quality was high for all 5 trials, although potential sources of bias included blinding of outcome raters but not participants in all and early stopping due to overwhelming efficacy in 4 trials (eTable 5 in Supplement 2).

Overall, 634 participants were assigned to the endovascular group and 653 participants to the medical therapy group. Characteristics of patients in each treatment group and in different time windows are shown in Table 1. The treatment groups were well matched with respect to age, sex, baseline stroke severity, site of target occlusion, and time to randomization (eTable 6 in Supplement 2). Although all trials administered IV tPA to all tPA-eligible patients in both treatment groups, randomized assignment resulted in slightly less frequent IV tPA use in the endovascular group than in the medical therapy group (83% for the endovascular group vs 87% for the medical therapy group, P = .04). The median time from symptom onset to randomization was 196 minutes (IQR, 142- 267; full range, 37-713) (eFigure 2 in Supplement 2).

Endovascular intervention was associated with a substantially lower degree of patient disability at 3 months, with mRS scores of 2.9 (95% CI, 2.7-3.1) in the endovascular group and 3.6 (95% CI, 3.5-3.8) in the medical therapy group. In the endovascular group, the cOR of a less-disabled outcome with thrombectomy was 2.49 (95% CI, 1.76-3.53); absolute risk difference (ARD), 38.1% (P < .001), with earlier treatment associated with greater magnitude of benefit (Table 2, Figure 1, and eTables 7-8 and eFigure 3 in Supplement 2). Considering all mRS disability levels concurrently, increasing delays were associated with higher levels of disability among patients in the endovascular group and there was no change over time in the medical therapy group (Table 2, Figure 1). The degree of benefit from thrombectomy nominally declined with longer times from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96-3.98), ARD forlower disability scores, 39.2%; cORat 6 hours, 1.98 (95% CI, 1.30-3.00), ARD, 30.2%; cOR at

Table 1. Selected Baseline Characteristics of Patients in Participating Trials According to Entry Time Window and by Treatment Group

	Symptom Onset-to-Randomization Time Interval, min				Treatment Group	
	30-120	121-240	241-360	>360	Endovascular Thrombectomy	Medical Therapy
No. of patients[a]	194	657	352	79	634	653
Age, mean (SD), y	68.7 (11.8)	66.5 (12.9)	65.8 (13.5)	64.5 (14.7)	66.3 (13.2)	66.7 (12.9)
Age, No. (%)						
18-79	159 (82)	548 (83.4)	307 (87.7)	68 (86.1)	527 (83.1)	558 (85.8)
≥80	35 (18)	109 (16.6)	43 (12.3)	11 (13.9)	107 (16.9)	92 (14.2)
Women, No. (%)	103 (53.1)	302 (46)	157 (44.7)	42 (53.2)	304 (47.9)	301 (46.2)
Medical history, No. (%)						
Atrial fibrillation	74 (38.1)	198 (30.1)	125 (35.6)	27 (34.2)	209 (33)	215 (33)
Hypertension	124 (63.9)	373 (56.8)	197 (56.1)	46 (58.2)	352 (55.5)	388 (59.5)
Hyperlipidemia	64 (33)	228 (34.7)	120 (34.2)	31 (39.2)	207 (32.6)	236 (36.2)
Diabetes	43 (22.2)	114 (17.4)	50 (14.2)	11 (13.9)	103 (16.2)	115 (17.6)
Prior stroke or TIA	27 (13.9)	78 (11.9)	42 (12)	7 (8.9)	79 (12.5)	76 (11.7)
Prior or current smoker	49 (30.4)	221 (35.4)	116 (34.4)	17 (26.2)	194 (33.2)	210 (34.7)
Baseline glucose, mean (SD), mg/dL	135.9 (90.4)	134.2 (83.5)	131.6 (43.5)	124.2 (31.3)	134.4 (83.6)	131.9 (62.1)
Prestroke mRS, No. (%)[b]						
0	154 (79.4)	532 (81)	297 (84.4)	72 (91.1)	524 (82.6)	533 (81.6)
1	30 (15.5)	92 (14)	36 (10.2)	4 (5.1)	78 (12.3)	84 (12.9)
2	6 (3.1)	19 (2.9)	10 (2.8)	2 (2.5)	20 (3.2)	17 (2.6)
3-5	4 (2.1)	14 (2.1)	9 (2.6)	1 (1.3)	12 (1.9)	19 (2.9)
NIHSS score, mean (SD)[c]	17.2 (5.6)	17 (5.3)	16.5 (5.1)	16.1 (5.5)	16.8 (5.1)	16.8 (5.5)
1-10	25 (13)	87 (13.3)	48 (13.7)	12 (15.4)	74 (11.7)	98 (15.1)
11-15	45 (23.3)	145 (22.1)	86 (24.5)	32 (41)	168 (26.6)	142 (21.9)
16-20	69 (35.8)	253 (38.6)	136 (38.7)	17 (21.8)	237 (37.6)	238 (36.7)
≥21	54 (28)	170 (26)	81 (23.1)	17 (21.8)	152 (24.1)	170 (26.2)
Mode of arrival, No. (%)						
Direct	187 (97.9)	496 (75.5)	133 (37.8)	52 (66.7)	441 (69.8)	428 (66)
Transfer	4 (2.1)	161 (24.5)	219 (62.2)	26 (33.3)	191 (30.2)	220 (34)
Pretreatment IV-tPA, No. (%)	166 (85.6)	585 (89.0)	306 (86.9)	36 (45.6)	526 (83.0)	569 (87.1)
Occlusion location, No. (%)						
ICA	62 (32.1)	141 (21.8)	55 (16.2)	17 (21.8)	133 (21.3)	144 (22.5)
M1 MCA	120 (62.2)	455 (70.2)	259 (76.2)	56 (71.8)	439 (70.5)	452 (70.6)
M2 MCA	11 (5.7)	52 (8)	26 (7.6)	5 (6.4)	51 (8.2)	44 (6.9)
ASPECTS, mean (SD)[d]	9 (1.4)	8.4 (1.7)	7.8 (2)	8.0 (1.6)	8.3 (1.7)	8.3 (1.8)
9-10	143 (75.3)	367 (56.2)	142 (41.2)	33 (45.8)	325 (52.4)	361 (56.1)
7-8	38 (20)	195 (29.9)	133 (38.6)	31 (43.1)	212 (34.2)	188 (29.2)
5-6	5 (2.6)	64 (9.8)	45 (13)	6 (8.3)	58 (9.4)	62 (9.6)
0-4	4 (2.1)	27 (4.1)	25 (7.2)	2 (2.8)	25 (4)	33 (5.1)
Symptom onset-to-randomization time, median (IQR), min	101 (86-112)	176 (148-207)	284 (262-314)	410 (383-525)	196 (142-260)	196 (142-270)

Abbreviations: ASPECTS, Alberta Stroke Program Early Computed Tomography Score; ICA, internal carotid artery; IQR, interquartile range; IV tPA, intravenous tissue plasminogen activator (alteplase); MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischemic attack.

[a] Sum of patients in the time interval columns is 5 fewer than the sum of patients in the treatment group columns because randomization time was not documented in 5 patients. eTable 2 provides further information on data availability for event times and outcomes (Supplement 2).

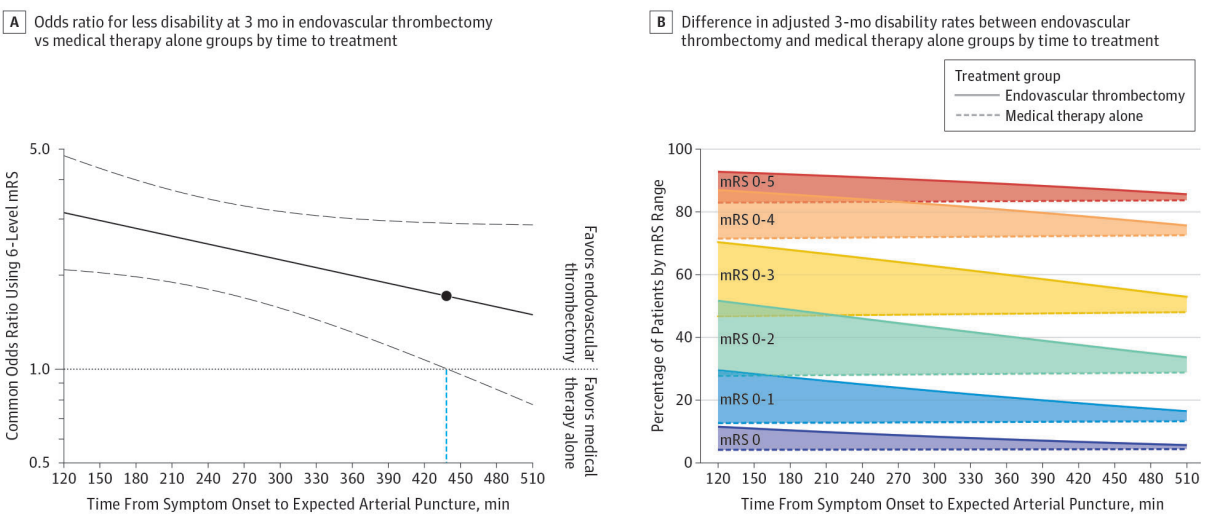
[b] The mRS ranges from 0 to 6, with higher scores indicating greater degree of disability.

[c] NIHSS ranges from 0 to 42, with higher scores indicating more severe neurologic deficits.

[d] ASPECTS ranges from 0 to 10, with higher scores indicating a smaller infarct core.

8 hours, 1.57 (95% CI, 0.86-2.88), ARD, 15.7%. Odds of functional independence (mRS 0-2) similarly declined: OR at 3 hours, 2.83 (95% CI, 2.07-3.86), ARD, 23.9% (95% CI, 12.5%-35.2%); OR at 6 hours, 2.32 (95% CI, 1.56-3.44), ARD, 18.1% (95% CI, 5.7%-30.5%); OR at 8 hours, 2.03 (95% CI, 1.03-3.99), ARD, 14.3% (95% CI, 0.1%- 28.5%). The time at which the lower 95% CI for estimated treatment benefit first crossed 1.0 and was no longer statistically significant was at an symptom onset-to-expected arterial puncture time of 7 hours and 18 minutes (Figure 1).

Figure 1. Association of Time From Symptom Onset to Expected Time of Endovascular Thrombectomy Procedure Start (Arterial Puncture) With Disability Levels at 3 Months in Endovascular (n = 633) vs Medical Therapy (n = 645) Groups



mRS indicates modified Rankin Scale. Time was analyzed as a continuous variable. Data were adjusted for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale), target occlusion location, and concomitant intravenous tissue plasminogen activator. A, The 6-level mRS combined ranks 5 and 6 into a single worst outcome rank. The solid curve indicates the best linear fit between the common odds ratio for improved outcome over the 6-level mRS. The dashed curves indicate 95% CIs. The *P* value for interaction was .07. The lower bound of the 95% CI crosses 1.0 at 438 minutes (vertical blue dashed line). When the 7-level mRS was analyzed, with rank 5 considered a better outcome than rank 6, the lower bound of the 95% CI crossed 1.0 at 418 minutes. B, Upper solid line of each colored band indicates outcome rate in the endovascular thrombectomy group; lower dashed line of each band indicates outcome rate in the medical care only group. The widths of the colored bands indicate the absolute differences between the endovascular thrombectomy and medical therapy groups for that mRS cut point at each time point. Categories are cumulative, so that mRS 0-3 includes all patients with outcomes of mRS 0-3. For example, at the symptom onset to expected arterial puncture time of 300 minutes, the x intercepts indicate outcome rates (mRS 0: 8.3% for the endovascular thrombectomy group vs 4.3% for the medical therapy group; mRS 0-1: 22.9% for the endovascular thrombectomy group vs 12.9% for the medical therapy group; mRS 0-2: 43.1% for the endovascular thrombectomy group vs 28.2% for the medical therapy group; mRS 0-3: 62.7% for the endovascular thrombectomy group vs 47.3% for the medical therapy group; mRS 0-4: 82.4% for the endovascular thrombectomy group vs 72.0% for the medical therapy group; mRS 0-5: 90.0% for the endovascular thrombectomy group vs 83.3% for the medical therapy group).

Table 2. Association of a 1-Hour Treatment Delay With Disability Level, Functional Independence (mRS 0-2), and Mortality at 3 Months in the Endovascular Thrombectomy vs Medical Therapy Groups

	Endovascular Thrombectomy		Medical Therapy		*P* Value for Interaction With Treatment Group
	OR (95% CI) per 1-Hour Delay	ARD, % (95% CI) per 1-Hour Delay[a]	OR (95% CI) per 1-Hour Delay	ARD, % (95% CI) per 1-Hour Delay[a]	
Symptom Onset-to-Randomization Time Interval					
mRS shift[b]	0.88 (0.81 to 0.96)	−4.7	0.98 (0.89 to 1.07)	−0.5	.10
mRS 0-2	0.87 (0.79 to 0.97)	−3.4 (−5.8 to −0.8)	0.92 (0.81 to 1.05)	−1.6 (−3.9 to 1.0)	.49
Mortality	1.11 (0.96 to 1.27)	1.4 (−0.5 to 3.4)	0.88 (0.76 to 1.03)	−1.9 (−3.9 to 0.5)	.03
Symptom Onset-to-Arterial Puncture Time Interval (Expected)[c]					
mRS shift[b]	0.88 (0.80 to 0.96)	−5.3	0.98 (0.89 to 1.08)	−0.5	.07
mRS 0-2	0.87 (0.78 to 0.96)	−3.4 (−6.1 to −1.0)	0.93 (0.82 to 1.06)	−1.4 (−3.7 to 1.2)	.37
Mortality	1.12 (0.97 to 1.30)	1.5 (−0.4 to 3.7)	0.88 (0.76 to 1.02)	−1.9 (−3.9 to 0.5)	.02
Symptom Onset-to-Reperfusion Time Interval (Expected)[d]					
mRS shift[b]	0.87 (0.79 to 0.95)	−6.1	0.99 (0.90 to 1.09)	−0.4	.046
mRS 0-2	0.85 (0.77 to 0.95)	−4.0 (−6.4 to −1.3)	0.94 (0.83 to 1.06)	−1.2 (−3.5 to 1.2)	.25
Mortality	1.16 (1.01 to 1.32)	2.0 (0.1 to 4.0)	0.88 (0.76 to 1.02)	−1.9 (−3.9 to 0.5)	.048
Symptom Onset-to-ED Arrival Time Interval					
mRS shift[b]	1.01 (0.93 to 1.09)	0	0.99 (0.91 to 1.08)	0	.79
mRS 0-2	1.00 (0.93 to 1.08)	0.0 (−1.8 to 1.9)	0.95 (0.81 to 1.10)	−1.0 (−3.9 to 1.9)	.52
Mortality	1.01 (0.88 to 1.16)	0.1 (−1.6 to 2.0)	0.90 (0.78 to 1.03)	−1.6 (−3.5 to 0.4)	.21
ED Arrival-to-Randomization Time Interval					
mRS shift[b]	0.56 (0.46 to 0.68)	−16.2	0.97 (0.81 to 1.16)	−1.2	<.001
mRS 0-2	0.55 (0.43 to 0.71)	−14.1 (−19.2 to −8.3)	0.96 (0.75 to 1.24)	−0.8 (−5.2 to 4.4)	.002
Mortality	1.42 (1.08 to 1.88)	5.1 (1.0 to 10.1)	0.95 (0.72 to 1.26)	−0.8 (−4.5 to 3.8)	.049
ED Arrival-to-Arterial Puncture Time Interval (Expected)[e]					
mRS shift[b]	0.56 (0.47 to 0.67)	−16.8	0.98 (0.82 to 1.16)	−1.2	<.001
mRS 0-2	0.55 (0.43 to 0.71)	−14.1 (−19.2 to −8.3)	0.94 (0.74 to 1.19)	−1.2 (−5.4 to 3.5)	.001
Mortality	1.44 (1.11 to 1.87)	5.4 (1.4 to 10.0)	0.98 (0.75 to 1.27)	−0.3 (−4.0 to 3.8)	.03
ED Arrival-to-Reperfusion Time Interval (Expected)[f]					
mRS shift[b]	0.57 (0.48 to 0.67)	−16.7	0.95 (0.80 to 1.12)	−2.2	<.001
mRS 0-2	0.56 (0.45 to 0.70)	−13.7 (−18.2 to −8.6)	0.91 (0.73 to 1.13)	−1.8 (−5.7 to 2.4)	.001
Mortality	0.91 (0.88 to 0.93)	−1.2 (−1.6 to −0.9)	1.06 (0.84 to 1.33)	0.9 (−2.5 to 4.8)	.02

Abbreviations: ARD, absolute risk difference; ED, emergency department; mRS, modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction; OR, odds ratio.

[a] Absolute risk difference (negative values indicate lower absolute rate with later therapy; positive values indicate higher absolute rate with later therapy).

[b] mRS shift: common OR over 6 levels of the 7-level modified Rankin Scale (with mRS strata 5 and 6 as the worst outcome level).

[c] Derived by adding to the actual symptom onset-to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated. Arterial puncture is considered procedure start.

[d] Derived by adding to the actual symptom onset-to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to substantial reperfusion (mTICI score of 2b or 3) of the trial in which they participated.

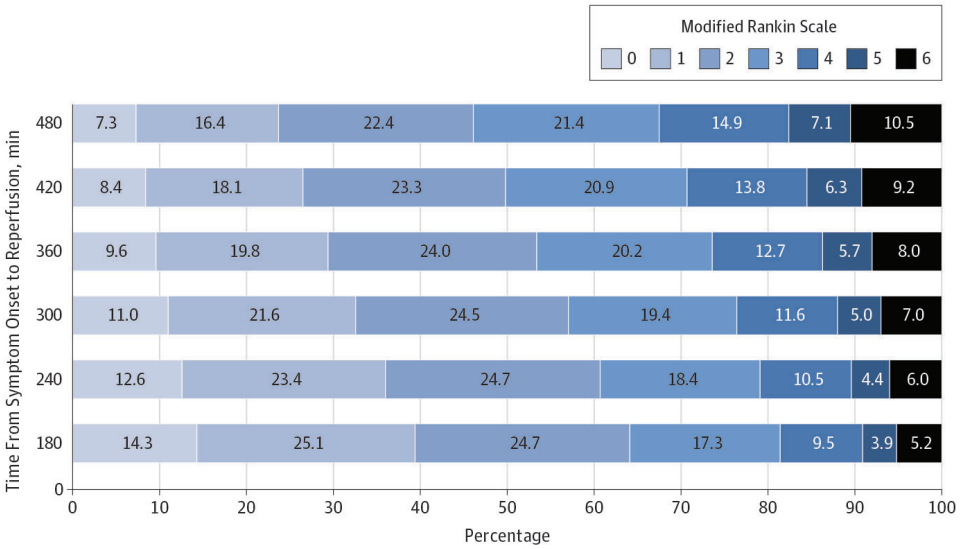
[e] Derived by adding to the actual ED arrival-to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated.

[f] Derived by adding to the actual ED arrival-to-randomization value for each patient in both the endovascular and medical groups, the study mean for the time from randomization to substantial reperfusion (mTICI score of 2b or 3) of the trial in which they participated.

Treatment effect was not significantly modified by the symptom onset-to-emergency department arrival time interval. However, pronounced treatment effect modification was observed with time intervals beginning from emergency-department arrival (Table 2). Excellent outcome (mRS 0-1), symptomatic hemorrhage, and major parenchymal hematoma did not show interactions of time with treatment group (eTable 9 and eFigure 4 in Supplement 2).

Among the 634 patients randomized to the endovascular group, arterial puncture was

Figure 2. Association of Time From Symptom Onset to Actual Reperfusion Among Patients in the Endovascular Thrombectomy Group Achieving Substantial Reperfusion With 90-Day Disability Outcomes Using an Adjusted Ordinal Logistic Regression Model



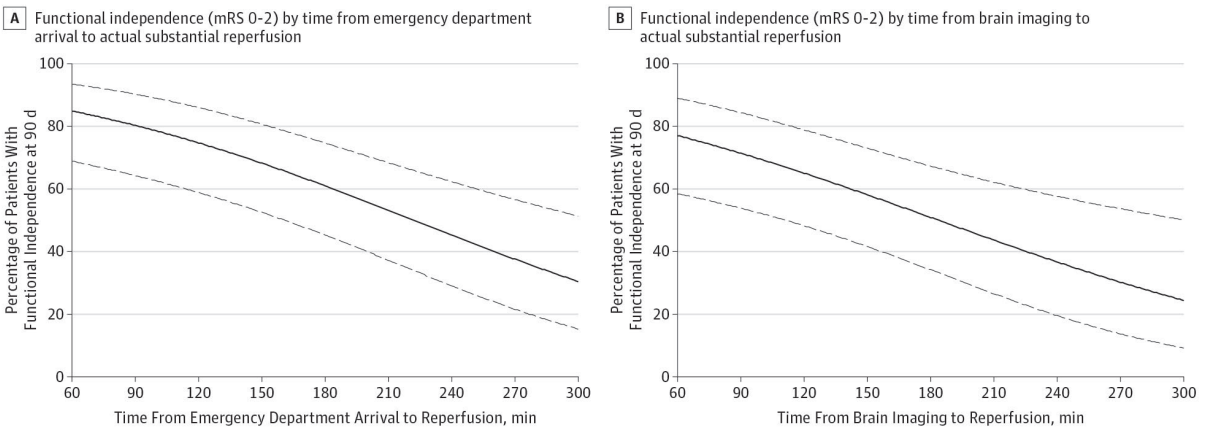
Data are from the 390 endovascular group patients in whom substantial reperfusion (modified Thrombolysis in Cerebral Infarction score of 2b or 3) was achieved. Rows are intercepts from a single model using all 390 patients, treating time as a continuous variable. Model adjusted for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale), target occlusion location, and concomitant intravenous tissue plasminogen activator.

performed in 607 (95.7%) and thrombectomy intervention in 563 (88.8%). The most common reason for nonintervention was interval resolution of target occlusion (eTable 10 in Supplement 2). Among the 549 patients who underwent an endovascular thrombectomy intervention and had resulting mTICI scores documented, substantial reperfusion was achieved in 390 (71.0%). Among the 607 patients who had an arterial access puncture, the median time from symptom onset to arterial puncture was 238 minutes (IQR, 180-302) and from symptom onset to reperfusion 301 minutes (IQR, 226-384) (eFigure 2 in Supplement 2).

Among the endovascular group patients in whom substantial reperfusion was achieved, delay in symptom symptom onset-to-reperfusion times was associated with increased

levels of 3-month disability (Figure 2; eTable 11 and eFigure 5 in Supplement 2). Considering outcome distributions across all mRS health states, for every 9-minute delay in symptom symptom onset-to-substantial endovascular reperfusion time, 1 of every 100 treated patients had a worse disability outcome (higher score by 1 or more levels on the mRS). The probability of functional independence (mRS 0-2) at 3 months declined from 64.1% with symptom onset- to-reperfusion time of 180 minutes to 46.1% with symptom onset-to-reperfusion time of 480 minutes (Figure 2). The associations of time delay with poorer outcomes were magnified in the time segment from emergency department arrival through reperfusion (Table 2; eFigure 6 in Supplement 2). Considering outcome distributions across all mRS health states, for every 4-minute delay in emergency department door-to-reperfusion time, 1 of every 100 treated patients had a worse disability outcome (eTable 12 in Supplement 2). Among direct arrival patients, functional independence at 3 months was more frequent both with faster emergency department door-to-reperfusion and brain imaging-to-reperfusion times (Figure 3). Rates of mortality, symptomatic intracranial hem-orrhage, and major parenchymal hematoma did not significantly change with longer delay to reperfusion (eTable 13 in Supplement 2).

Figure 3. Relation Between In-Hospital Treatment Speeds and Functional Independence (mRS 0-2) at 3 Months Among Direct Arrival Patients in the Endovascular Thrombectomy Group Achieving Substantial Reperfusion (mTICI score, 2b or 3)



mRS indicates modified Rankin Scale; mTICI, modified Thrombolysis in Cerebral Infarction. Data are from the 390 endovascular group patients in whom substantial reperfusion (mTICI score, 2b or 3) was achieved. Curves were obtained from logistic regression of outcome on time as a continuous variable, after adjustment for age, sex, baseline stroke severity (National Institutes of Health Stroke Scale), target occlusion location, and concomitant intravenous tissue plasminogen activator. Solid curves indicate point estimates. Dashed curves indicate 95% CIs. Substantial reperfusion was defined as mTICI score of 2b or 3 flow at the end of intervention.

Rates of functional independence at 3 months declined with delay in symptom onset-to-reperfusion time in a parallel manner in 6 of the 7 analyzed subgroups: age, baseline stroke severity, clot location, initial extent of cerebral infarction (ASPECTS), patient arrival directly or by transfer, and time from symptom onset to IV tPA start (eFigure 7 in Supplement 2). In contrast, rates of independent outcome declined more steeply in patients treated with IV tPA vs tPA-ineligible patients (7.4% per hour [95% CI, 3.8% to 10.9%] for patients treated with IV tPA vs 3.4% [95% CI, -0.5% to 7.3%] for tPA-ineligible patients, P = .047).

Workflow time intervals differed between direct arrival patients and transfer patients (eTable 11 and eFigure 8 in Supplement 2). Transfer patients had faster processes of care at the endovascular hospital than direct arrival patients, with emergency department door-to-arterial puncture times of 81 minutes (IQR, 58-105) for transfer patients vs 116 minutes (IQR, 83-160) for direct arrival patients, P < .001. But the longer symptom onset to arrival times (207 minutes [IQR, 160-256] for transfer patients vs 65 minutes [IQR, 44-116] for direct arrival patients, P < .001) resulted in overall longer symptom onset-to-randomization intervals (260 minutes [IQR, 215-310] for transfer patients vs 165 minutes [IQR, 125-226] for direct arrival patients, P < .001). Considering all endovascular group patients, high proportions (62%-81%) were treated within the time intervals recommended by multispecialty guidelines in effect at the time of study conduct,[20] but low proportions (4%-13%) were treated within more recently promulgated "ideal" target intervals (eTable 14 in Supplement 2).[21]

DISCUSSION

This study provides additional evidence regarding the association between treatment time and the benefit of endovascular reperfusion. Compared with best medical therapy alone, endovascular thrombectomy therapy was associated with improved outcomes when procedure start (arterial puncture) could be performed within the first 7.3 hours after symptom onset among patients meeting the brain imaging entry criteria for inclusion in these randomized trials. Moreover, within this period, functional outcomes were better the sooner after symptom onset that endovascular reperfusion was achieved, emphasizing the importance of programs to enhance patient awareness, out-of-hospital care, and in-hospital management to shorten symptom onset-to-treatment times.

The magnitude of the association between time to treatment and outcome was clinically meaningful. Based on the current study, and assuming the findings are generalizable to the population of patients with acute ischemic stroke due to large-vessel occlusion, among every 1000 patients achieving substantial endovascular reperfusion, for every 15-minute faster emergency department door-to-reperfusion time, an estimated 39 patients would have a less-disabled outcome at 3 months, including 25 more who would achieve functional independence (mRS 0-2). The findings that in-hospital processes of care are directly associated with improved functional outcome is noteworthy. In addition to faster time from emergency department door to reperfusion, faster time from brain imaging to reperfusion was associated with better 3-month functional outcomes. These findings are largely consistent with those of prior endovascular intervention observational cohorts and trials[22-24] and of studies of intravenous thrombolysis.[25,26]

Use of brain imaging to exclude patients with a large core of permanently infarcted brain tissue in the trials in this pooled analysis may have influenced the strength of the association between symptom onset-to-randomization and symptom onset-to-reperfusion times and outcomes. Four of the 5 trials formally excluded patients with large ischemic cores evident on initial brain imaging from study participation.[2-5] The fifth trial required investigator and treating physician uncertainty regarding patient potential to benefit from therapy,[1] which may have resulted in informal exclusion of some patients with large cores.

In the current study, patients with moderate infarct core volumes (ASPECT score, 7-8) had a shallower decline in benefit with longer symptom onset-to-reperfusion than patients with minor infarct core volumes (ASPECT score, 9-10). The exclusion of patients with even larger cores from the trials likely attenuated the relationship between symptom onset-to-reperfusion time and frequency of good functional outcomes. Similarly, in a population with more patients with large, already-established infarcts, symptom onset-to-reperfusion time would likely have greater association with mortality than in the trials pooled in this study.[24]

A time-by-treatment group interaction was observed for the interval from emergency department arrival to randomization, but not from symptom onset to emergency department arrival. There are several possible reasons the stronger association of time intervals after arrival with outcome. One is the application of study entry criteria after emergency department arrival. By eliminating patients with clinical features that indicated a very mild ischemic injury, and clinical and brain imaging features that indicated an advanced and extensive injury, the entry criteria likely filtered out patients who experienced very slow or very fast progression during the symptom onset-to-emergency department door period. A second likely source is differential reliability of documented times for stroke onset vs emergency department arrival. Time of emergency department arrival is generally accurately documented in patient medical records. In contrast, the time of stroke onset (last known well) is often imprecisely determined or documented.[27] In some patients, symptom onset occurs during sleep and the actual symptom onset time is not known. In others, the neurologic deficit may render the patient unable to accurately observe or report the time of symptom onset. A third possibility is physiological. Human cerebral ischemic injury may follow an exponential or sigmoid growth trajectory, with more rapid progression at intermediate after-symptom onset times than early after-symptom onset times. Available human serial brain imaging studies have not strongly suggested that the infarct growth curve has a sigmoid shape but have been relatively small and underpowered.[28,29]

Patient characteristics also were related to the association of symptom onset-to-reperfusion time with outcomes. At all symptom onset-to-reperfusion times, absolute rates of functional independence at 3 months were higher for patients younger than 80 years than those 80 years and older, although both declined at a similar pace with longer treatment intervals. Absolute rates were also higher at all time points (with parallel declines

with longer symptom onset-to-reperfusion time) for patients with moderate-presenting neurologic deficits (NIHSS score, 10-19) compared with severe (NIHSS score, ≥20). In contrast, although longer symptom onset-to-reperfusion times were associated with a lower frequency of functional independence for M1 MCA occlusions, these longer times tended not to be associated with functional independence rates for ICA occlusions. ICA occlusions had relatively modest rates of functional independence at all analyzed symptom onset-to-reperfusion intervals. Potentially, patients with ICA occlusions who were prone to rapid infarct progression were excluded from the studies by the requirement for small or moderate core infarct size at entry. Patients receiving IV tPA had steeper declines in functional independence with longer symptom onset-to-reperfusion times than tPA-ineligible patients. These findings may reflect that the comorbidities constituting contraindications to tPA in the tPA-ineligible patients limited their ability to achieve high functional independence rates, even when reperfusion occurred early.

The results of this study reinforce guideline recommendations to pursue endovascular treatment when arterial puncture can be initiated within 6 hours of symptom onset,[7-9] and provide evidence that potentially supports strengthening of recommendations for treatment from 6 through 7.3 hours after symptom onset. Although point estimates suggested that benefit may continue to accrue up to and beyond 8 hours, there were insufficient numbers of patients in the extended time window to provide firm insights. These observations underline the importance of enrollment of brain imaging-selected patients in ongoing randomized trials evaluating endovascular reperfusion patients in longer time windows (NCT02142283, NCT02586415).

The findings also provide data useful for the refinement of guidelines on speed-of-care processes in patients undergoing endovascular reperfusion. The process time intervals in the pooled trial data set fall between the extremely lenient current multispecialty recommendations and extremely stringent ideal recommendations.[20,21] These time windows represent a good foundation upon which to further improve in practice as centers become proficient at routinely performing endovascular therapies and the need to obtain research informed consent is no longer present. For continuous quality improvement programs, reasonable time targets for care processes might be those near the best 25th percentile in the pooled trial database, which would include 50 minutes for brain imaging-to-arterial puncture time, 75 minutes for emergency department door-to-arterial puncture time, and

110 minutes for emergency department door-to-reperfusion time.

Several potential limitations should be considered in interpreting the results of this study. First, differences in entry criteria and patient characteristics among the trials is a source of potential bias; random-effects models were used to mitigate potential confounding. Second, several different time intervals in the delivery of endovascular thrombectomy are potentially relevant when analyzing treatment delay and treatment group interaction, including symptom onset to randomization, symptom onset to expected procedure start, and symptom onset to expected reperfusion. The primary analysis used the time interval that is the focus of national guideline recommendations, symptom onset to expected arterial puncture, and results for other intervals were also analyzed.[7-9] Third, functional outcomes were assessed at 3 months. Some further improvement may occur subsequently, especially among patients with more severe strokes. However, studies have shown that functional status at 3 months correlates well with functional status at 1 year.[30] Fourth, the definition of symptomatic intracranial hemorrhage varied in minor ways across studies; to mitigate this, a uniform radiologic variable was also examined-major parenchymal hematoma. Fifth, the results of this study are not generalizable to patients who would not meet the entry criteria of the component trials. However, the pooled patients were treated at many centers in multiple countries on 4 continents, suggesting wide applicability.

CONCLUSIONS

In this individual patient data meta-analysis of 5 randomized clinical trials of patients with large-vessel ischemic stroke, earlier treatment with endovascular thrombectomy + medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months. Benefit was greatest with time from symptom onset to arterial puncture for thrombectomy of under 2 hours and became nonsignificant after 7.3 hours.

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Supplementary Appendix

eTable 1. PubMed Search Strategy (Adapted from Lambrinos A et al.[1])

1. exp Brain Ischemia/ (198337)
2. ((isch?emi* adj3 (stroke* or apoplex* or cerebr* or brain or encephalopath* or neur*)) or AIS).tw. (198076)
3. exp Stroke/ (189703)
4. (stroke* adj3 (acute or cerebr* or attack* or accident* or lacunar or cardioembol*)).tw. (76907)
5. Intracranial Arteriosclerosis/ (10347)
6. exp "Intracranial Embolism and Thrombosis"/ (367169)
7. Carotid Artery Thrombosis/ (5356)
8. ((occlus* or block* or infarct* or clot* or termination) adj6 (carotid or cerebr* or MCA or ACA)).tw.(96218)
9. or/1-8 (786703)
10. exp Thrombectomy/ (15008)
11. Embolectomy/ (4255)
12. ((Mechanical adj3 (thromb* or embol* or clot disruption* or clot retrieval*)) or ((clot* or thromb* or embol*) adj3 (retriev* or disruption* or fragmentation)) or ((stent* or stent-assisted) adj3 retriev*) or stentriever*).tw. (9056)
13. ((Merci or Trevo or Penumbra or Solitaire) adj3 (retriever* or system* or device*)).mp. (1233)
14. or/10-13 (24914)
15. 9 and 14 (14515)
16. exp Animals/ not (exp Animals/ and Humans/) (8045601)
17. 15 not 16 (14213)
18. (case reports or congresses).pt. (1780093)
19. 17 not 18 (13866)
20. limit 19 to english language [Limit not valid in CDSR,DARE; records were retained] (12321)
21. limit 20 to yr="2005 -Current" [Limit not valid in DARE; records were retained] (9737)
22. 21 use pmoz,cctr,coch,dare,clhta,cleed (970)
23. exp Brain Ischemia/ (198337)
24. ((isch?emi* adj3 (stroke* or apoplex* or cerebr* or brain or encephalopath* or

neur*)) or AIS).tw. (198076)
25. exp Cerebrovascular Accident/ (189703)
26. Stroke Patient/ (13478)
27. (stroke* adj3 (acute or cerebr* or attack* or accident* or lacunar or cardioembolic)).tw. (76838)
28. exp Occlusive Cerebrovascular Disease/ (26483)
29. exp Carotid Artery Obstruction/ (25862)
30. Brain Embolism/ (8515)
31. ((occlus* or block* or infarct* or clot* or termination) adj6 (carotid or cerebr* or MCA or ACA)).tw. (96218)
32. or/23-31 (478286)
33. Mechanical Thrombectomy/ (1828)
34. © 2016 American Medical Association. All rights reserved.
35. Thrombectomy/ (10732)
36. Embolectomy/ (4255) ((Mechanical adj3 (thromb* or embol* or clot disruption* or clot retrieval*)) or ((clot* or thromb* or embol*) adj3 (retriev* or disruption* or fragmentation)) or ((stent* or stent-assisted) adj3 retriev*) or stentriever*).tw. (9056)
37. ((Merci or Trevo or Penumbra or Solitaire) adj3 (retriever* or system* or device*)).mp. (1233)
38. or/33-37 (22583)
39. 32 and 38 (4742)
40. exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (38090949)
41. exp humans/ or exp human experimentation/ or exp human experiment/ (29700691)
42. 40 not 41 (8416467)
43. 39 not 42 (4642)
44. case report/ or conference abstract.pt. (5381946)
45. 43 not 44 (2728)
46. limit 45 to english language [Limit not valid in CDSR,DARE; records were retained] (2466)
47. limit 46 to yr=”2005 -Current” [Limit not valid in DARE; records were retained] (2248)
48. 47 use emez (1362)
49. 22 or 48 (2332)
50. remove duplicates from 49 (1624)

eTable 2: Patient Characteristics by Trial

	Study				
	MR CLEAN 2015[2]	**ESCAPE 2015[3]**	**EXTEND-IA 2015[4]**	**REVASCAT 2015[5]**	**SWIFT PRIME 2015[6]**
N	500	315	70	207	195
Age (years), mean (SD)	64.9 (13.8)	69 (14)	69.4 (12)	66.5 (10.5)	65.6 (11.9)
Age 18-79	430 (86%)	230 (73%)	55 (78.6%)	195 (94.7%)	175 (90.7%)
Age 80+	70 (14%)	85 (27%)	15 (21.4%)	11 (5.3%)	18 (9.3%)
Female	208 (41.6%)	165 (52.4%)	36 (51.4%)	97 (47.1%)	99 (51%)
Medical history					
Atrial fibrillation	135 (27%)	121 (38.4%)	23 (32.9%)	72 (35%)	73 (37.4%)
Hypertension	227 (45.4%)	213 (67.6%)	44 (62.9%)	134 (65%)	122 (62.6%)
Hyperlipidemia	129 (25.8%)	124 (39.4%)	28 (40%)	116 (56.3%)	46 (23.6%)
Diabetes	68 (13.6%)	72 (22.9%)	10 (14.3%)	41 (19.9%)	27 (13.8%)
Prior stroke or TIA	54 (10.8%)	49 (15.6%)	10 (14.3%)	30 (14.6%)	12 (6.2%)
Prior or current smoking	143 (28.6%)	65 (29%)	29 (41.4%)	87 (42%)	80 (42.3%)
Baseline glucose, mean (SD)	137.6 (104.2)	129.2 (45.9)	132.8 (56)	130.1 (34.1)	131.2 (46.5)
Prestroke mRS					
0	404 (80.8%)	262 (83.2%)	63 (90%)	169 (81.6%)	159 (81.5%)
1	50 (10%)	39 (12.4%)	7 (10%)	36 (17.4%)	30 (15.4%)
2	25 (5%)	8 (2.5%)	0 (0%)	1 (0.5%)	3 (1.5%)
3-5	21 (4.2%)	6 (1.9%)	0 (0%)	1 (0.5%)	3 (1.5%)
NIHSS at baseline Mean (SD)	17.6 (5.6)	16.5 (5.5)	15.2 (5.6)	16.3 (4.6)	16.6 (4.6)
NIHSS 1-10	57 (11.4%)	51 (16.4%)	16 (22.9%)	26 (12.6%)	22 (11.5%)
NIHSS 11-15	107 (21.4%)	80 (25.7%)	20 (28.6%)	51 (24.8%)	52 (27.1%)
NIHSS 16-20	176 (35.2%)	111 (35.7%)	21 (30%)	89 (43.2%)	78 (40.6%)

	Study				
	MR CLEAN 2015[2]	ESCAPE 2015[3]	EXTEND-IA 2015[4]	REVASCAT 2015[5]	SWIFT PRIME 2015[6]
NIHSS 21+	160 (32%)	69 (22.2%)	13 (18.6%)	40 (19.4%)	40 (20.8%)
Mode of arrival					
Direct	279 (55.8%)	258 (83%)	65 (92.9%)	141 (68.1%)	126 (65.6%)
Transfer	221 (44.2%)	53 (17%)	5 (7.1%)	66 (31.9%)	66 (34.4%)
Pretreatment IV-tPA	89% (445)	238 (75.6%)	70 (100%)	150 (72.5%)	98.5% (192)
Occlusion location					
ICA	138 (27.8%)	84 (27.2%)	22 (31.4%)	1 (0.5%)	32 (17.3%)
M1 MCA	319 (64.3%)	216 (69.9%)	38 (54.3%)	184 (90.6%)	134 (72.4%)
M2 MCA	39 (7.9%)	9 (2.9%)	10 (14.3%)	18 (8.9%)	19 (10.3%)
ASPECTS at baseline Mean (SD)	8.3 (1.9)	8.6 (1.5)	9.2 (0.9)	7.3 (2)	8.4 (1.4)
9-10	284 (57.3%)	185 (60.1%)	55 (78.6%)	57 (29.1%)	105 (54.1%)
7-8	137 (27.6%)	102 (33.1%)	14 (20%)	78 (39.8%)	69 (35.6%)
5-6	45 (9.1%)	15 (4.9%)	1 (1.4%)	42 (21.4%)	17 (8.8%)
0-4	30 (6%)	6 (1.9%)	0 (0%)	19 (9.7%)	3 (1.5%)
Symptom onset to randomization					
Mean (SD), mins	209.1 (71.8)	222 (142.6)	177.7 (53.6)	236.6 (87.9)	199.3 (76.1)
30-120m	50 (25.8%)	84 (43.3%)	10 (5.2%)	17 (8.8%)	33 (17.0%)
121-240m	286 (43.5%)	126 (19.2%)	48 (7.3%)	101 (15.4%)	96 (14.6%)
241-360m	153 (43.5%)	56 (15.9%)	12 (3.4%)	69 (19.6%)	62 (17.6%)
>360m	9 (11.4%)	49 (62.0%)	0 (0.0%)	20 (25.3%)	1 (1.3%)

TIA: transient ischemic attack. mRS: modified Rankin Scale, range from 0 to 6, with higher scores indicating greater degree of disability. NIHSS: National Institutes of Health Stroke Scale, range from 0 to 42, with higher scores indicating more severe neurologic deficits. ASPECTS: The Alberta Stroke Program Early CT Score, range from 0 to 10, with higher scores indicating a smaller infarct core. IV-tPA: intravenous tissue plasminogen activator (alteplase). ICA = internal carotid artery. MCA = middle cerebral artery. IQR = interquartile range. SD = standard deviation

eTable 3: Unadjusted Functional and Imaging Outcomes According to Treatment Group by Trial

	MR CLEAN 2015[2]		ESCAPE 2015[3]		EXTEND-IA 2015[4]		REVASCAT 2015[5]		SWIFT PRIME 2015[6]	
	Endovascular Group	Medical Group	Endovascular Group	Medical Group	Endovascular Group	Medical Group	Endovascular Group	Medical Group	Endovascular Group	Medical Group
mRS at 90d										
0	6 (2.6%)	1 (0.4%)	24 (14.6%)	11 (7.5%)	9 (25.7%)	6 (17.1%)	7 (6.8%)	6 (5.8%)	17 (17.3%)	8 (8.6%)
1	21 (9%)	15 (5.6%)	34 (20.7%)	15 (10.2%)	9 (25.7%)	4 (11.4%)	18 (17.5%)	7 (6.8%)	25 (25.5%)	10 (10.8%)
2	48 (20.6%)	36 (13.5%)	29 (17.7%)	17 (11.6%)	7 (20%)	4 (11.4%)	20 (19.4%)	16 (15.5%)	17 (17.3%)	15 (16.1%)
3	43 (18.5%)	44 (16.5%)	27 (16.5%)	22 (15%)	6 (17.1%)	4 (11.4%)	19 (18.4%)	20 (19.4%)	12 (12.2%)	16 (17.2%)
4	53 (22.7%)	80 (30%)	22 (13.4%)	36 (24.5%)	1 (2.9%)	6 (17.1%)	8 (7.8%)	17 (16.5%)	15 (15.3%)	20 (21.5%)
5	13 (5.6%)	32 (12%)	11 (6.7%)	18 (12.2%)	0 (0%)	4 (11.4%)	12 (11.7%)	21 (20.4%)	3 (3.1%)	12 (12.9%)
6	49 (21%)	59 (22.1%)	17 (10.4%)	28 (19%)	3 (8.6%)	7 (20%)	19 (18.4%)	16 (15.5%)	9 (9.2%)	12 (12.9%)
Functional Independence (mRS 0-2) at 90d	75 (32.2%)	52 (19.5%)	87 (53%)	43 (29.3%)	25 (71.4%)	14 (40%)	45 (43.7%)	29 (28.2%)	59 (60.2%)	33 (35.5%)
Freedom from Disability (mRS 0-1) at 90d	27 (11.6%)	16 (6%)	58 (35.4%)	26 (17.7%)	18 (51.4%)	10 (28.6%)	25 (24.3%)	13 (12.6%)	42 (42.9%)	18 (19.4%)
Mortality	49 (21%)	59 (22.1%)	17 (10.4%)	28 (19%)	3 (8.6%)	7 (20%)	19 (18.4%)	16 (15.4%)	9 (9.2%)	12 (12.9%)
SICH	18 (7.7%)	17 (6.4%)	6 (3.6%)	4 (2.7%)	0 (0%)	2 (5.7%)	4 (3.9%)	2 (1.9%)	0 (0%)	3 (3.1%)
PH2	18 (7.9%)	21 (8.2%)	4 (2.4%)	3 (2%)	3 (8.6%)	3 (8.6%)	3 (2.9%)	2 (1.9%)	4 (4.1%)	5 (5.2%)

mRS: modified Rankin Scale, range from 0 to 6, with higher scores indicating greater degree of disability. SICH: symptomatic intracranial hemorrhage. PH2: Parenchymal hematoma type 2

eTable 4. Availability of Data for Times and Outcomes

	Endovascular Group n/N (percent)	**Medical Group** n/N (percent)
Times		
Onset (last known well)	634/634 (100.0%)	650/653 (99.5%)
ED Arrival	625/634 (98.6%)	639/653 (97.9%)
Randomization	632/634 (99.7%)	650/653 (99.5%)
Arterial Puncture	607/611 (99.3%)	N/A
Reperfusion	385/390 (98.7%)	N/A
Outcomes		
mRS at 90d	633/634 (99.8%)	645/653 (98.8%)
Vital Status at 90d	633/634 (99.8%)	646/653 (98.9%)
Symptomatic Intracranial Hemorrhage Status	634/634 (100.0%)	653/653 (100.0%)
Parenchymal Hematoma Type 2 Status	629/634 (99.2%)	641/653 (98.2%)

mRS: modified Rankin Scale, range from 0 to 6, with higher scores indicating greater degree of disability. ED: Emergency Department. N/A: Not applicable. Symptomatic intracranial hemorrhage was defined using each study's definition applied to that study's cases.

eTable 5. Risk of Bias Assessed Using the GRADE Guideline[7]

Domain	Feature Reducing Risk of Bias	MR CLEAN 2015[2]	ESCAPE 2015[3]	EXTEND-IA 2015[4]	REVASCAT 2015[5]	SWIFT PRIME 2015[6]
Allocation Concealment Pre-Randomization	Those enrolling patients are unaware of the group to which next patient will be allocated	+	+	+	+	+
Blinding	Patient/Caregiver	--	--	--	--	--
	Outcome Assessor	+	+	+	+	+
	Data Analyst	+	+	+	+	+
Data Completeness	Low loss to follow-up	+	+	+	+	+
	Use of intention-to-treat principle	+	+	+	+	+
Outcome Reporting	Reporting of outcomes regardless of results	+	+	+	+	+
Other	Full enrollment (not stopped early for benefit)	+	--	--	--	--
	Use of validated outcome measures	+	+	+	+	+
	No carryover effects	+	+	+	+	+
	Randomization at individual participant level	+	+	+	+	+

GRADE: Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.
+: Feature present. --: Feature absent.

eTable 6. Collinearity of Prognostic Variables

Characteristic	Age	Sex	NIHSS	ASPECTS	Clot location	IV tPA given	Onset to randomization	Onset to reperfusion
Age	--	-0.12*	0.10*	0.17*	0.02	-0.07*	-0.07*	-0.09
Sex		--	0.04	-0.06*	-0.02	0.02	0.03	-0.01
NIHSS			--	-0.16*	-0.09*	-0.01	-0.06*	-0.07
ASPECTS				--	-0.03	0.03	-0.28*	-0.23*
Clot location					--	-0.04	0.07*	-0.01
IV tPA given						--	-0.13*	-0.24

The table shows Spearman's rho as a measure of correlation among the covariates prespecified for inclusion in adjusted models: age (a linear variable), sex (binary variable), baseline stroke severity (National Institutes of Health Stroke Scale [NIHSS] score), target occlusion location [a three-level categorical variable – internal carotid artery (ICA), M1 middle cerebral artery (MCA), M2 MCA], entry Alberta Stroke Program Early CT Score (ASPECTS, linear variable), and pretreatment intravenous (IV) tissue plasminogen activator (tPA, alteplase) (binary variable), along with key time variables. *Asterisk indicates correlations that are statistically significant. Several correlations were noted, but the magnitude of these was modest, with none reaching a magnitude of 0.30.

eTable 7. Unadjusted Rates of Functional and Imaging Outcomes According to Treatment Group and Category of Onset to Expected Treatment Start Time

	30-120m		121-240m		241-360m		>360m	
	Endovascular Group	Medical Group	Endovascular Group	Medical Group	Endovascular Group	Medical Group	Endovascular Group	Medical Group
mRS at 90d								
0	12 (12.2%)	7 (7.4%)	34 (10.2%)	15 (4.6%)	12 (7.7%)	7 (3.6%)	5 (10.9%)	3 (9.7%)
1	26 (26.5%)	14 (14.9%)	57 (17.2%)	18 (5.5%)	17 (11.0%)	16 (8.2%)	7 (15.2%)	3 (9.7%)
2	19 (19.4%)	9 (9.6%)	57 (17.2%)	49 (15.1%)	35 (22.6%)	28 (14.4%)	8 (17.4%)	2 (6.5%)
3	11 (11.2%)	11 (11.7%)	58 (17.5%)	62 (19.1%)	30 (19.4%)	30 (15.5%)	8 (17.4%)	3 (9.7%)
4	19 (19.4%)	22 (23.4%)	52 (15.7%)	69 (21.2%)	23 (14.8%)	59 (30.4%)	5 (10.9%)	9 (29.0%)
5	3 (3.1%)	15 (16.0%)	19 (5.7%)	42 (12.9%)	12 (7.7%)	22 (11.3%)	5 (10.9%)	8 (25.8%)
6	8 (8.2%)	16 (17.0%)	55 (16.6%)	70 (21.5%)	26 (16.8%)	32 (16.5%)	8 (17.4%)	3 (9.7%)
Functional Independence (mRS 0-2) at 90d	57 (58.2%)	30 (31.9%)	148 (44.6%)	82 (25.2%)	64 (41.3%)	51 (26.3%)	20 (43.5%)	8 (25.8%)
Freedom from Disability (mRS 0-1) at 90d	38 (38.8%)	21 (22.3%)	91 (27.4%)	33 (10.2%)	29 (18.7%)	23 (11.9%)	12 (26.1%)	6 (19.4%)
Mortality	8 (8.2%)	16 (17.0%)	55 (16.6%)	70 (21.5%)	26 (16.8%)	32 (16.4%)	8 (17.4%)	3 (9.7%)
SICH	4 (4.0%)	1 (1.1%)	14 (4.2%)	19 (5.8%)	10 (6.5%)	8 (4.1%)	0 (0.0%)	0 (0.0%)
PH2	2 (2.0%)	0 (0.0%)	17 (5.2%)	21 (6.6%)	11 (7.1%)	13 (6.8%)	2 (4.3%)	0 (0.0%)

mRS: modified Rankin Scale, range from 0 to 6, with higher scores indicating greater degree of disability. SICH: symptomatic intracranial hemorrhage. PH2: Parenchymal hematoma type 2

eTable 8. Association of Treatment Delay with Odds of Improved Disability Outcome with Endovascular compared with Medical Therapy

Time from Symptom Onset to Arterial Puncture (expected)*	cOR**	95% CI
120 min	3.13	(2.06, 4.76)
180 min	2.79	(1.96, 3.98)
240 min	2.49	(1.79, 3.47)
300 min	2.22	(1.55, 3.16)
360 min	1.98	(1.30, 3.00)
420 min	1.76	(1.06, 2.92)
480 min	1.57	(0.86, 2.88)
540 min	1.40	(0.68, 2.86)
600 min	1.25	(0.54, 2.86)

*Onset to Arterial Puncture (expected) derived by adding to the actual onset-to-randomization value, for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated. Arterial puncture is considered procedure start. Symptom onset is last known well time. Rows are intercepts from a single model using 632 endovascular and 650 medical patients with full data, treating time as a continuous variable. Model adjusted for age, sex, baseline stroke severity (NIHSS), target occlusion location, and concomitant IV tPA.

**Common odds ratio for better outcome over 6 levels of the modified Rankin Scale (ranks 5 and 6 combined into single worst outcome rank). Values higher than 1.0 indicate better outcomes with endovascular than medical therapy.

eTable 9. Association of Treatment Delay with Freedom from Disability (mRS 0-1) at 3 Months and Hemorrhagic Transformation in Endovascular vs Medical Groups

Time Interval	Outcome	Endovascular Group OR per 1h delay (95%CI)	Medical Group OR per 1h delay (95%CI)	P for interaction with Rx group
Onset to Randomization	mRS 0-1	0.89 (0.79-1.00)	0.93 (0.79-1.11)	0.61
	SICH	1.05 (0.81-1.36)	0.90 (0.67-1.21)	0.42
	PH2	1.34 (1.07-1.67)	1.20 (0.91-1.44)	0.37
Onset to Arterial Puncture (expected)*	mRS 0-1	0.88 (0.79-0.99)	0.94 (0.80-1.10)	0.53
	SICH	1.07 (0.83-1.38)	0.91 (0.68-1.21)	0.40
	PH2	1.34 (1.09-1.64)	1.16 (0.93-1.45)	0.35
Onset to Reperfusion (expected)**	mRS 0-1	0.88 (0.78-0.98)	0.94 (0.81-1.10)	0.45
	SICH	1.08 (0.84-1.39)	0.91 (0.68-1.20)	0.34
	PH2	1.34 (1.07-1.68)	1.17 (0.92-1.48)	0.39
Onset to ED arrival	mRS 0-1	0.97 (0.87-1.08)	0.99 (0.85-1.15)	0.85
	SICH	0.99 (0.78-1.26)	0.79 (0.59-1.06)	0.24
	PH2	1.17 (0.94-1.44)	0.96 (0.76-1.22)	0.22
ED arrival to Randomization	mRS 0-1	0.64 (0.47-0.85)	0.85 (0.61-1.19)	0.20
	SICH	1.22 (0.78-1.89)	1.46 (0.96-2.23)	0.55
	PH2	1.38 (0.92-2.05)	1.62 (1.11-2.36)	0.56
ED arrival to Arterial Puncture (expected) †	mRS 0-1	0.62 (0.47-0.83)	0.85 (0.62-1.16)	0.14
	SICH	1.27 (0.84-1.92)	1.47 (0.98-2.2)	0.60
	PH2	1.42 (0.98-2.06)	1.66 (1.16-2.37)	0.55
ED arrival to Reperfusion (expected)††	mRS 0-1	0.62 (0.47-0.81)	0.83 (0.62-1.11)	0.11
	SICH	1.32 (0.91-1.93)	1.44 (0.98-2.11)	0.74
	PH2	1.41 (1.00-1.99)	1.63 (1.16-2.29)	0.54

OR: odds ratio. ED: Emergency Department. .mRS: modified Rankin Scale, range from 0 to 6, with higher scores indicating greater degree of disability.

* Onset to Arterial Puncture (expected) times: derived by adding to the actual onset-to-randomization value, for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated. Arterial puncture is considered procedure start.

**Onset to Reperfusion (expected) times: derived by adding to the actual onset-to-randomization value, for each patient in both the endovascular and medical groups, the study mean for the time from randomization to substantial reperfusion (mTICI 2b/3) of the trial in which they participated.

†ED Arrival to Arterial Puncture (expected) times: derived by adding to the actual ED arrival-to-randomization value, for each patient in both the endovascular and medical groups, the study mean for the time from randomization to arterial puncture of the trial in which they participated

††ED Arrival to Reperfusion (expected) times: derived by adding to the actual ED arrival-to-randomization value, for each patient in both the endovascular and medical groups, the study mean for the time from randomization to substantial reperfusion (mTICI 2b/3) of the trial in which they participated

eTable 10. Reasons for Non-Intervention in Patients Assigned to Endovascular Group

Reason	Frequency No./Total No. (%)
Endovascular intervention performed	563/634 (88.8%)
Clinical improvement so no puncture performed	9/634 (1.4%)
No target occlusion seen on diagnostic catheterization angiography	34/634 (5.4%))
Unable to access target occlusion	16/634 (2.5%)
Other or Reason not documented	12/634 (1.9%)

eTable 11. Association of treatment delay with outcomes in endovascular group patients with substantial reperfusion after interventional procedure

Time Interval	Outcome	Odds ratio (95%CI) per 1h delay in patients with substantial reperfusion
Onset to Randomization (n=390)	mRS shift	0.88 (0.79-0.98)
	mRS 0-2	0.85 (0.75-0.97)
	mRS 0-1	0.87 (0.76-1.00)
	Mortality	1.06 (0.87-1.29)
	SICH	0.97 (0.64-1.47)
	PH2	1.35 (1.00-1.82)
Onset to Actual Arterial Puncture (n=390)	mRS shift	0.86 (0.77-0.96)
	mRS 0-2	0.82 (0.72-0.94)
	mRS 0-1	0.85 (0.74-0.98)
	Mortality	1.07 (0.88-1.31)
	SICH	1.00 (0.67-1.49)
	PH2	1.40 (1.05-1.87)
Onset to Actual Reperfusion (n=390)	mRS shift	0.84 (0.76-0.93)
	mRS 0-2	0.81 (0.72-0.92)
	mRS 0-1	0.85 (0.74-0.97)
	Mortality	1.13 (0.94-1.35)
	SICH	1.15 (0.82-1.61)
	PH2	1.43 (1.09-1.88)
ED Arrival to Actual Reperfusion, in Direct Mode of Arrival Patients (n=274)	mRS shift	0.54 (0.41-0.70)
	mRS 0-2	0.51 (0.38-0.70)
	mRS 0-1	0.54 (0.38-0.76)
	Mortality	1.49 (1.06-2.08)
	SICH	1.22 (0.67-2.19)
	PH2	1.51 (0.89-2.54)
Imaging to Actual Reperfusion, in Direct Mode of Arrival Patients (n=274)	mRS shift	0.57 (0.42-0.77)
	mRS 0-2	0.54 (0.38-0.78)
	mRS 0-1	0.52 (0.35-0.79)
	Mortality	1.49 (1.01-2.21)
	SICH	1.33 (0.70-2.55)
	PH2	0.75 (0.96-3.17)

OR: odds ratio; ED: Emergency Department. mRS shift: common odds ratio over 6 strata of the modified Rankin Scale (with mRS 5 and 6 combined in a single worst outcome level). mRS 0-1: Modified Rankin Scale score at 3 months of 0 or 1. mRS 0-2: Modified Rankin Scale score at 3 months of 0, 1 or 2. Reperfusion: mTICI 2b or 3. SICH: symptomatic intracranial hemorrhage. PH2: Parenchymal hematoma type 2.

eTable 12. Number Needed to Treat, Benefit Per Thousand, and Minutes Needed to Treat for Faster Reperfusion Times

	Onset to Reperfusion		ED Arrival to Reperfusion	
	Less Disability	Functional Independence	Less Disability	Functional Independence
Benefit per thousand per 15 min faster*	16	9	39	25
NNTB per 15 min faster	62	112	26	40
Minutes Faster Needed to Treat (MNT)	9	17	4	6

ED: Emergency Department
NNTB: Number needed to treat for benefit – the number of patients needed to have reperfusion achieved 15 minutes faster for 1 more patient to have a better outcome. MNT: Minutes faster needed to treat – the number of minutes faster reperfusion needs to be achieved for 1 more reperfusion patient out of 100 to have a better outcome (lower 3 month disability by 1 or more grades on the 7 level mRS).
*Benefit per thousand: For every 15 minute faster achievement of substantial reperfusion, number of patients who would have improved outcomes among 1000 patients experiencing reperfusion.

eTable 13. Time and Workflow Intervals

Time Interval	Direct from field		Transfer		All patients		Direct vs Transfer
	N	Median (IQR) minutes	N	Median (IQR) minutes	N	Median (IQR) minutes	P value
Onset to Study Center ED door							
Endovascular Group	437	65 (45, 120)	187	199 (155, 256)	625	99 (52, 191)	<0.001
Medical Group	421	65 (43, 110)	218	212.5 (164, 259)	639	103 (53, 206)	<0.001
Door to imaging							
Endovascular Group	432	21 (14, 38)	176	15 (7.8, 24.6)	609	19 (11.7, 32.8)	<0.001
Medical Group	419	21 (13.5, 39)	197	15.7 (9.5, 27)	616	19 (11.5, 32.8)	<0.001
Imaging to randomization							
Endovascular Group	435	48 (31, 71.7)	179	29 (20.5, 41.4)	616	40.4 (26.6, 62.1)	<0.001
Medical Group	425	52 (34, 77)	199	28.5 (19.5, 40)	625	41.8 (26.5, 68)	<0.001
Door to IV-tPA							
Endovascular Group	342	35 (25, 50)			342	35 (25, 50)	
Medical Group	356	35.5 (26, 51.5)			356	35.5 (26, 51.5)	
Onset to IV-tPA							
Endovascular Group	342	102.5 (75, 141)	181	97 (75, 126)	524	101 (75, 135)	0.18
Medical Group	361	104 (75, 150)	207	98 (75, 135)	570	100 (75, 146)	0.21
Door to randomization							
Endovascular Group	436	81 (57, 114)	186	46 (33, 61)	623	69 (47, 103)	<0.001
Medical Group	421	82 (60, 114)	218	45.5 (31, 61)	639	68 (46, 103)	<0.001
IV-tPA to randomization							
Endovascular Group	311	48 (22, 78)	176	149 (122, 200)	488	78 (34.5, 136)	<0.001
Medical Group	327	48 (20, 82)	205	152 (116, 193)	534	85 (37, 142)	<0.001
Onset to arterial puncture	421	210 (158, 270)	184	295 (255, 342.5)	607	238 (180, 302)	<0.001
Door to arterial puncture	420	116 (82.5, 160)	181	81 (58, 105)	602	104 (74, 148)	<0.001
Imaging to arterial puncture	416	81 (55.3, 118)	173	61.7 (42.5, 86)	591	76 (51, 108.3)	<0.001
Randomization to arterial puncture	420	31.5 (19, 49)	183	31 (17, 49)	605	32 (19, 49)	0.66
Onset to reperfusion	269	251 (193, 334)	115	345 (298, 394)	385	286 (215, 363)	<0.001
Door to reperfusion	268	159 (116, 202)	114	135 (109, 173)	383	148 (112, 197)	0.005
Randomization to reperfusion	269	76 (50, 108)	115	85 (57, 111)	385	79 (51, 108)	0.17
Puncture to reperfusion	268	43 (25.5, 61)	115	47 (31, 75)	384	44 (27, 64.5)	0.023

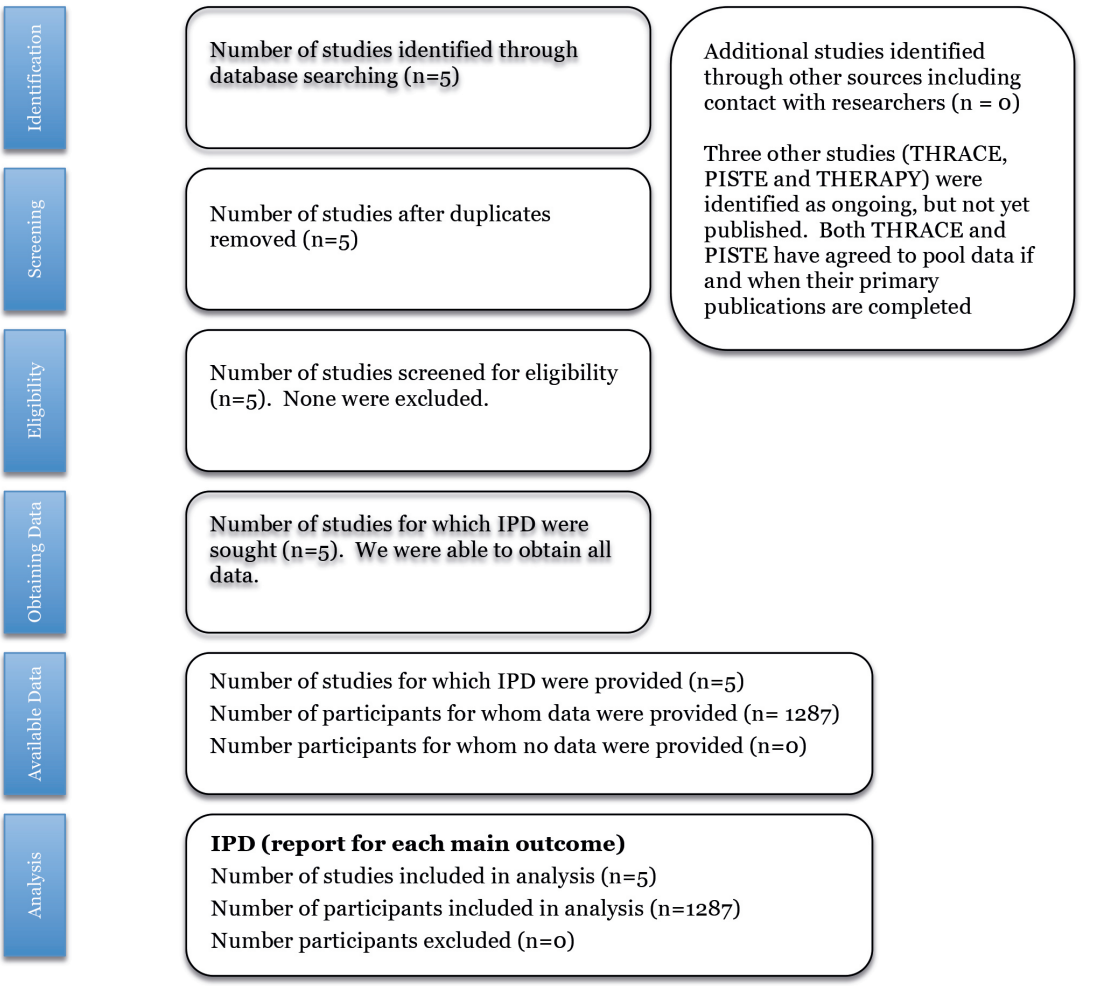
ED: Emergency Department. IV-tPA: intravenous tissue plasminogen activator (alteplase). Reperfusion: mTICI 2b or 3

eTable 14. Proportion of Endovascular-Treated Patients Treated within Society-Recommended Timeframes

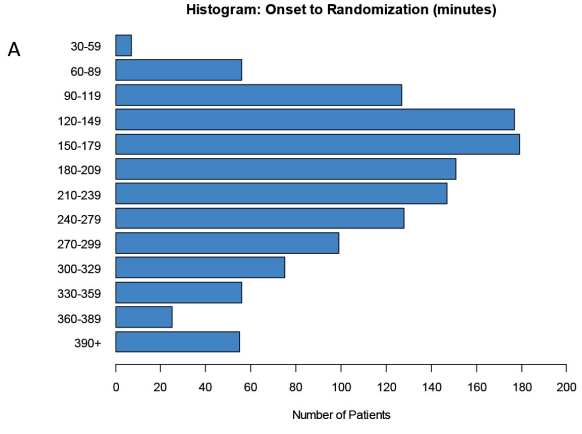
Time Interval	Multispecialty 2013 Guidelines		SNIS 2015 Guideline "Ideal"	
	Target	Percent (n/N)	Target	Percent (n/N)
Door to Arterial Puncture	≤120 mins	62% (372/602)	≤60 mins	13% (79/602)
Picture to Arterial Puncture	≤95 mins	69% (406/591)	≤30 mins	4% (26/591)
Door to Reperfusion	≤210 mins	81% (316/389)	≤90 mins	13% (50/389)

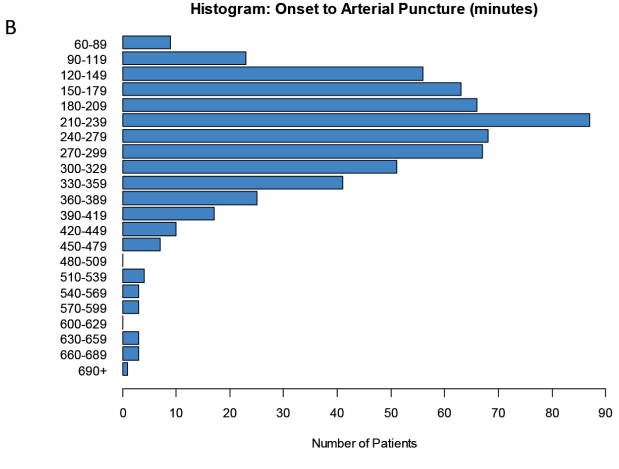
SNIS: Society of Neurointerventional Surgery. Reperfusion: mTICI 2b or 3.

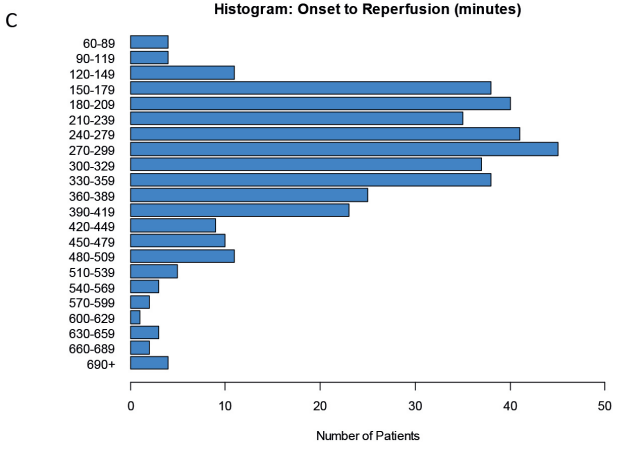
eFigure 1. PRISMA Flow Diagram Individual Patient Data Systematic Reviews



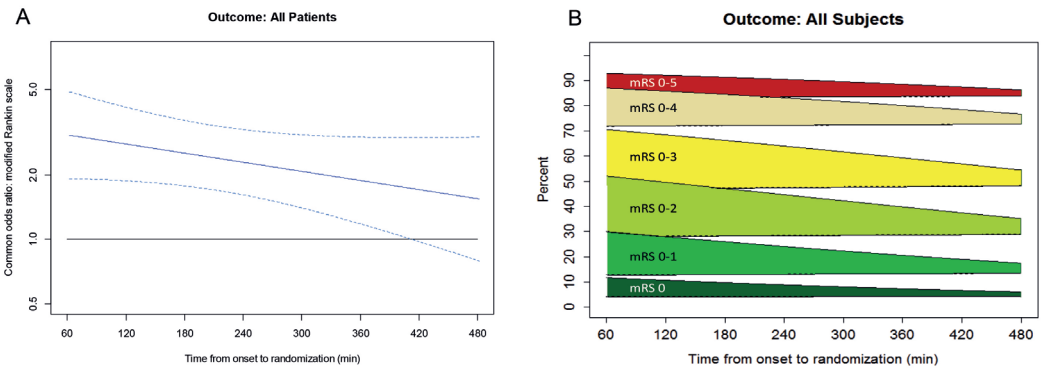
eFigure 2. Time Distributions for Onset to Randomization (n=1287); B) Onset to Arterial Puncture (n=607); C) Onset to Reperfusion (n=390)







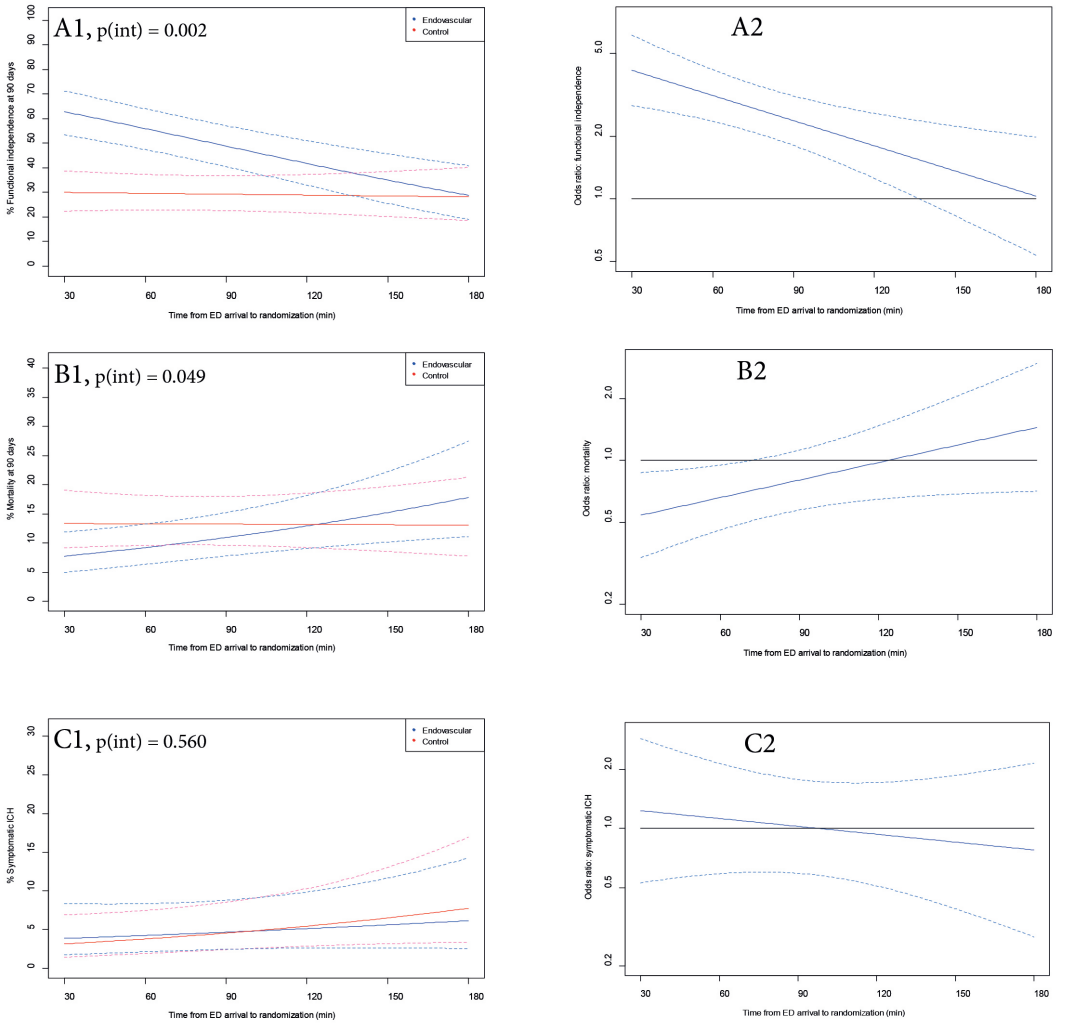
eFigure 3. Association of time from onset to randomization with disability levels at 3 months, endovascular versus medical therapy groups, after adjustment for age, sex, baseline stroke severity (NIHSS), target occlusion location, and concomitant IV tPA



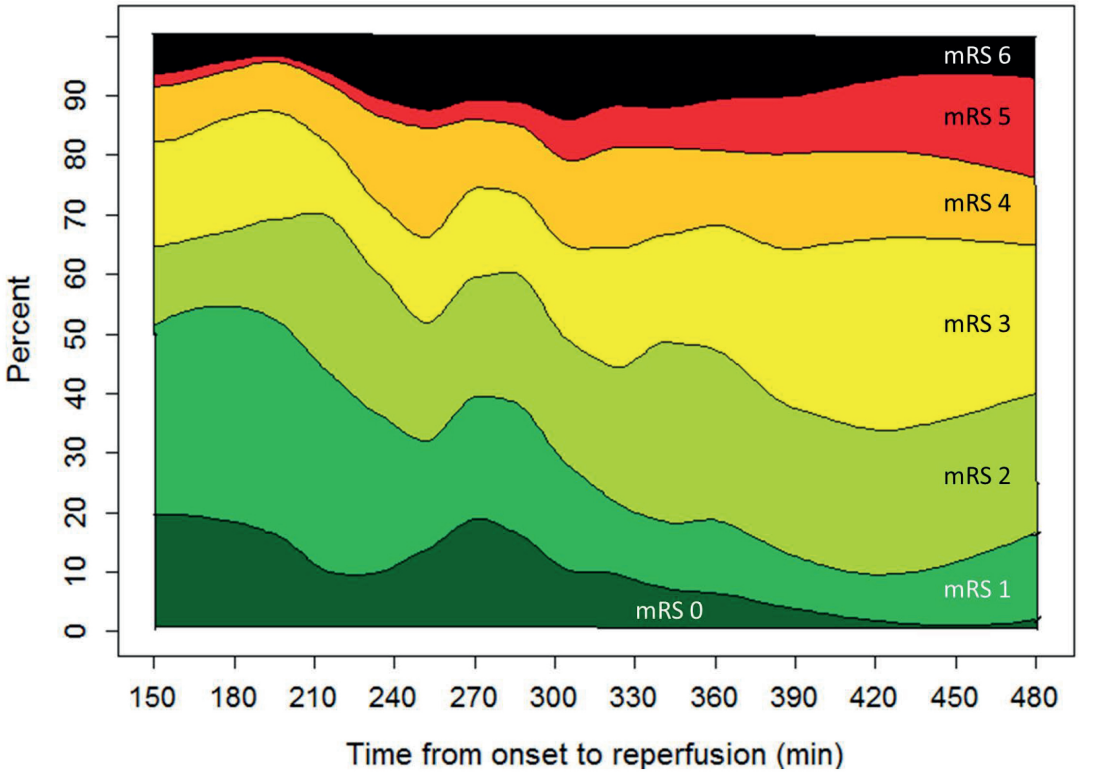
A) Odds ratio for better outcome in endovascular versus medical care only Group. The dark blue line is the best linear fit between the common odds ratio for improved outcome over 6 strata of the modified Rankin Scale (with mRS 5 and 6 combined in a single worst outcome level), with time analyzed as a continuous variable. The light blue lines are 95% confidence intervals. Odds ratio values higher than 1 indicate less disability with endovascular than medical therapy.

B) Output from same model showing the adjusted outcome rates in both treatment groups Groups, for all disability level cut points of the modified Rankin Scale. Upper line of each band is outcome rate in the endovascular Group; lower line of each band is outcome rate in the medical care only Group. The widths of the color bands indicate the difference in outcome rates with endovascular and medical care only Groups. Outcomes for the various mRS cut-points (0, 0-1, 0-2, etc.) were obtained from an ordinal logistic regression model with a cumulative logit link, incorporating a priori baseline covariates as well as random effects to account for between-study variance and an interaction term between time and treatment assignment. The displayed results represent predicted rates for time from onset to randomization.

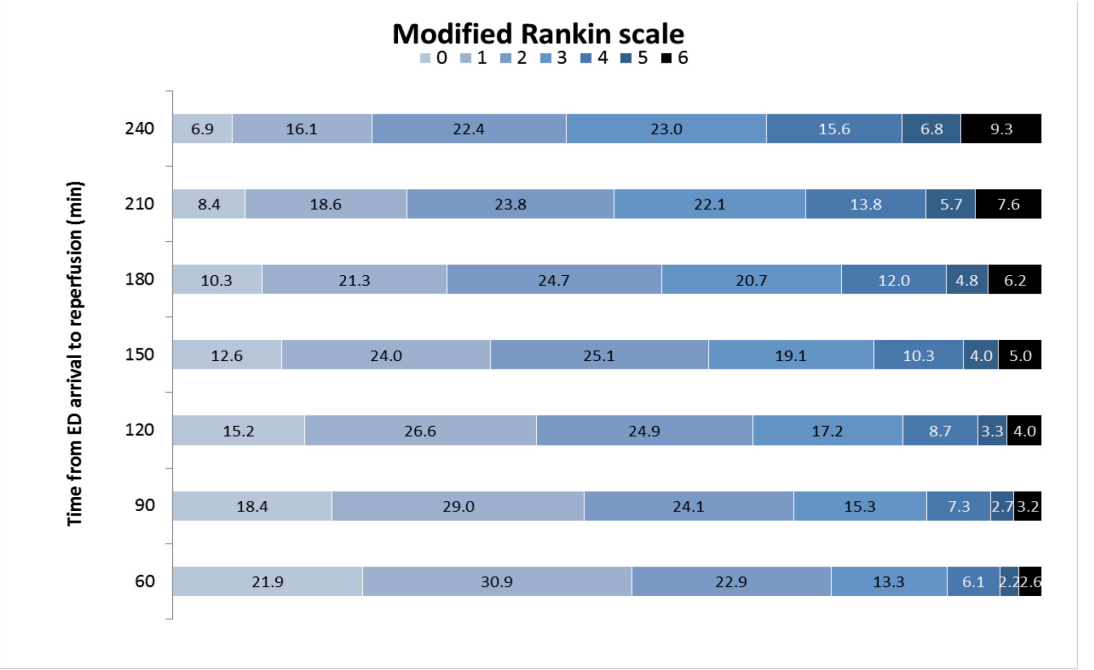
eFigure 4. Relation of time from ED arrival to randomization with functional independence, mortality, and symptomatic intracranial hemorrhage. A1) functional independence (mRS 0-2) at 90 days in endovascular and medical Groups, A2) odds ratio for functional independence; B1) mortality by 90 days in endovascular and medical Groups, B2) odds ratio for mortality; C1) SICH in medical and endovascular Groups, C2) odds ratio for SICH. Outcomes were obtained from logistic regression models with a logit link, incorporating a priori baseline covariates as well as random effects to account for between-study variance and an interaction term between time and treatment assignment. The displayed results represent predicted rates of outcome adjusted for time from ED arrival to randomization



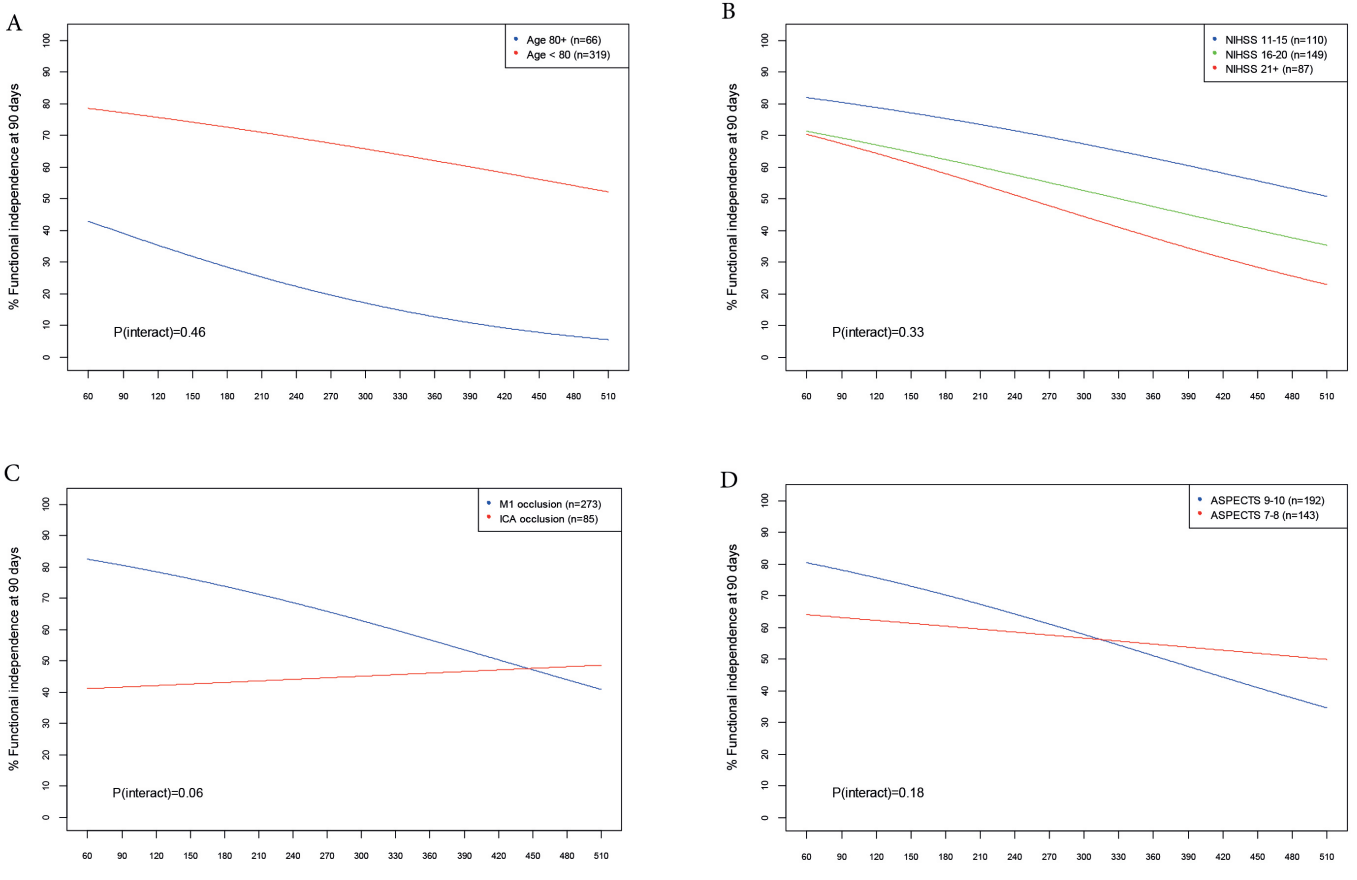
eFigure 5. Non-linear analysis of relation between time from onset to substantial reperfusion (mTICI 2b/3) and all 7 mRS disability outcomes. Patients are all endovascular Group patients with substantial reperfusion (mTICI 2b/3) at end of procedure (n=385). Each mRS outcome is analyzed in a separate, dichotomous model. Estimated probabilities from these models are plotted using a locally weighted function (LOWESS). The width of colored bands indicates the proportion of patients at each particular mRS level. The frequency of excellent outcomes (mRS 0, mRS 1) peaks at rapid onset to reperfusion times (150-180m); moderate outcomes (mRS 2, mRS 3) peak at intermediate onset to reperfusion times (340-420m); and severe outcomes (mRS 5, mRS 6) peak at later onset to reperfusion times (450-480m). Steep declines in rates of cumulative excellent and good outcomes (mRS 0-1, mRS 0-2) are noted with onset to reperfusion times between 190-390m; rates of excellent and good outcomes then relatively plateau, stable from 390-480 minutes.



eFigure 6. Association of time from ED arrival to actual endovascular reperfusion with predicted 90-day disability outcomes, using adjusted ordinal logistic regression model. Data are from the 390 endovascular Group patients in whom substantial reperfusion was achieved.



eFigure 7. Association of time to substantial reperfusion among reperfusing endovascular Group patients with functional independence (mRS 0-2) at 3 months in different patient groups: A) Age, B) presenting NIHSS, C) target occlusion location, D) ASPECTS (Alberta Stroke Program Early CT Score) at presentation, E) IV tPA used vs ineligible, F) direct-arriving vs interfacility-transfer, G) early IV tPA vs later IV tPA. Outcomes for functional independence were obtained from a logistic regression model with a logit link, incorporating a priori baseline covariates as well as random effects to account for between-study variance and an interaction term between time and subgroup. The displayed results represent predicted rates of outcome by subgroup adjusted for time from onset to reperfusion.



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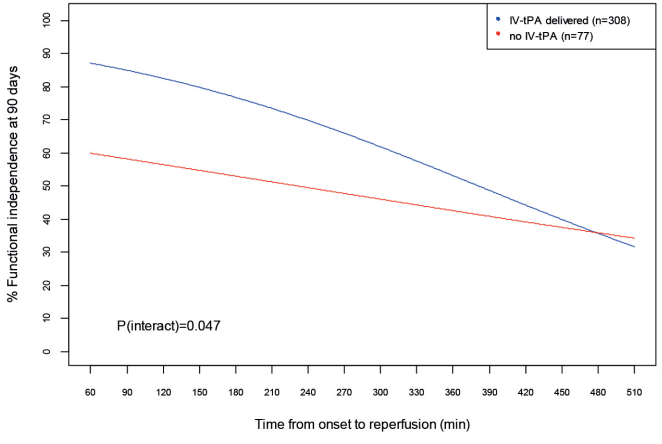
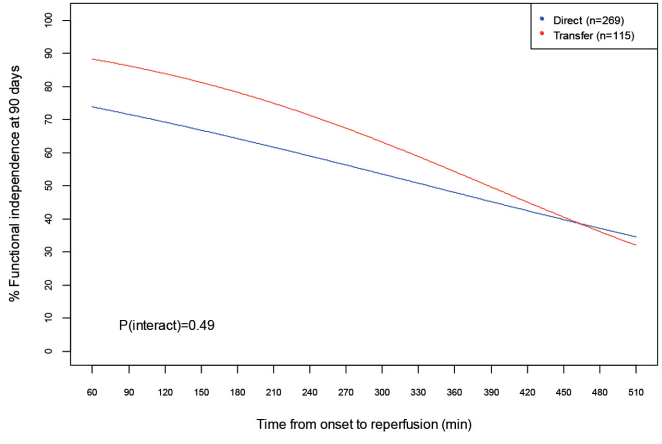
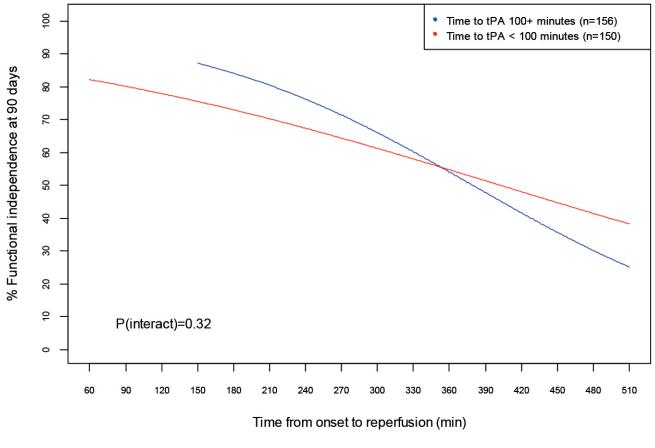

IV-tPA delivered (n=308)
no IV-tPA (n=77)
% Functional independence at 90 days
P(interact)=0.047
Time from onset to reperfusion (min)

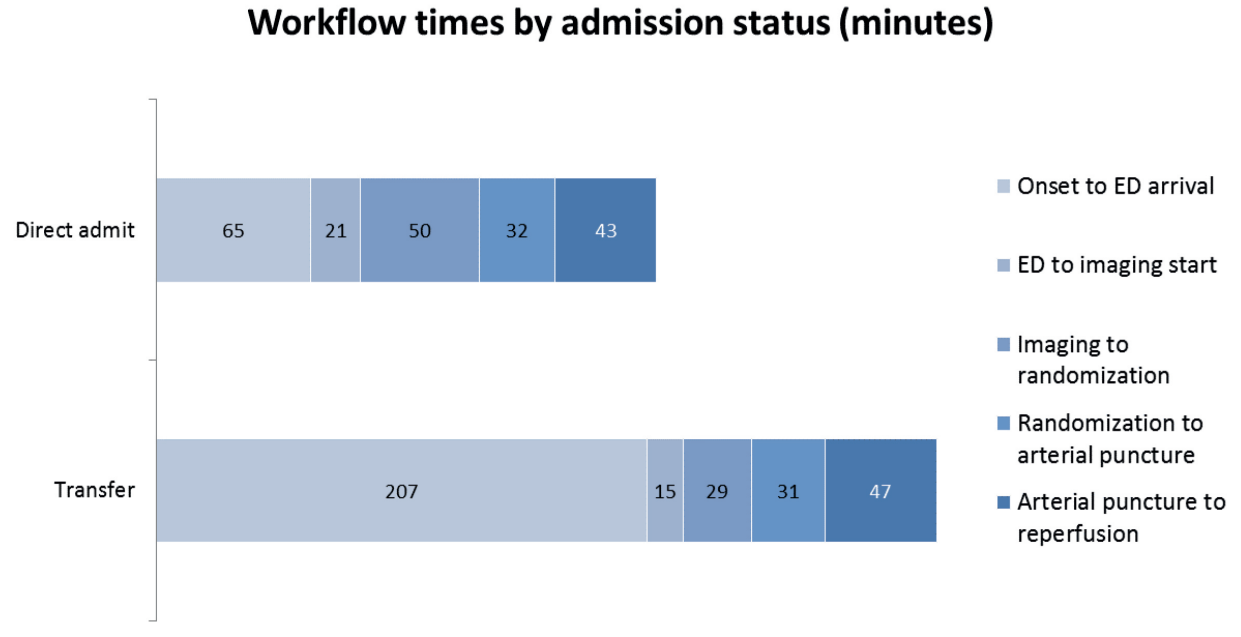
F


Direct (n=269)
Transfer (n=115)
% Functional independence at 90 days
P(interact)=0.49
Time from onset to reperfusion (min)

G


Time to tPA 100+ minutes (n=156)
Time to tPA < 100 minutes (n=150)
% Functional independence at 90 days
P(interact)=0.32
Time from onset to reperfusion (min)

eFigure 8. Workflow time intervals in Direct-Arriving and Inter-Hospital-Transfer Patients. Median time values, in minutes, are shown.



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CHAPTER 4

Imaging Variables And Outcome

4.1 - Recanalization And Clinical Outcome Of Occlusion Sites At Baseline CT Angiography In The Interventional Management Of Stroke III Trial

4.2 - Correlation Between Clinical Outcomes And Baseline CT And CT Angiographic Findings In The SWIFT PRIME Trial

4.3 - Multiphase CT Angiography: A New Tool For The Imaging Triage Of Patients With Acute Ischemic Stroke

4.4 - Regional Comparison Of Multiphase CT Angiography And CT Perfusion For Prediction Of Tissue Fate In Ischemic Stroke

4.5 - Imaging Features And Safety And Efficacy Of Endovascular Stroke Treatment: A Meta-Analysis Of Individual Patient-Level Data

CHAPTER 4.1

Recanalization And Clinical Outcome Of Occlusion Sites At Baseline CT Angiography In The Interventional Management Of Stroke III Trial

Based upon:
Recanalization and Clinical Outcome of Occlusion sites at Baseline CT Angiography in theInterventional Management of stroke III Trial
Andrew M. Demchuk, Mayank Goyal, Sharon D. Yeatts, Janice Carrozzella, MSN Lydia D. Foster, MS Emmad Qazi, Michael D. Hill, Tudor G. Jovin, Marc Ribo, Bernard Yan, Osama O. Zaidat, Donald Frei, Rüdiger von Kummer, Prof Dr med Kevin M. Cockroft, , Pooja Khatri, , David S. Liebeskind, Thomas A. Tomsick, Yuko Y. Palesch, Joseph P. Broderick, For the IMS III Investigators
Radiology. 2014 Oct;273(1):202-10.

ABSTRACT

Purpose

To use baseline computed tomographic (CT) angiography to analyze imaging and clinical end points in an Interventional Management of Stroke III cohort to identify patients who would benefit from endovascular stroke therapy.

Materials and Methods

The primary clinical end point was 90-day dichotomized modified Rankin Scale (mRS) score. Secondary end points were 90-day mRS score distribution and 24-hour recanalization. Prespecified subgroup was baseline proximal occlusions (internal carotid, M1, or basilar arteries). Exploratory analyses were subsets with any occlusion and specific sites of occlusion (two-sided a = .01).

Results

Of 656 subjects, 306 (47%) underwent baseline CT angiography or magnetic resonance angiography. Of 306, 282 (92%) had arterial occlusions. At baseline CT angiography, proximal occlusions (n = 220) demonstrated no difference in primary outcome (41.3% [62 of 150] endovascular vs 38% [27 of 70] intravenous [IV] tissue-plasminogen activator [tPA]; relative risk, 1.07 [99% confidence interval: 0.67, 1.70]; P = .70); however, 24-hour recanalization rate was higher for endovascular treatment (n = 167; 84.3% [97 of 115] endovascular vs 56% [29 of 52] IV tPA; P , .001). Exploratory subgroup analysis for any occlusion at baseline CT angiography did not demonstrate significant differences between endovascular and IV tPA arms for primary outcome (44.7% [85 of 190] vs 38% [35 of 92], P = .29), although ordinal shift analysis of full mRS distribution demonstrated a trend toward more favorable outcome (P = .011). Carotid T- or L-type occlusion (terminal internal carotid artery [ICA] with M1 middle cerebral artery and/or A1 anterior cerebral artery involvement) or tandem (extracranial or intracranial) ICA and M1 occlusion subgroup also showed a trend favoring endovascular treatment over IV tPA alone for primary outcome (26% [12 of 46] vs 4% [one of 23], P = .047).

Conclusion

Significant differences were identified between treatment arms for 24-hour recanalization in proximal occlusions; carotid T- or L-type and tandem ICA and M1 occlusions showed greater recanalization and a trend toward better outcome with endovascular treatment. Vascular imaging should be mandated in future endovascular trials to identify such occlusions.

Inthe Interventional Management of Stroke (IMS) III trial, the approach of combining intravenous (IV) tissue-plasminogen activator (tPA) with endovascular therapies was tested in an attempt to improve revascularization and clinical outcomes compared with IV tPA alone in the setting of moderate to severe acute ischemic stroke. The overall results were neutral, with no significant improvement in clinical outcome with the endovascular approach added to IV tPA compared with IV tPA alone (1). Vascular imaging was not mandated for trial enrollment but was performed at a number of centers routinely as part of standard clinical care. Subjects with lower baseline National Institutes of Health Stroke Scale (NIHSS) scores (scores 8-9) were also eligible for the trial if a proximal occlusion was identified at baseline vascular imaging after protocol amendment 3 was implemented in January 2009. At centers where baseline computed tomographic (CT) angiography was performed routinely, the absence of a visible intracranial occlusion served as an exclusion from eligibility after amendment 5 was enacted in June 2011.

The subgroup of IMS III subjects for whom baseline CT angiography or magnetic resonance (MR) angiography was performed may provide valuable insight into which subgroups of patients with moderate or severe acute ischemic stroke may benefit from endovascular therapy versus IV tPA alone. The trial mandated follow-up (24-hour) CT

ADVANCES IN KNOWLEDGE

- In the prespecified analysis of subjects with proximal occlusion observed at baseline CT angiography, combined intravenous (IV) tissue-plasminogen activator (tPA) and endovascular treatment has higher 24-hour recanalization rates (84.3%) compared with standard IV tPA (56%) as identified with CT angiography and MR angiography (P , .0001).
- Terminal and tandem occlusions of the internal carotid artery (ICA) and M1 segment showed greater recanalization (83.3% vs 27.8%, P = .0001) and a trend toward better outcomes (26% vs 4%, P = .047) with endovascular treatment as compared with IV tPA alone in post hoc analysis.
- Future endovascular and/or thrombolytic trial design should include baseline vascular imaging and focus on enrollment of patients with evidence of intracranial occlusion, particularly involving the ICA, given the wide differences in clinical effects and recanalization according to occlusion sites seen in the Interventional Management of Stroke III study.

IMPLICATIONS FOR PATIENT CARE

- Recanalization rates at 24 hours are higher for endovascular treatment compared with standard IV tPA.
- Subjects with a large thrombus burden identified at CT angiography, involving the extracranial or intracranial ICA and M1 middle cerebral artery, are unlikely to achieve good outcomes with standard IV tPA.

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Abbreviations:

ICA = internal carotid artery
IMS = Interventional Management of Stroke IV = intravenous
mRS = modified Rankin Scale
NIHSS = National Institutes of Health Stroke Scale SICH = symptomatic intracerebral hemorrhage
tPA = tissue-plasminogen activator

Author contributions:

Guarantors of integrity of entire study, A.M.D., T.A.T., J.P.B.; study concepts/study design or data acquisition or data analysis/interpretation, all authors; manuscript drafting or manuscript revision for important intellectual content, all authors; approval of final version of submitted manuscript, all authors; literature research, A.M.D., M.D.H., M.R., O.O.Z., D.F., K.C., P.K., T.A.T., J.P.B.; clinical studies, A.M.D., M.G., J.C., M.D.H., T.G.J., D.F., R.v.K., K.C., P.K., D.S.L., T.A.T., Y.Y.P., J.P.B.; experimental studies, T.A.T.; statistical analysis, S.D.Y., L.D.F., Y.Y.P.; and manuscript editing, A.M.D., M.G., S.D.Y., M.D.H., T.G.J., M.R., B.Y., O.O.Z., D.F., R.v.K., K.C., P.K., D.S.L., T.A.T., Y.Y.P., J.P.B.

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Conflicts of interest are listed at the end of this article.

angiography or MR angiography to evaluate recanalization rates for all subjects in both treatment arms. We present analyses to evaluate this baseline (pre-V tPA) CT angiography and MR angiography information within the IMS III trial as a predictor of both the imaging end point of 24-hour recanalization and 90-day modified Rankin Scale (mRS) score for the two treatment groups.

MATERIALS and METHODS

The study was funded by the National Institutes of Health and the National Institute of Neurologic Diseases and Stroke (grant numbers UC U01NS052220, MUSC U01NS054630, and U01NS077304). Genentech supplied the drug used for intraarterial tPA in the endovascular group. EKOS, Concentric, and Cordis Neurovascular supplied the study catheters during the period when amendments 1-3 were in effect. In Europe, IMS III investigator meeting support was provided in part by Boehringer Ingelheim.

Patients and Procedures

Patient eligibility criteria and IMS III trial methods have been detailed previously (1,2). Subjects were recruited from August 25, 2005, to April 17, 2012. The identification of a proximal arterial occlusive lesion was centrally adjudicated by the CT Imaging Analysis Centre at the University of Calgary (the central core laboratory). Each CT angiography or MR angiography study was interpreted by a consensus panel of two readers (stroke neurologists A.M.D. and M.D.H. and neuroradiologist M.G., each with at least 10 years of stroke imaging experience) at each session. Guidance for 24-hour CT angiography imaging parameters was provided (see Appendix E1 [on-line]), but specific CT angiography or MR angiography protocols were not mandated. Each segment of the extracranial and intracranial arterial vasculature was assessed for the presence of contrast material within the lumen and was graded for any stenosis or occlusion. The grading of segments for stenosis and occlusion and occlusion site locations are described in Appendix E1 (online). Recanalization according to specific site of occlusion by comparing the baseline and follow-up CT angiography and MR angiography findings is defined in Appendix E1 (online).

The primary clinical end point was a functionally independent outcome as manifested by mRS score of 0-2 at 90 days. One of the secondary clinical end points was 90-day mRS score distribution. Recanalization was measured in those who demonstrated intracranial occlusion at baseline CT angiography and/or MR angiography. Successful recanalization was defined as grade 3-5 flow in previously occluded (grade 1-2) segments of symptomatic intracranial arteries at 24-hour CT angiography and/or MR angiography. Subjects without 24-hour CT angiography and/or MR angiography data were excluded from further recanalization analysis. The primary safety outcomes were mortality within 90 days and symptomatic intracerebral hemorrhage (SICH), defined as an intracranial hemorrhage temporally related to a decline in neurologic status, as well as new or worsening neurologic symptoms in the judgment of the clinical investigator that may warrant medical intervention within 30 hours of IV tPA initiation.

Statistical Analysis

The analysis of mRS scores 0-2 among subjects with internal carotid artery (ICA), M1, or basilar arterial occlusions was prespecified (1). Subjects with 90-day outcome missing or collected outside the pre-specified window were assigned an mRS score higher than 2. Other subgroup analyses, according to presence or absence of any occlusion or various specific occlusion locations, were considered exploratory. Within each subgroup, treatment arms were compared with respect to both effectiveness (clinical and recanalization) and safety end points. The x2 test, or Fisher exact test in the case of small cell counts, was used to compare the treatment arms with respect to binary end points. The effect of treatment on recanalization was further described via risk difference and corresponding 95% confidence intervals, derived according to the Newcombe score. The distribution of ordinal mRS scores was analyzed by using the generalized Wilcoxon test; subjects with mRS score missing or obtained outside of the prespecified window were excluded from this analysis, and mRS scores 5 and 6 were combined into one category.

For the specific sites of occlusion, baseline differences between treatment arms were tested (and considered significant if P was less than .01) for the following variables: age; sex; baseline NIHSS score; baseline Alberta Stroke Program Early CT Score, or ASPECTS; atrial fibrillation (according to electrocardiography findings or medical history); time from onset to IV tPA treatment time; and baseline glucose level. Given the exploratory nature of the various analyses described that were not prespecified for the different occlusion

sites, as well as the number of analyses anticipated, significance required a P value less than .01 to minimize false-positive results that arose from multiple hypothesis testing.

RESULTS

Of the 656 subjects enrolled in the IMS III trial, 306 (47%) underwent baseline vascular imaging, including 292 CT angiography examinations and 14 MR angiography examinations. Heretofore, subjects who underwent either baseline CT angiography or MR angiography are referred to as subjects who underwent baseline CT angiography. In 78% (45 of 58) of enrollment centers in the trial, at least one subject underwent baseline CT angiography. Of the 282 subjects with any occlusion at baseline CT angiography, 66 had no 24-hour CT angiography or MR angiography data, of whom nine died within 31 hours. The remaining 216 subjects had both baseline and 24-hour vascular imaging data that were used for analysis of 24-hour recanalization.

Baseline CT Angiography versus No Baseline CT Angiography

The baseline demographics of subjects with baseline CT angiography data versus those without are shown in Table 1. Significantly (P , .01) less hyperlipidemia and shorter times from IV tPA bolus to groin puncture time and from groin puncture to start of endovascular therapy were observed in the CT angiography group. This could be explained by the high rate of direct to comprehensive stroke center enrollment in the baseline CT angiography population (95%) compared with only 77% in those where baseline CT angiography was not performed.

Among direct to comprehensive stroke center subjects, no differences were seen in the time from IV tPA bolus to groin puncture (P = .08); however, time from groin puncture to start of intraarterial therapy was still shorter in the CT angiography group (P = .002). Subjects who underwent CT angiography were more likely to have a favorable clinical outcome (mRS score of 0-2) versus those who did not (45.4% [139 of 306] vs 35.4% [124 of 350], P= .009). Related to safety, the mean baseline creatinine level was similar in both the baseline CT angiography and no CT angiography subgroups (92.4 mmol/L 6

Table 1

Baseline Characteristics: Baseline CT Angiography versus No Baseline CT Angiography Performed

Parameter	Baseline CT Angiography ($n = 306$)	No Baseline CT Angiography ($n = 350$)
Median age (y)*	70 (23–83)	68 (23–89)
No. of men	163 (53.3)	177 (50.6)
No. of black, African American, and African Canadian subjects	25 (8.2)	45 (12.8)
No. of Hispanic or Latino subjects	11 (3.6)	12 (3.4)
Median baseline NIHSS score*	17 (7–40)	17 (9–40)
No. of subjects with ASPECTS score of 8–10	177 (57.8)	201 (57.4)
Presumptive stroke location		
Left hemisphere	151 (49.3)	179 (51.1)
Right hemisphere	147 (48.0)	159 (45.4)
Brain stem and/or cerebellum	7 (2.3)	7 (2.0)
Unknown location and/or multiple locations	1 (0.3)	5 (1.4)
No. of subjects with atrial fibrillation	111 (36.3)	112 (32.0)
No. of subjects with history of hypertension	227 (74.2)	263 (75.1)
No. of subjects with history of diabetes	58 (19.0)	90 (25.7)
Mean baseline glucose level (mmol/L)†	7.3 ± 2.8	7.6 ± 3.1
No. of subjects with history of congestive heart failure	28 (9.2)	53 (15.1)
No. of subjects with history of coronary artery disease	71 (23.2)	103 (29.4)
No. of subjects with history of hyperlipidemia‡	135 (44.1)	192 (54.8)
Mean time from onset to IV tPA initiation (min)†	123 ± 33.4	121.1 ± 34.0
Mean time from IV tPA to groin puncture (min)†‡	80.7 ± 26.3	90.1 ± 35.5
Mean time from groin puncture to intraarterial therapy administration (min)†‡	40.5 ± 21.6	49.9 ± 24.2

Note.—Unless specified otherwise, numbers in parentheses are percentages. ASPECTS = Alberta Stroke Program Early CT Score.

* Numbers in parentheses are ranges.

† Data are mean ± standard deviation.

‡ Differences were considered significant at the $P < .01$ level.

29.9 and 94.4 mmol/L 6 34.3, respectively) and was not different on day 5 (or at discharge) (77.1 mmol/L 6 29.2 and 79.4 mmol/L 6 47.8, respectively). In the IV tPA treatment arm, no differences in favorable clinical outcome were observed in the study sample that underwent baseline CT angiography versus those that did not (39% [37 of 95] versus 38.6% [49 of 127], P = .956).

Baseline CT angiography demonstrated an occlusion in 282 of 306 subjects (92.2%). The occlusion sites were distributed as follows: two isolated extracranial ICA occlusions, four

intracranial ICA occlusions only, 58 ICA T- or L-type occlusions, 11 tandem ICA and M1 occlusions, 60 proximal M1 occlusions without ICA involvement, 79 distal M1 occlusions without ICA involvement, 54 M2 occlusions with or without ICA involvement; five M3 and M4 occlusions, five basilar artery (with or without vertebral artery) occlusions, and four posterior cerebral artery occlusions.

Baseline CT Angiography Subgroups

The only prespecified baseline CT angiography analysis was a comparison of treatment arms in the subset of subjects with proximal occlusions (ICA, M1, or basilar arteries; n = 220) with regard to 90-day mRS score of 0-2 and 24-hour recanalization. No difference in the primary outcome was seen (41.3% [62 of 150] endovascular vs 38% [27 of 70] IV tPA; relative risk, 1.07 [99% confidence interval: 0.67, 1.70]). Figure 1 illustrates the 90-day mRS distribution of the two treatments for this prespecified subgroup (generalized Wilcoxon test, P = .11); eight subjects were excluded from this analysis because outcome data were missing or were obtained outside the 90-day assessment window. The rate of recanalization at 24 hours was better with endovascular therapy (84.3% [97 of 115] endovascular versus 56% [29 of 52] IV tPA, P , .001).

Figure 1

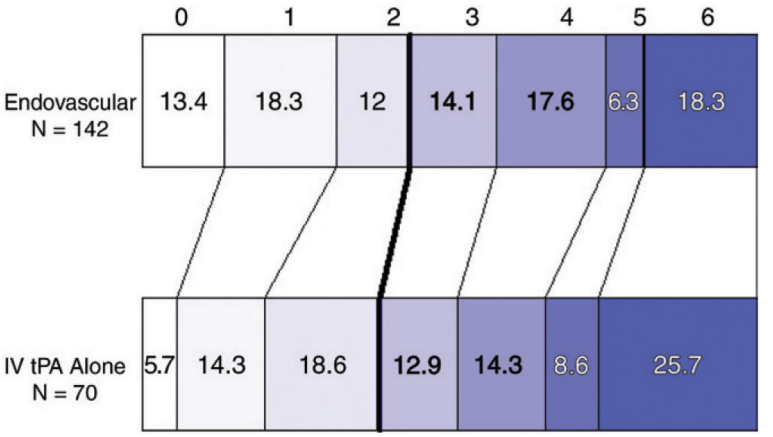

Figure 1: Diagram shows prespecified baseline CT angiography distribution of proximal occlusions (ICA, M1, basilar artery). The mRS distribution was not significantly different (generalized Wilcoxon test, *P* = .1068).

Subsequent analyses were all performed post hoc. The baseline CT angiography population was divided into subjects with no baseline occlusion and those with a baseline occlusion for subsequent analyses. Among subjects with no occlusion, a 90-day mRS score of 0-2 occurred in 81% (17 of 21) in the endovascular arm versus 67% (two of three) in the IV tPA arm (P = .52). Only one of 89 subjects (1%) with baseline NIHSS score of at least 20 had no visible occlusion, and 23 of 217 subjects (10.6%) with baseline NIHSS score of 8-19 had no visible occlusion. Within the endovascular arm, there were three of 20 subjects without visible occlusion at CT angiography that had evidence of intracranial occlusion at conventional angiography (M2 middle cerebral artery in two subjects and M3 middle cerebral artery in one subject). Median 24-hour infarct volume was 0.3 mL (interquartile range, 0-5.0 mL) in this group, and 10 of 23 subjects with follow-up CT data had no visible infarct.

Table 2

Baseline Characteristics: Population with Baseline Occlusions in the Two Treatment Arms

Parameter	Endovascular Therapy (*n* = 190)	IV tPA Only (*n* = 92)
Median age (y)*	70 (23–83)	70 (38–83)
No. of men	94 (49.5)	55 (60)
No. of black, African American, and African Canadian subjects	19 (10.0)	6 (6)
No. of Hispanic or Latino subjects	7 (3.7)	3 (3)
Median baseline NIHSS score*	17 (7–40)	17 (8–30)
No. of subjects with ASPECTS score of 8–10	99 (52.1)	55 (60)
Presumptive stroke location		
Left hemisphere	96 (50.5)	42 (46)
Right hemisphere	90 (47.4)	48 (52)
Brain stem and/or cerebellum	4 (2.1)	1 (1)
Unknown location and/or multiple locations	0 (0)	1 (1)
No. of subjects with atrial fibrillation	76 (40.0)	33 (36)
No. of subjects with history of hypertension	141 (74.2)	72 (78)
No. of subjects with history of diabetes	35 (18.4)	18 (20)
Mean baseline glucose level (mmol/L)†	7.2 ± 2.7	7.5 ± 3.0
No. of subjects with history of congestive heart failure	17 (8.9)	9 (10)
No. of subjects with history of coronary artery disease	41 (21.6)	26 (28)
No. of subjects with history of hyperlipidemia	80 (42.1)	46 (50)
Mean time from onset to IV tPA initiation (min)†	124.0 ± 32.7	118.3 ± 33.5

Note.—Unless specified otherwise, numbers in parentheses are percentages. ASPECTS = Alberta Stroke Program Early CT Score.

* Numbers in parentheses are ranges.

† Data are mean ± standard deviation.

The baseline CT angiography occlusion subgroup includes all sites of occlusion detected. Baseline demographics were all similar in the two treatment arms (Table 2). The baseline CT angiography occlusion subgroup did not demonstrate significant differences between the endovascular and IV tPA (alone) arms for the primary effectiveness outcome (44.7% [85 of 190] vs 38% [35 of 92], P = .29) and safety end points (SICH, 7.9% [15 of 190] vs 6% [six of 92], P = .68; 90-day mortality, 14.7% [28 of 190] vs 26% [24 of 92], P = .021). The full mRS distribution is shown in Figure 2, with a direction of treatment effect favoring endovascular therapy (P = .011). This excludes eleven subjects without mRS information (missing or obtained outside the assessment window).

Figure 2

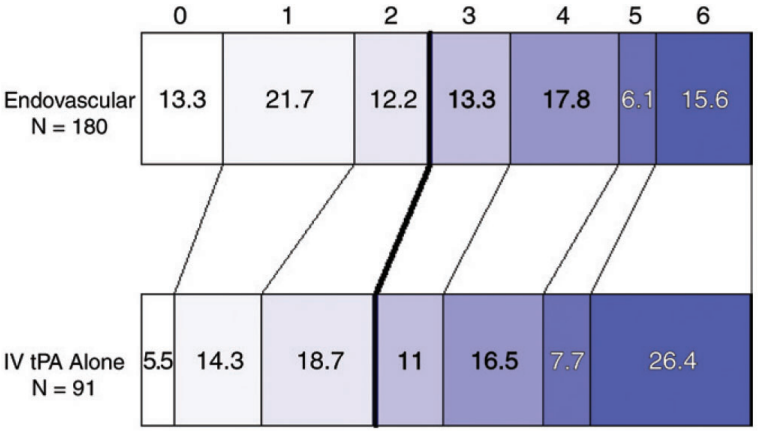

Figure 2: Diagram shows post hoc baseline CT angiography distribution of any visible occlusions. The mRS distribution was not significantly different (generalized Wilcoxon test, *P* = .011).

Individual sites of occlusion were subdivided in an exploratory fashion to identify any potentially unique differences in clinical outcomes between treatment arms. The 24-hour recanalization rates according to specific site of occlusion are reported in Table 3.

The carotid T- and L-type occlusions were combined with tandem ICA and M1 occlusions, as these occlusions represent the largest thrombus volumes. No significant baseline imbalances between treatment arms were present. In this subgroup, the direction of

Table 3

24-Hour Recanalization Rates in Each Treatment Arm according to CT Angiography–based Site of Occlusion

Baseline Primary Occlusion Vessel Category	Percentage of Occlusions Recanalized in Subjects with 24-Hour CT Angiography Data		
	Endovascular Therapy	IV tPA Only	Treatment Difference
All occlusions*	86.3 (79.6, 91.4)	64.7 (52.2, 75.9)	21.6 (9.4, 34.3)
Proximal ICA, M1, basilar artery occlusion	84.3 (76.4, 90.5)	55.8 (41.3, 69.5)	28.6 (13.8, 43.1)
ICA T- or L-type occlusion or tandem ICA and M1 occlusion	83.3 (65.3, 94.4)	27.8 (9.7, 53.5)	55.6 (26.9, 73.5)
Proximal M1 occlusion, no ICA involvement	90.3 (74.3, 98.0)	80.0 (44.4, 97.5)	10.3 (−10.6, 42.0)
Distal M1 occlusion, no ICA involvement	85.1 (71.7, 93.8)	85.7 (63.7, 97.0)	−0.6 (−16.4, 21.1)
M2 occlusion with or without ICA involvement	88.5 (69.9, 97.6)	78.6 (49.2, 95.3)	9.9 (−12.4, 37.1)
M3 and M4 occlusion with or without ICA involvement	100.0 (NA)	100.0 (NA)	NA
Basilar artery, vertebral artery with basilar artery, posterior cerebral artery occlusion	83.3 (35.9, 99.6)	33.3 (0.8, 90.6)	50.0 (−10.7, 80.4)

Note.—Numbers in parentheses are 95% confidence intervals. NA = not applicable.

* Two subjects with isolated extracranial ICA occlusions were excluded.

treatment effect was in favor of endovascular treatment compared with IV tPA alone for the primary effectiveness end point (26% [12 of 46] vs 4% [one of 23], P = .047). The safety end points (SICH, 11% [five of 46] vs 13% [three of 23], P. .99; 90-day mortality, 37% [17 of 46] vs 48% [11 of 23], P = .39) were not significantly different. The full mRS distribution is shown in Figure 3a, with a direction of treatment effect favoring endovascular therapy (P = .02).

The proximal M1 involvement (but no ICA occlusion) subgroup showed no treatment effect between the endovascular (n = 41) and IV tPA (alone) (n = 19) arms for both primary effectiveness (46% [19 of 41] vs 42% [eight of 19], P = .76) and safety end points (SICH, 7% [three of 41] vs 5% [one of 19], P . .99; 90-day mortality, 17% [seven of 41] vs 16% [three of 19], P . .99). Analysis of the full mRS distribution (Fig 3b) was not significant (P = .93). The distal M1 involvement (but no ICA occlusion) subgroup showed no treatment effect between endovascular and IV tPA (alone) arms for both the primary effectiveness (50% [27 of 54] vs 64% [16 of 25], P = .25) and the safety end points (SICH, 7% [four of 54] vs 0% [zero of 25], P = .30; 90-day mortality, 2% [one of 54] vs 12% [three of 25], P = .09). Analysis of the full mRS distribution (Fig 3c) was also not significant (P = .47).

The M2 segment with or without ICA occlusion subgroup showed no treatment effect between the endovascular and IV tPA (alone) arms for both the primary effectiveness

(50% [18 of 36] vs 44% [eight of 18], P = .70) and SICH end point (6% [two of 36] vs 11% [two of 18], P = .59). A trend in favor of endovascular treatment was seen for 90-day mortality (6% [two of 36] vs 33% [six of 18], P = .012). The analysis of the full mRS distribution (Fig 3d) was not significant (P = .14).

Figure 3

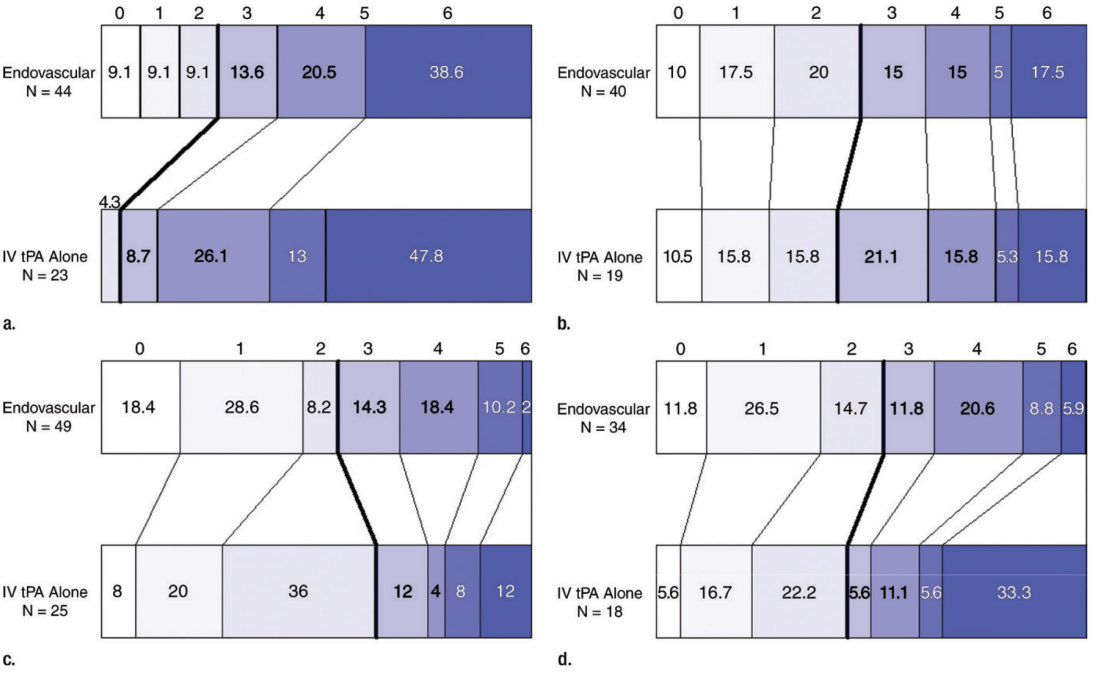

Figure 3: Diagrams show distribution of findings at baseline CT angiography. **(a)** Carotid T- or L-type occlusions or tandem ICA and M1 occlusions. The mRS distribution was not significantly different (generalized Wilcoxon test, *P* = .02). **(b)** Proximal M1 occlusions without ICA involvement. The mRS distribution was not significantly different (generalized Wilcoxon test, *P* = .93). **(c)** Distal M1 occlusions without ICA involvement. The mRS distribution was not significantly different (generalized Wilcoxon test, *P* = .48). **(d)** M2 occlusion with or without ICA involvement. The mRS distribution was not significantly different (generalized Wilcoxon test, *P* = .14).

There were too few subjects in the subgroup with M3 and M4 involvement or anterior cerebral artery involvement with or without ICA occlusion (n = 5) and the subgroup with posterior circulation (basilar artery alone, vertebral artery and basilar artery, posterior cerebral artery) occlusion (n = 9) to make useful comparisons.

DISCUSSION

This baseline CT angiography subgroup of the IMS III trial represents a large cohort of randomized subjects with prerandomization vascular imaging information. Few randomized acute stroke trials have served to capture baseline vascular imaging with standardized follow-up imaging, and none have involved comparison of IV tPA and IV tPA followed by endovascular therapy. This current analysis demonstrated no differences in the primary outcome measure for the prespecified subgroup of subjects with the proximal occlusion subgroup of ICA, M1, and basilar arteries as identified with baseline vascular imaging. However, in a post hoc analysis of the entire baseline CT angiography subgroup with an intracranial occlusion, a trend toward better outcomes with endovascular treatment versus IV tPA alone was observed. This effect was largely driven by the subpopulation of occlusions that involved the ICA (carotid T- and L-type or tandem ICA and M1 occlusions). In the subgroup of the trial with both baseline and 24-hour CT angiography information available, recanalization at 24 hours was significantly more frequent in the endovascular arm than the IV tPA arm. This difference was also most evident in subjects with ICA occlusions where a low rate of 24-hour recanalization was seen with IV tPA alone. The large differential recanalization and clinical treatment effects with endovascular treatment in tandem ICA and M1 occlusions or terminal ICA occlusions is the most important finding and implies that in future clinical trials, investigators should pay particular attention to this subgroup and perhaps even stratify enrollment on the basis of the presence of a carotid T- or L-type or tandem ICA and M1 occlusion (3).

Another important finding of this analysis was the safety (4) of baseline vascular imaging in reperfusion treatment trials of IV tPA versus combined therapy. No differences in clinical outcome were seen in the trial subgroup that received IV tPA alone and underwent CT angiography versus those that did not, suggesting no evidence for impaired thrombolytic effect of radiographic contrast material on tPA activity as postulated in the cardiac literature (5,6). Contrast material-induced nephropathy was not prominent, and no differences in creatinine levels were seen on day 5 or in discharge rates between those that underwent baseline CT angiography and those that did not. A wide variability in the rate of recanalization and clinical outcome with IV tPA administration according to the specific site of occlusion has been reported previously in nonrandomized cohort

studies (7-13). The IV tPA 1-2 hour recanalization rates for intracranial ICA occlusion have been reported as being very low (4%-8%) (7,10) with correspondingly low rates of 90-day good outcome (0%-29%) (3,12-15). Rates of recanalization for intracranial ICA occlusions exceed 50% after endovascular treatment (16). Good clinical outcome with endovascular treatment in ICA occlusions ranges from 10% to 56%. Cervical ICA occlusions are associated with better outcomes than terminal ICA occlusions (15). Isolated M1 occlusions fare much better with systemic thrombolysis alone, with 1-2 hour recanalization rates of 26%-32% (7,10) and good outcome in the 24%-67% range, depending on exact origin of occlusion within the M1 segment (13). Endovascular treatment has been associated with high rates of good clinical outcome in M1 occlusions (17,18). The differential effects of endovascular treatment according to the presence and site of occlusion are consistent with prior trials, such as the Echoplanar Imaging Thrombolytic Evaluation Trial, or EPITHET, where the ICA occlusion population had very poor outcomes despite undergoing IV tPA treatment (3). This analysis provides compelling data, from a randomized trial, that a treatment effect in favor of endovascular treatment over standard IV tPA may exist for ICA occlusions. The planned third International Stroke Trial, or IST-3, analysis of prerandomization vascular imaging data to compare IV tPA with placebo will provide an interesting set of data to compare with those in the IMS III (19). On the basis of prior literature, the two unexpected results of the study were the high rates of good outcome with IV tPA alone in M1 occlusions and the lack of relationship between higher 24-hour recanalization and better rates of good outcome. Twenty-four-hour recanalization rates of M1 occlusions were similar and were high in the two treatment arms. Distal M1 occlusions did particularly well with IV tPA treatment alone, perhaps owing to smaller clot length. Very early treatment and larger sample sizes are likely to be required in future trials when comparing newer endovascular technologies (ie, stentrievers or aspiration) to IV tPA alone in M1 occlusions. The proximal occlusion subgroup had a 25% higher rate of 24-hour recanalization with endovascular therapy, but this translated into only a 3% higher rate of favorable clinical outcome. Patient selection (20,21), use of general anesthesia (22), endovascular treatment delays (23), extent of reperfusion despite recanalization (24), and endovascular treatment-related adverse events are possible explanations that require further study. The 24-hour recanalization end point may also be too late and have less effect on clinical outcome than an early (1-2 hour posttreatment) recanalization or reperfusion end point.

This analysis of baseline CT angiography and recanalization has limitations. Only 47% of all enrolled subjects in the IMS III trial underwent baseline vascular imaging. Baseline CT angiography was performed in at least one subject at 78% of all enrollment sites in the trial. Although this subgroup may not fully represent the entire IMS III population, baseline characteristics were similar to those of the population who did not undergo baseline CT angiography, with the exception of shorter time to endovascular treatment. This reflects a bias that centers where baseline CT angiography is performed follow a direct to comprehensive stroke center model in which patients are transported directly to a hospital where they may undergo endovascular treatment. Pertaining to the 24-hour recanalization end point, some subjects did not undergo repeat CT angiography, potentially creating a bias toward those with higher recanalization rates and better outcomes among those well enough to undergo repeat imaging. Another limitation is the use of a nonstandardized assessment of CT angiography recanalization; no CT angiography-based recanalization scales have been published to date. We focused specifically on the proximal intracranial arterial occlusive lesion and not downstream lesions, which may have led to the overestimation of the degree of recanalization overall. We also cannot comment on tissue-based reperfusion because single-phase CT angiography is limited to a snapshot in time in the arterial or early venous phase of imaging. This is best accomplished with conventional angiography, time-resolved and/or multiphase CT angiography, or CT perfusion imaging.

We conclude from this analysis that no clear differences in outcome were identified in the population with proximal occlusion in the IMS III trial. A post hoc analysis of carotid T- or L-type occlusions and tandem ICA and M1 occlusions showed greater recanalization and a trend toward better outcomes with endovascular treatment compared with IV tPA alone. A pooled analysis of recently completed and current endovascular trials is needed to confirm this encouraging finding in favor of endovascular treatment. Future comparisons of endovascular and thrombolytic treatment with thrombolytic treatment alone should include baseline vascular imaging in trial design, given the safety of CT angiography and wide differences in clinical effects and recanalization according to occlusion site seen in the IMS III trial. In such trials, investigators could then stratify enrollment on the basis of the presence of a carotid T- or L-type occlusion or a tandem ICA and M1 occlusion.

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Supplementary Appendix

Recanalization Grading Methods

The individual arterial segments were each graded 1–5 according to the following: grade 1, complete occlusion; grade 2, hairline lumen; grade 3, more than 50% stenosis; grade 4, up to 50% stenosis; and grade 5, normal. The occlusion locations were defined by the grade of stenosis and/or occlusion and specific segments involved:

Carotid T- or L-type: Grade 1 or 2 flow was present in the terminal ICA segment distal to the posterior communicating artery and proximal half of the M1 segment with or without grade 1 or 2 flow in the A1 segment (T-type if A1 was involved, L-type without A1 involvement).

Tandem ICA with M1 involvement: Grade 1 or 2 flow was present in any or all segments of the extracranial and intracranial ICA (except the terminal ICA segment distal to the posterior communicating artery) and the proximal or distal M1 segment.

Proximal M1: Grade 1 or 2 flow was present in the proximal half of the M1 segment, without any ICA segment having grade 1 or 2 flow.

Distal M1: Grade 1 or 2 flow was present in the distal half of the M1 segment, without any ICA segment having grade 1 or 2 flow, and grade 3–5 flow occurred in the proximal half of the M1 segment.

M2 with or without ICA involvement: Grade 1 or 2 flow was present in a single M2 segment or multiple M2 segments, with or without any involved segments of the ICA graded 1 or 2. Grade 3–5 flow was present in all M1 segments.

M3 and M4 with or without ICA involvement: Grade 1 or 2 flow present in a single M3 segment or multiple M3 segments, with or without any involved segments of the ICA graded 1 or 2. Grade 3–5 flow was present in all M1 and M2 segments.

Anterior cerebral artery: Grade 1 or 2 flow was present in a single A1 or A2 segment or multiple A1 or A2 segments. Grade 3–5 flow was present in all M1 and M2 segments.

Basilar artery and vertebral artery: Grade 1 or 2 flow was present in at least one basilar segment and vertebral artery segment.

Basilar artery: Grade 1 or 2 flow was present in at least one basilar segment, without grade 1 or 2 involvement in any vertebral artery segment.

Posterior cerebral artery: Grade 1 or 2 flow was present in at least one segment of the posterior cerebral artery, without grade 1 or 2 flow in any segments of the basilar or vertebral artery segments.

Recanalization was defined as improvement in flow to grade 3–5 (nonocclusive) from grade 1–2 (occlusive or near occlusive) in specific segments, depending on the site of occlusion. The specific segments that were used to define recanalization for carotid T- or L-types were the terminal ICA distal to the posterior communicating artery and the proximal half of the M1 segment. In tandem ICA and M1 recanalization, all segments of the ICA and M1 were required. In tandem vertebral and basilar artery recanalization, all basilar segments were required. In all other occlusion locations, the previously occluded proximal intracranial segments that were used to define the occlusion location required flow improvement (ie, proximal M1 was the proximal M1 segment, and M2 was one or both M2 segments).

Suggested 24-Hour CT Angiography Protocol

The IMS III protocol required that CT angiography of the intracranial vasculature be performed at 24 hours - 6 after index treatment (to be performed at the time of the safety CT), unless it was unavailable or the subject had a contraindication to CT (ie, an allergy to contrast material).

Parameters for CT angiography of the Circle of Willis included use of a multisection scanner with the subject in the supine position to view the orbital medial line landmark. IV contrast agent was used at a dose of 100 mL injected at a rate of 4 mL/sec (more may

be used for a slower scanner, and an attempt was made to use the highest concentration available [ie, iohexol 300 or higher]).

Ideally, automatically triggered bolus timing was used, with the region of interest placed over the aortic arch or, alternatively, a timed scanning approach was acceptable, with a scout position of 90°, scout tube potential of 120 kV, and scout amperage of 10 mA. Helical CT acquisition of the Circle of Willis was performed from the base of the skull to the centrum semiovale with a gantry angle of 0° and use of a standard algorithm with a section thickness of 2.5 mm, image spacing of 2.5 mm, table feed of 3.75 mm, pitch of 0:75:1, use of HQ mode with 120 kV, 280 mA, rotation time of 0.8 seconds, field of view of 15 cm of the head, and display field of view of 22 cm.

Retrospective helical reconstructions were performed by keeping the anterior-posterior and right-left coordinates consistent between the groups. Section thickness was set at 1.25 mm with 0.625-mm spacing. (If the scanner is slow and such thin-section imaging is not practically feasible, please contact the Calgary Imaging Coordinating Centre.) A field of view of 18 cm was used.

Multiplanar volume reformats in the sagittal, axial, and coronal planes were acquired with a section thickness of 4 mm, with 1-mm spacing and a field of view of 13 cm.

CHAPTER 4.2

Correlation Between Clinical Outcomes And Baseline CT And CT Angiographic Findings In The SWIFT PRIME Trial

Based upon:

Correlation Between Clinical Outcomes and Baseline CT and CT Angiographic Findings in the SWIFT PRIME Trial

Ashutosh P. Jadhav, Hans-Christopher Diener, Alain Bonafe, Vitor M. Pereira, EladI. Levy, Blaise W. Baxter, Tudor G. Jovin, Raul G. Nogueira, Dileep R. Yavagal, Chritoph Cognard, Dirk D. Purcell, Bijoy K. Menon, Reza Jahan, Jeffrey L. Saver, and Mayank Goyal.

AJNR Am J Neuroradiol. 2017 Dec;38(12):2270-2276.

ABSTRACT

Background and Purpose

Patient selection for endovascular therapy remains a great challenge in clinic practice. We sought to determine the effect of baseline CT and angiography on outcomes in the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial and to identify patients who would benefit from endovascular stroke therapy.

Materials and Methods

The primary end point was a 90-day modified Rankin Scale score of 0-2. Subgroup and classification and regression tree analysis was performed on baseline ASPECTS, site of occlusion, clot length, collateral status, and onset-to-treatment time.

Results

Smaller baseline infarct (n = 145) (ASPECTS 8-10) was associated with better outcomes in patients treated with thrombectomy versus IV tPA alone (66% versus 41%; rate ratio, 1.62) compared with patients with larger baseline infarcts (n = 44) (ASPECTS 6-7) (42% versus 21%; rate ratio, 1.98). The benefit of thrombectomy over IV tPA alone did not differ significantly by ASPECTS. Stratification by occlusion location also showed benefit with thrombectomy across all groups. Improved outcomes after thrombectomy occurred in patients with clot lengths of >8 mm (71% versus 43%; rate ratio, 1.67). Outcomes stratified by collateral status had a benefit with thrombectomy across all groups: none-fair collaterals (33% versus 0%), good collaterals (58% versus 44%), and excellent collaterals (82% versus 28%). Using a 3-level classification and regression tree analysis, we observed optimal outcomes in patients with favorable baseline ASPECTS, complete/ near-complete recanalization (TICI 2b/3), and early treatment (mean mRS, 1.35 versus 3.73), while univariate and multivariate logistic regression showed significantly better results in patients with higher ASPECTS.

Conclusion

While benefit was seen with endovascular therapy across multiple subgroups, the greatest response was observed in patients with a small baseline core infarct, excellent collaterals, and early treatment.

Patient selection for mechanical thrombectomy in acute ischemic strokes presents a major challenge in achieving good outcomes. First-generation randomized controlled trials investigating the benefit of intra-arterial therapy failed to demonstrate improved rates of independence in the treatment group. A limitation of these trials was the large baseline core infarcts at the time of enrollment. In the Interventional Management of Stroke III (IMS III) trial, 40% of patients had lower Alberta Stroke Program Early CT Scores on presentation (ASPECTS 0-7).[1] In patients with lower ASPECTS, there was a 2-fold less likelihood of benefit with IV or intra-arterial therapy compared with patients with higher ASPECTS. In the Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) trial, the core baseline infarct was 36 mL at enrollment with only 21% of patients achieving functional independence at 90 days (modified Rankin Scale score, 0-2).[2] To overcome these constraints, the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment for Acute Ischemic Stroke (SWIFT PRIME) trial limited enrollment to patients with small-moderate core infarcts as defined by head CT, CT angiography, and/or CT perfusion. We have previously reported on the primary outcomes of the SWIFT PRIME trial[3] and the secondary prespecified analysis of baseline CT perfusion imaging and follow-up infarct volume and outcomes.[4,5] In this study, we describe the effect of the baseline CT and CTA findings on clinical outcome.

MATERIALS and METHODS

The study design of the SWIFT PRIME trial has been previously described.[3,6] Primary outcomes for all 196 patients have been previously reported,[3] while a subset of 151 patients has been evaluated and presented for outcomes based specifically on perfusion imaging.[4] In this article, we report, for the first time, the effects of imaging parameters (including ASPECTS and collateral status), substantial reperfusion, and time to treatment on clinical outcomes. An independent core imaging lab evaluated all imaging. Baseline head CT was available for review in 185 patients. CT angiography was available for review in 88% of patients. The ASPECTS is a 10-point semiquantitative topographic score for assessing stroke burden in the middle cerebral artery distribution on CT.7 Enrollment (after the first 71 patients) was restricted to patients with ASPECTS scores of >5. For the first 71 patients, the inclusion criteria were based on a CT perfusion study as follows: ischemic core lesion volume, <50 mL; time-to-maximum, >10 seconds; lesion volume, <100 mL; mismatch volume, >15 mL; and mismatch ratio, >1.8. Ischemic core was defined as an area with >70% reduction in CBF (relative CBF < 0.3) in comparison with the mean CBF of normally perfused brain parenchyma. An ischemic core lesion defined by CT perfusion corresponds to an ASPECTS of >5.

For subgroup analysis according to ASPECTS, we made 2 comparisons of higher-versus-lower ASPECTS: ASPECTS 8-10 versus ASPECTS 6 -7 and ASPECTS 9-10 versus ASPECTS 6-8. The site of occlusion was defined by baseline head CTA: ICA occlusion, proximal M1 occlusion, middle M1 occlusion, and distal M1/M2 occlusion. Clot length was measured on CTA or MRA as the length of a vessel that was nonopacified/nonvisualized using 5-mm multiplanar MIP reformations. Contrast-enhanced MRA was used whenever possible. In a subset of cases in which the distal end of the clot could not be identified, CT perfusion source images allowed visualization and measurement of the clot. The earlier phases of CTP were used to determine the proximal end of the clot, while the later phases were used to determine the distal end of the clot. Prior studies have identified a thrombus length of >8 mm in the middle cerebral artery as being refractory to recanalization from intravenous thrombolysis,[8] which can potentially impact clinical outcomes. To understand the impact of clot length on responsiveness to endovascular therapy, clinical outcomes were compared in patients with >8 mm of thrombus.

Collateral Scoring on CTA

Collateral assessment was defined on CTA as excellent, good, fair, poor, minimal, or none.[9] Definitions were as follows: excellent, increased or normal prominence and extent of pial vessels beyond the occluded artery within the symptomatic hemisphere; good, slightly reduced prominence and extent of pial vessels beyond the occluded artery within the symptomatic hemisphere; fair, moderately reduced prominence and extent of pial vessels beyond the occluded artery within the symptomatic hemisphere; poor, decreased prominence and extent and regions with no vessels in some part of the occluded territory; minimal, compared with the asymptomatic contralateral hemisphere, just a few vessels visible in the occluded vascular territory; and none, no vessels visible within the occluded vascular territory.[9]

Statistical Analysis

All available data were used for analyses. Statistical tests for binary variables were performed with the Fisher exact test, and for continuous variables, they were performed with the Student *t* test. Univariate and multivariate logistic regressions were used to test relationships between potential predictor variables and outcomes defined by the modified Rankin Scale score of 0-2 at 90 days. Classification and regression tree analysis were used to further investigate relationships among study variables. All statistical tests were 2-sided. with P values < .05 considered statistically significant. All analyses were performed in R, Version 3.0 or above (R Foundation for Statistical Computing; Vienna, Austria; http://www.R-project.org).

RESULTS

Baseline CT ASPECTS

A higher baseline ASPECTS of 8-10 was noted in 145 patients (74 in the IV tPA arm; 71 in the endovascular and IV tPA arm), of whom 142 had mRS available at 90 days. Good outcomes (mRS 0-2) at 90 days were observed in 66% of patients in the treatment arm compared with 41% of patients in the control arm (P = .004). Lower baseline ASPECTS

of 6-7 was noted in 44 patients (24 in the IV tPA arm; 20 in the endovascular and IV tPA arm). Good outcomes were observed in 42% of patients in the treatment arm compared with 21% of patients in the control arm (P = .2; Fig 1). In univariate and multivariate logistic regression analyses, a higher baseline ASPECTS was associated with better outcomes, particularly when dichotomized for ASPECTS of 9-10 versus <8 (Tables 1 and 2).

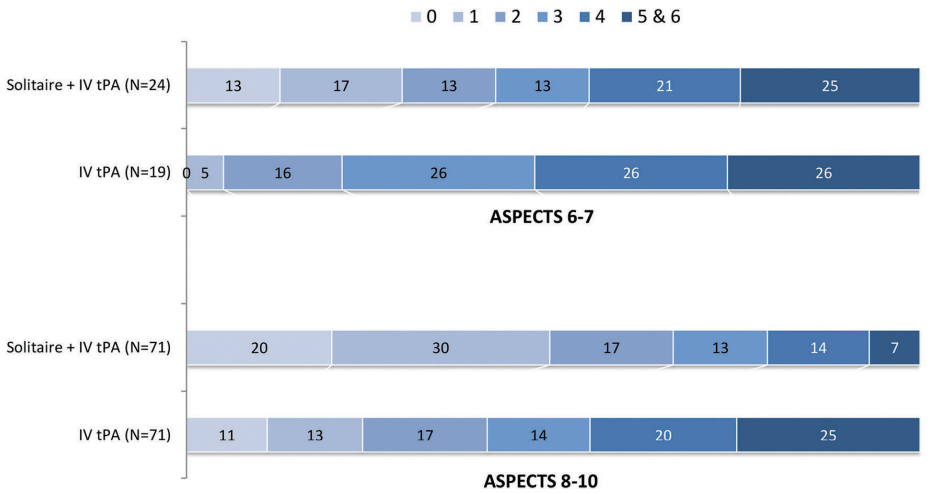

FIG 1. Influence of baseline CT ASPECTS on outcome (90-day mRS), indicating better outcomes with higher ASPECTS and better outcome with endovascular therapy irrespective of ASPECTS.

Site of Occlusion

Distribution of the site of occlusion was as follows: ICA (20 patients), proximal M1 (39 patients), middle M1 (55 patients), and distal M1/M2 (49 patients). Treatment effect with endovascular therapy was noted across all sites of occlusion (Fig 2), with the greatest treatment effect in patients with a proximal M1 occlusion (88% versus 14%, P < .0001). The site of occlusion was not significantly associated with good outcome in the univariate analysis (Table 1).

Table 1: Univariate predictors of functional independence (mRS 0–2) at 90 days, endovascular arm only[a]

Predictor	No. Total	No. Category	Odds Ratio	Lower CI	Upper CI	*P* Value
ASPECTS (per unit)	95	NA	1.53	1.09	2.15	.015
ASPECTS 8–10 (vs 6–7)	95	71/24	2.74	1.06	7.08	.037
ASPECTS 9–10 (vs 6–8)	95	52/43	3.43	1.45	8.09	.005
M1 occlusion (vs non-M1)	95	60/35	2.12	0.90	4.97	.085
Onset-to-groin puncture (per 60 min)	94	NA	0.68	0.48	0.98	.040
TICI 3 postprocedure (vs ≤TICI 2b)	80	56/24	2.11	0.79	5.61	.13
TICI 2b/3 postprocedure (vs ≤TICI 2a)	80	70/10	1.80	0.47	6.82	.39
Collateral grade (per unit)	56	NA	2.77	1.13	6.82	.026
Clot length (per mm)	50	NA	1.12	0.96	1.30	.14
Clot length of ≥8 mm (vs <8 mm)	50	44/6	2.38	0.42	13.40	.32
Clot length of ≥13 mm (vs <13 mm)	50	23/27	2.48	0.71	8.66	.16

Note:—No. reflects the number of data points available for each variable; NA, not applicable.
[a] Univariate logistic regression analysis of patients undergoing endovascular therapy was performed with the following variables: ASPECTS (as scored on preprocedural head CT, 6–7 vs 8–10 and 6–8 vs 9–10), site of occlusion (M1 versus non-M1), onset to groin puncture, quality of recanalization (TICI scale), collateral grade, and clot length (>8 mm versus <8 mm).

Table 2: Multivariate predictors of functional independence (mRS 0–2) at 90 days, endovascular arm only[a]

Predictor	No. Total	No. Category	Odds Ratio	Lower CI	Upper CI	*P* Value
ASPECTS 9–10 (vs 6–8)	48	28/20	4.25	1.06	17.10	.042
Onset-to-groin puncture (per 60 min)	48	NA	0.79	0.44	1.42	.43
TICI 2b/3 postprocedure (vs ≤TICI 2a)	48	43/5	1.03	0.12	8.46	.98
Collateral grade (per unit)	48	NA	2.85	0.90	9.08	.076

Note:—No. reflects the number of data points available for each variable; NA, not applicable.
[a] Multivariate logistic regression analysis of patients undergoing endovascular therapy was performed with the following variables: ASPECTS (as scored on preprocedural head CT), onset to groin puncture, quality of recanalization (TICI scale), and collaterals.

Length of Clot

Clot length was available in 111 patients, of whom 89% had >8-mm clot length. In this subgroup, 71% of patients having undergone thrombectomy versus 43% of patients receiving IV tPA alone had good outcomes (P = .005, Fig 3). Median clot length was 13 mm. In 59 patients with a clot length greater than the median, 79% of patients having undergone thrombectomy versus 34% of patients with IV tPA alone had good outcomes (P =.001). In univariate analysis, clot length was not associated with good outcome in the subgroup of patients treated with endovascular therapy (Table 1).

Quality of Collaterals

Collateral status on baseline head CTA was available for review in 113 patients. Poor collaterals (none-to-fair) were noted in 19% of patients with a median baseline ASPECTS of 8 and a mean core infarct volume of 18.9 mL. High-quality collaterals (good-to-excellent) were associated with a median baseline ASPECTS of 9 and a mean core infarct volume of 7.4 mL. A beneficial effect of endovascular therapy was observed over IV tPA alone across all levels of collateral flow, with the greatest effect in patients with excellent collaterals (82% versus 28%, P = .008; Fig 4). In univariate and multivariate analysis, a good collateral grade was associated with good outcome (statistically significant in univariate analysis and a trend toward significance in multivariate analysis) (Tables 1 and 2).

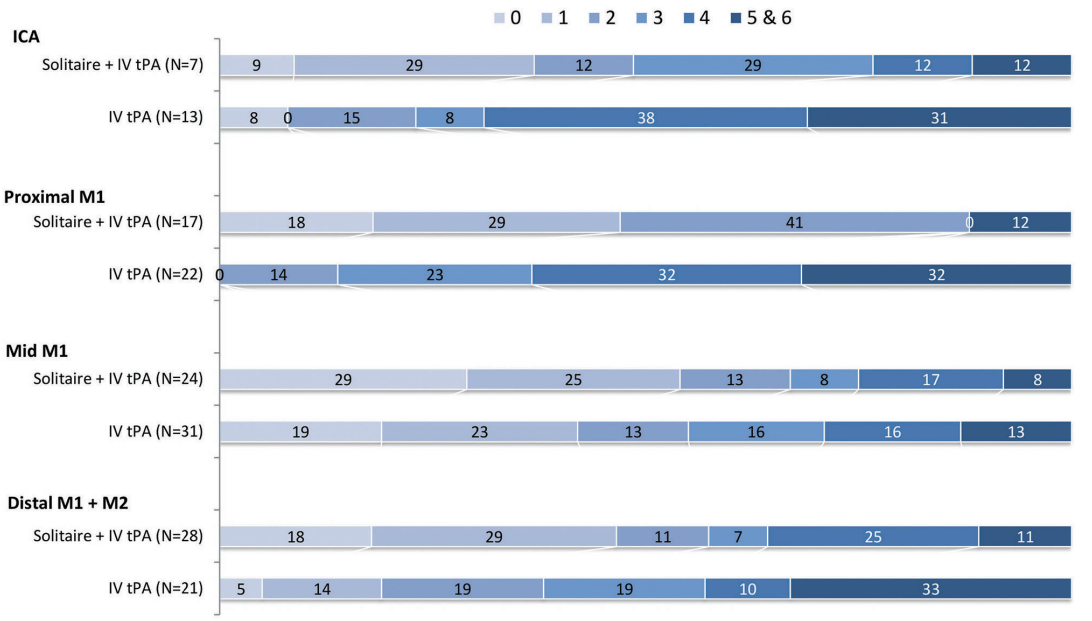

FIG 2. Influence of the site of occlusion on outcome (90-day mRS), indicating better outcome with endovascular therapy irrespective of site and the greatest treatment effect in proximal M1 occlusions.

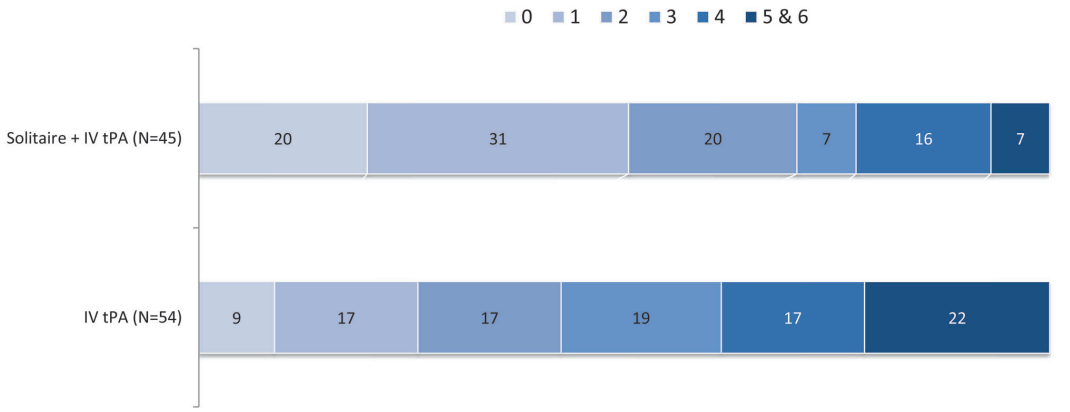

FIG 3. Outcomes (90-day mRS) in patients with a clot length of ≥8 mm, indicating statistically superior outcomes with endovascular therapy in these clots.

Classification and Regression Tree Analysis

Univariate analysis revealed that favorable ASPECTS, earlier treatment, good collaterals, and complete recanalization are associated with better outcomes (Table 1). With the classification and regression tree algorithm, binary cut points affecting outcome were identified as dichotomized ASPECTS (ASPECTS 9 -10 versus ASPECTS 6-8), onset-to-puncture time (within 4 hours versus beyond 4 hours), and quality of recanalization (TICI 3 versus TICI 2b or less). Of 98 patients undergoing thrombectomy, better outcomes were observed in patients with favorable ASPECTS, early treatment, and complete recanalization (Fig 5). In the patients undergoing thrombectomy, the average time from symptom onset to recanalization was 260 minutes and the rate of TICI 2b/3 recanalization was 88% (70/80).

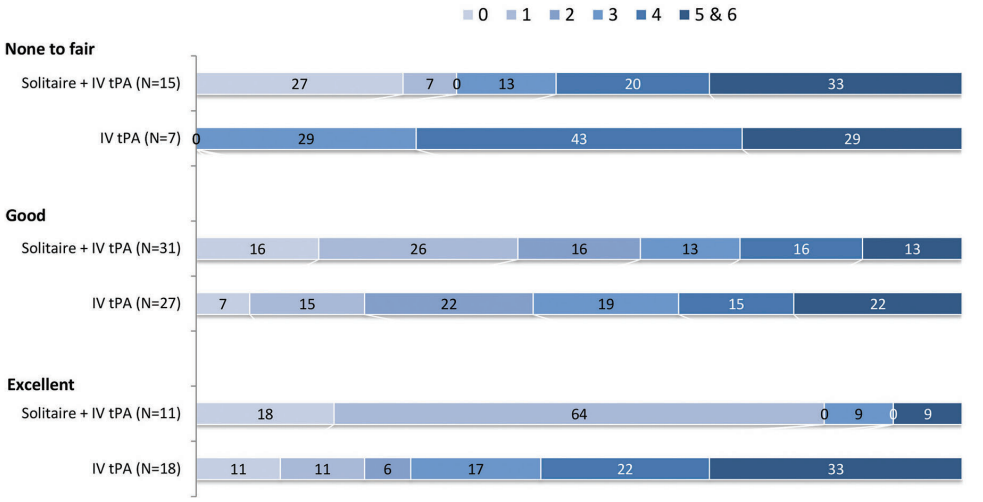

FIG 4. Influence of baseline collateral status on outcome (90-day mRS), indicating better outcomes with better collaterals, better outcomes with endovascular therapy irrespective of collateral quality, and the greatest treatment effect associated with excellent collaterals.

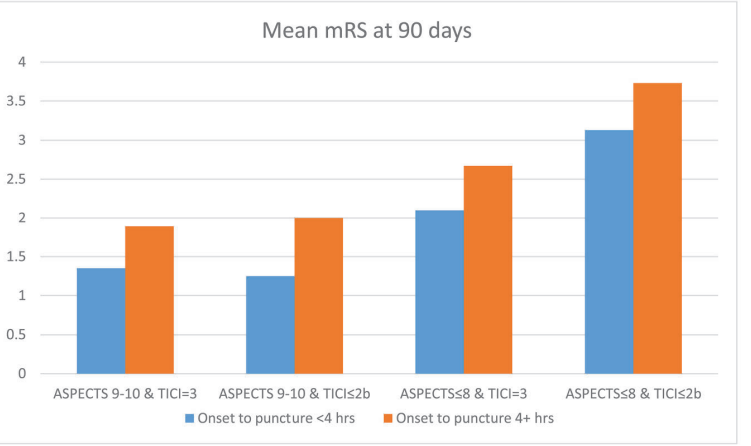

FIG 5. Mean mRS in dichotomized subgroups identified by classification and regression tree analysis indicating time to recanalization, initial ASPECTS, and TICI scores posttreatment as substantial predictors of outcome with the displayed cut-points for dichotomization.

DISCUSSION

While the primary results of the SWIFT PRIME study revealed a benefit of endovascular therapy over intravenous thrombolysis alone in patients with acute ischemic stroke, several questions remain about understanding subsets of patients most likely to benefit from intra-arterial therapy. In this report, we found that the benefit of endovascular therapy persisted across multiple subgroups, with the highest likelihood of benefit noted in patients with higher ASPECTS, early treatment, and favorable collaterals.

Previous studies of endovascular therapy (Intra-arterial Prourokinase for Acute Ischemic Stroke [PROACT II] and IMSI) demonstrated a strong interaction between favorable ASPECTS (8 -10)[10,11] and outcome; however, a similar analysis of IMS III did not confirm this relationship.[1] Failure to appreciate this relationship in IMS III has been attributed to long onset-to-treatment times as well as the low reperfusion rates in the treatment arm. In contrast, the SWIFT PRIME trial had fast treatment times and high rates of reperfusion. Furthermore, the baseline ASPECTSs in SWIFT PRIME were much higher, with 72% of patients having an ASPECTS of 8 -10 compared with 58% of patients in IMS III.[1] We found that patients with higher ASPECTS had better clinical outcomes, particularly with endovascular therapy. This finding is in keeping with numerous other studies demonstrating that baseline ASPECTS is an important predictor of final outcome.

In the SWIFT PRIME trial, patients were selected for enrollment on the basis of small core infarcts on presentation. Accordingly, the current analysis is limited to patients with overall favorable ASPECTS. The benefit of complete or near-complete recanalization of patients with poor ASPECTS (<5) remains unclear and may warrant further investigation,[12] particularly in younger patients in whom recanalization may limit further infarct growth. Such a clinical result may not be well-captured in a dichotomized mRS outcome of 0 -2 versus 3- 6, but it may spare a young patient hemicraniectomy, respiratory compromise, or other stroke-related complications. Furthermore, a population with a poor ASPECTS may be well-suited for bridging neuroprotection therapies in which recanalization along with adjunctive therapy may result in acceptable outcomes.[13]

ASPECTS alone is a single freeze-frame in the evolution of necrosing brain tissue. Additional information about the speed and extent of infarct burden can be inferred by clinical examination (a large deficit suggests large tissue at risk), perfusion imaging, and collateral status. The presence of robust collateral blood circulation indicates brain tissue that is more likely to be reperfused and, when reperfused, more likely to have a favorable response.[14] Additionally, patients with robust collaterals are likely to have smaller core infarcts on presentation. Furthermore, previous studies have indicated that reperfusion therapies in patients with poor baseline collateral circulation do not typically have a favorable response, and this feature eventually results in a higher likelihood of infarct growth.[15] Most interesting, we found trends toward benefit in patients with poor baseline collateral status after endovascular therapy, though the overall numbers are small and not statistically significant. This population will require further examination because the natural history tends to be quite poor and treatment options are limited. A caveat with collateral assessment is that single-phase CTAs may mislabel patients with moderate-to-good collaterals as poor in CTAs that are mistimed (acquired in the early arterial phase). Collateral assessment with multiphase CTA is a potential solution.[16] Arguably, patients with poor collateral circulation presenting at early time windows may continue to benefit from thrombectomy if achieved in ultrarapid fashion. Given the quickly growing core infarct in this population, there may be a role for additional therapies designed to arrest stroke progression, such as neuroprotective therapy[17] or hypothermia.

The site of occlusion and thrombus burden is associated with failure of IV tPA to recanalize large-vessel occlusion. Distal occlusions such as M2 or distal M1 are particularly responsive to IV tPA, whereas proximal occlusions such as ICA or proximal M1 are more refractory to IV tPA.[18] While benefit was observed with endovascular therapy across groups, the highest benefit was noted in proximal M1 occlusions compared with distal M1 occlusions. Similarly, IV tPA is less effective as thrombus burden increases. In 1 study of patients undergoing intravenous thrombolysis for acute stroke, hardly any patients (<1%) with clot measuring >8 mm had successful recanalization.[8] One limitation of measuring clot length on CTA is that it does not accurately define the thrombus extent because the lack of distal contrast opacification may be related to delayed distal filling rather than a true filling defect. In univariate analysis, the site of occlusion and clot length did not predict 90-day mRS 0 -2 after endovascular therapy. It is possible that the effectiveness of endovascular therapy to recanalize such clots may mitigate the role of

clot length in predicting good clinical outcomes. A priori identification of IV tPA nonresponders may ultimately guide future management strategies in which IV thrombolysis may be bypassed in favor of a direct intra-arterial therapy.[18]

Limitations

There are important limitations to our study. First, the sample size is relatively small, so further validation of our findings will require analysis in a larger cohort of patients. Second, given the nature of the study design and focus on patients re-presenting with small core infarcts, very few patients in our analysis had large core infarcts on initial presentation. The extent of benefit in this larger core population remains unanswered. Additionally, the participating clinical sites in the SWIFT PRIME trial were specifically selected on the basis of clinical volume and expertise. The generalizability of these results across additional centers remains untested. Finally, this study included post hoc analysis, so additional confirmation will require prospective studies of specific subgroups and patient features.

CONCLUSIONS

Overall, this report supports the selection of patients for intra-arterial therapy on the basis of favorable patient characteristics (small core, good collateral circulation) and low likelihood of recanalization with intravenous thrombolysis (large and proximal clot burden). Additional studies will be needed to further understand the continued benefit of intra-arterial treatment for patients with larger infarct burden or distal occlusions.

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CHAPTER 4.3

Multiphase CT Angiography: A New Tool For The Imaging Triage Of Patients With Acute Ischemic Stroke

Based upon:

Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke

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ABSTRACT

Background and Purpose

To describe the use of an imaging selection tool, multiphase computed tomographic (CT) angiography, in patients with acute ischemic stroke (AIS) and to demonstrate its interrater reliability and ability to help determine clinical outcome.

Materials and Methods

The local ethics board approved this study. Data are from the pilot phase of PRoveIT, a prospective observational study analyzing utility of multimodal imaging in the triage of patients with AIS. Patients underwent baseline unenhanced CT, single-phase CT angiography of the head and neck, multiphase CT angiography, and perfusion CT. Multiphase CT angiography generates time-resolved images of pial arteries. Pial arterial filling was scored on a six-point ordinal scale, and interrater reliability was tested. Clinical outcomes included a 50% or greater decrease in National Institutes of Health Stroke Scale (NIHSS) over 24 hours and 90-day modified Rankin Scale (mRS) score of 0-2. The ability to predict clinical outcomes was compared between single-phase CT angiography, multiphase CT angiography, and perfusion CT by using receiver operating curve analysis, Akaike information criterion (AIC), and Bayesian information criterion (BIC).

Results

A total of 147 patients were included. Interrater reliability for multiphase CT angiography is excellent (n = 30, k = 0.81, P , .001). At receiver operating characteristic curve analysis, the ability to predict clinical outcome is modest (C statistic = 0.56, 95% confidence interval [CI]: 0.52, 0.63 for $50% decrease in NIHSS over 24 hours; C statistic = 0.6, 95% CI: 0.53, 0.68 for 90-day mRS score of 0-2) but better than that of models using single-phase CT angiography and perfusion CT (P , .05 overall). With AIC and BIC, models that use multiphase CT angiography are better than models that use single-phase CT angiography and perfusion CT for a decrease of 50% or more in NIHSS over 24 hours (AIC = 166, BIC = 171.7; values were lowest for multiphase CT angiography) and a 90-day mRS score of 0-2 (AIC = 132.1, BIC = 137.4; values were lowest for multiphase CT angiography).

Conclusion

Multiphase CT angiography is a reliable tool for imaging selection in patients with AIS.

In the past few years, the treatment of acute ischemic stroke (AIS) has changed dramatically.[1] Newer mechanical devices offer rapid and successful recanalization in the majority of patients who undergo treatment.[2-4] Even with this progress, many patients who have undergone treatment do not do well clinically.[5,6] Nonetheless, data from previous trials show that clinical outcome improves if patients have a salvageable brain at presentation and (b) undergo early recanalization.[6-8] Every 30-minute delay in treatment could increase the risk of poor clinical outcome by around 14%.[9] Thus, an ideal imaging selection tool should enable one to detect a salvageable brain quickly and reliably and should be widely available.

Current imaging techniques include unenhanced computed tomography (CT), single-phase CT angiography, perfusion CT, and magnetic resonance (MR) imaging. Unenhanced CT has moderate interrater reliability, even among experts.[10-13] Reliability in interpreting early ischemic changes is less in patients who present within 90 minutes after stroke symptom onset and in those who are aged, and it is affected by patient motion.[14] Single-phase CT angiography does not have temporal resolution; therefore, collateral status is mislabeled in many patients.[15] Both perfusion CT and MR imaging are susceptible to patient motion and require trained personnel to process the data.[16,17] Dynamic CT angiography is a technique that derives time-resolved images of pial arterial filling from perfusion CT images; however, it needspostprocessing and whole-brain perfusion CT. [18,19] Conventional angiographyis invasive, resource intensive, and not feasible as a fast diagnostic tool.[20]

Thus, we developed an imaging tool, multiphase CT angiography, that gives clinicians information on degree and extent of pial arterial filling in the whole brain in a time-resolved manner. Furthermore, this technique is quick to perform and yields images that are easy to acquire and interpret. In this study, we used pilot data from the PRoveIT (Precise and Rapid assessment of collaterals using multi-phase CTA in the triage of patients with acute ischemic stroke for IA Therapy) study, an ongoing prospective observational study that seeks to understand the utility of multimodal imaging in the imaging triage of patients with AIS. Herein, we will describe the tool, its interrater reliability, and its utility for making clinical decisions in patients with AIS.

ADVANCES IN KNOWLEDGE

- Multiphase CT angiography is an imaging tool that provides three time-resolved images of pial arterial filling in the whole brain, unlike conventional single-phase CT angiography.
- Interrater reliability for multiphase CT angiography is excellent (n = 30, k= 0.81, P , .001).
- At receiver operating curve analysis, the ability to predict clinical outcome ($50% decrease in National Institutes of Health Stroke Scale from baseline to 24 hours) based on assessment of pial arterial filling in the ischemic region is modest (C statistic = 0.56; 95% confidence interval [CI]: 0.52, 0.63) but higher than that for single-phase CT angiography (C statistic = 0.55; 95% CI: 0.49, 0.6), perfusion CT mismatch ratio greater than 1.8 (C statistic = 0.49; 95% CI: 0.45, 0.52), mismatch ratio greater than 3 (C statistic = 0.47; 95% CI: 0.41, 0.53), and perfusion CT infarct volume greater than 80 mL (C statistic = 0.46; 95% CI: 0.4, 0.5) (P = .01 for comparison of C statistic).

IMPLICATIONS FOR PATIENT CARE

- Multiphase CT angiography is an imaging tool with excellent interrater reliability that can be used to predict clinical outcomes in patients with acute ischemic stroke.
- Unlike perfusion CT, multiphase CT angiography does not need any mathematical algorithm or complex postprocessing at an independent workstation; it also requires a lower radiation dose and no additional contrast material.

Abbreviations:

AIC = Akaike information criterion
AIS = acute ischemic stroke
BIC = Bayesian information criterion
CBF = cerebral blood flow
CI = confidence interval
MCA = middle cerebral artery
mRS = modified Rankin Scale
NIHSS = National Institutes of Health Stroke Scale
TICI = Thrombolysis in Cerebral Infarction

MATERIALS and METHODS

Inclusion criteria for the study are as follows: (a) patient presented to the emergency department with symptoms consistent with ischemic stroke, (b) patients older than 18 years, and (c) baseline imaging included multiphase CT angiography performed within 12 hours of stroke symptom onset and initiated before recanalization therapy. Exclusion criteria were as follows: (a) intracranial hemorrhage identified at baseline CT; (b) previous moderate to large stroke in the ipsilesional hemisphere; (c) modified Rankin scale (mRS) score greater than 2 at baseline; (d) patient unable to undergo CT angiography because of recent estimated creatinine clearance of less than 60 mL/min, contrast material allergy, or other reasons; (e) participation in another study that results in the patient receiving an investigational or therapy; and (f) any terminal illness (patient not expected to survive longer than 1 year). We analyzed two clinical outcomes in this study, namely (a) major neurologic improvement at 24-hour follow-up, defined as a 50% decrease in National Institutes of Health Stroke Scale (NIHSS) over 24 hours and (b) mRS score of 0-2 at 90 days. The local institutional review board approved the study.

Imaging Protocol and Analysis

All patients underwent standard unenhanced CT with 5-mm section thickness followed by head and neck CT angiography, including multiphase CT angiography and perfusion CT.

Multiphase CT angiography.-This technique generates time-resolved cerebral angiograms of brain vasculature from the skull base to the vertex in three phases after contrast material injection (Figs 1, 2). Aortic arch vertex CT angiography performed with a multidetector CT scanner made up the first phase. Image acquisition was timed to occur during the peak arterial phase in the healthy brain and was triggered by bolus monitoring. The remaining two phases are from the skull base to the vertex in the equilibrium/peak venous and late venous phases in the healthy brain. Images were acquired with a 0.625-mm section thickness. The first phase of CT angiography from the arch to the vertex was acquired in less than 7 seconds, with an average dose length product of 700-800 mGy·cm. The second phase was acquired after a delay of 4 seconds that allows for table repositioning to the

Figure 1

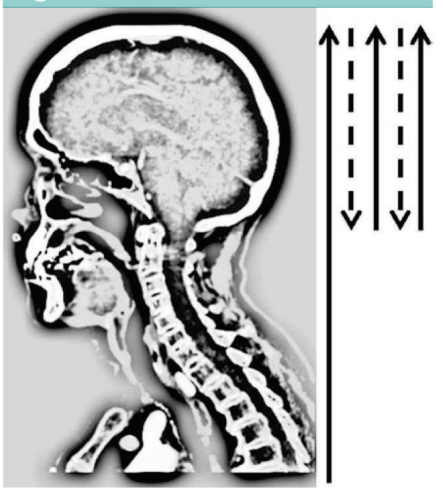

Figure 1: Multiphase CT angiography image, with each phase represented by an arrow. The first phase (long solid arrow) is conventional arch-to-vertex CT angiography. The next two phases (short solid arrows) are sequential skull base–to-vertex acquisitions performed in the midvenous and late venous phases. Dashed arrows indicate movement of the scanner in between image acquisitions.

skull base. Scanning duration for each additional phase was 3.4 seconds. Thus, the three phases were each 8 seconds apart. A total of 80 mL of contrast material (68% ioversol, Optiray 320; Mallinckrodt, St Louis, Mo) was injected at a rate of 5 mL/sec and followed by a 50-mL normal saline chase at a rate of 6 mL/sec. The axial images were reconstructed at 1-mm overlapping sections, and multiplanar reconstructions for axial, coronal, and sagittal images of the circle of Willis were performed with 3-mm thickness at 1-mm intervals. Thick-section axial maximum intensity projections at 24-mm thickness and 4-mm intervals were also reconstructed. An important feature of our imaging protocol was that the two additional phases of multiphase CT angiography use no additional contrast material; the total radiation dose as per our imaging protocol was less than that in many established stroke centers[21] (Table 1). In addition, we used an AccuProbe meter (RadCal, Monrovia, Calif) equipped with a 20X5-3 ion chamber and a human head phantom to measure the total absorbed radiation dose (in milligrays) for the eye with single-phase CT angiography, multiphase CT angiography, and perfusion CT (Table 1). This analysis

Figure 2

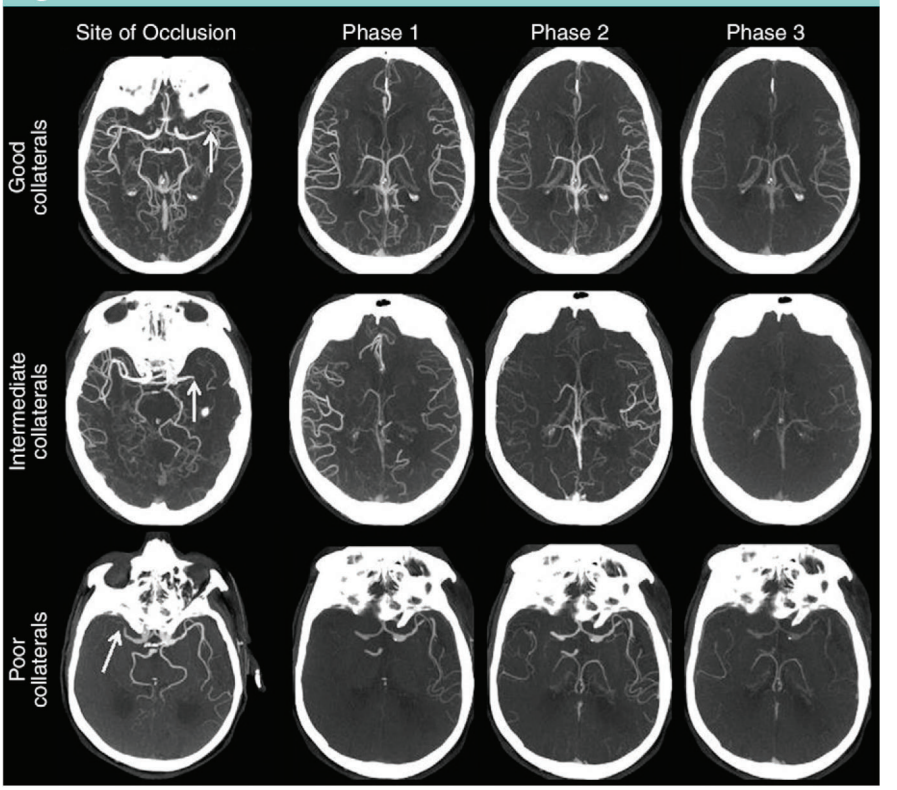

Figure 2: Multiphase CT angiography images. Top row: Images in a patient with a left M1 MCA occlusion (arrow) and good collaterals (backfilling arteries). Middle row: Images in a patient with a left M1 MCA occlusion (arrow) and intermediate collaterals. Bottom row: Images in a patient with a right M1 MCA occlusion (arrow) and poor collaterals (minimal backfilling arteries).

revealed that the total radiation dose for the eye with multiphase CT angiography was well within the acceptable limits (as per the International Commission on Radiological Protection Guidelines 2012) and significantly less than that with perfusion CT.[22]

All postprocessing with multiphase CT angiography is automated and available for review within 2-3 minutes of CT angiography. Pial arterial filling in the ischemic territory was measured in the first phase of CT angiography (single-phase CT angiography) and during multiphase CT angiography by comparing it to similar arteries in the unaffected hemisphere by using a six-point scale (Fig 3). If no occlusion was evident, pial filling of the

Table 1

Mean Effective Radiation Dose with Our Protocol for Multimodal Imaging Including Multiphase CT Angiography When Compared with a Conventional Protocol for Multimodal Imaging

Type of Examination	Mean Estimated Effective Dose in an Established Center (mSv)*	Mean Estimated Effective Dose at Our Center (mSv)	Radiation Dose to the Eye (mGy)†
Unenhanced head CT	2.7 ± 0.3	2.0 ± 0.5	NA
Routine head and neck CT angiography	5.4 ± 2.2	5.0 ± 0.5	15
Two additional phases of multiphase CT angiography	NA	1.0 ± 0.5	45
CT perfusion	4.9 ± 0.0	3.5 ± 0.5	200
Contrast-enhanced head CT	2.6 ± 0.2	NA	NA
Smart prep	0.1 ± 0.1	0.1 ± 0.1	NA
Total dose	16	12	…

Note.—NA = not applicable.
* Center data is from Mnyusiwalla et al (21).
† Measured by using the aforementioned meter equipped with a 20X5–3 ion-chamber and a human head phantom. These radiation doses conform to the 2012 International Commission on Radiological Protection guidelines (22).

Figure 3

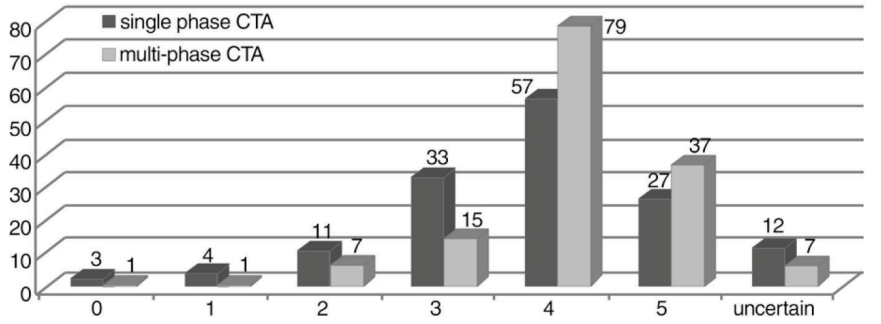

Figure 3: Pial arterial filling at single-phase CT angiography *(CTA)* and multiphase CT angiography shows incongruence between the scores and mislabeling of many patients with better pial arterial filling at multiphase CT angiography as having a poor score at single-phase CT angiography.

symptomatic hemisphere was compared with that of the contralateral side. The six-point scale was then trichotomized into three categories of pial arterial filling. The method for scoring pial arterial filling at single-phase and multiphase CT angiography is described in Table 2. Two raters (B.K.M., M.A.) who were blinded to treatment decisions, perfusion

Table 2

Pial Arterial Filling Score within the Symptomatic Ischemic Territory Using Single- and Multiphase CT Angiography

Score	Single-Phase CT Angiography	Multiphase CT Angiography
5	When compared with asymptomatic contralateral hemisphere, there is increased or normal prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is no delay and normal or increased prominence of pial vessels/normal extent within the ischemic territory in the symptomatic hemisphere
4	When compared with the asymptomatic contralateral hemisphere, there is slightly reduced prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of one phase in filling in of peripheral vessels, but prominence and extent is the same
3	When compared with the asymptomatic contralateral hemisphere, there is moderately reduced prominence and extent of pial vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of two phases in filling in of peripheral vessels or there is a one-phase delay and significantly reduced number of vessels in the ischemic territory
2	When compared with the asymptomatic contralateral hemisphere, there is decreased prominence and extent and regions with no vessels within the ischemic territory in the symptomatic hemisphere	When compared with the asymptomatic contralateral hemisphere, there is a delay of two phases in filling in of peripheral vessels and decreased prominence and extent or a one-phase delay and some ischemic regions with no vessels
1	When compared with the asymptomatic contralateral hemisphere, there are just a few vessels visible in the occluded vascular territory	When compared with the asymptomatic contralateral hemisphere, there are just a few vessels visible in any phase within the occluded vascular territory
0	When compared with the asymptomatic contralateral hemisphere, there are no vessels visible within the ischemic territory	When compared with the asymptomatic contralateral hemisphere, there are no vessels visible in any phase within the ischemic vascular territory

CT, and follow-up data scored unenhanced CT, single-phase CT angiography, and multiphase CT angiography images by consensus.

CT perfusion.-A total of 45 mL of the same contrast agent was injected at a rate of 4.5 mL/sec followed by a saline chase of 40 mL at a rate of 6 mL/sec. Axial shuttle (step-and-shoot) mode was used to cover an 8-cm section of the brain, including the intracranial artery at a 5-mm section thickness. Scanning began after a 5-second delay after contrast material injection, with 24 passes performed over 66 seconds. Total exposure time was 19.20 seconds. See Appendix E1 (online) for CT perfusion postprocessing details. *Recanalization and reperfusion.*-Recanalization and reperfusion were assessed either on conventional cerebral angiograms obtained at the end of the intraarterial procedure (by using the Thrombolysis in Cerebral Infarction [TICI] score) or on CT angiograms of the circle of Willis obtained within 2-4 hours after baseline imaging in patients who underwent only intravenous tissue plasminogen activator by using the TICI CT angiography score. Successful recanalization was defined as a modified TICI score of 2b/3 or a TICI CT angiography score of 2b/3.[23]

Testing Multiphase CT Angiography

The various steps in testing multiphase CT angiography are described in Figure E1 (online).

Interrater reliability.-Two raters (B.K.M., M.A.) independently assessed multiphase CT angiography in 30 randomly chosen subjects by using the six-point ordinal scale that was then reclassified into three clinically relevant categories (ie, good, intermediate, and poor pial arterial filling) (Table 2). Interrater reliability was measured by using unweighted k values. (Details on the statistical method are given in Appendix E1 [online]).

Agreement on clinical decision making.-Since we did not have a reference standard with which to assess concurrent validity (agreement) of multiphase CT angiography vis-á-vis other imaging tools, we compared its ability to assist in making a clinical decision with that of other available imaging tools. We did this by designing an imaging experiment in which two authors (B.K.M., M.A.) assessed unenhanced CT followed by single-phase CT angiography, multiphase CT angiography, and perfusion CT to answer the following two questions: Is the patient a candidate for intravenous tissue plasminogen activator? Is the patient a candidate for intraarterial therapy? All patients were assumed to have fulfilled clinical characteristics for treatment eligibility when images were being read. The readers were not provided information on the time from when normal images were last obtained. Responses recorded for each imaging modality were "yes," "no," or "uncertain." Uninterpretable images were classified as uncertain. The raters used clinically relevant commonly used prespecified rules for image interpretation. These rules are described in detail in Appendix E1 (online). Salvageable brain was measured by using predefined perfusion thresholds and two predefined mismatch ratios (ie, .1.8 and .3.0).[24,25] Baseline infarct volume of 80 mL or more at perfusion CT was considered large; therefore, in such cases the response was "no" for both intravenous tissue plasminogen activator and intraarterial therapy.[26,27] Severe noncorrectable patient motion (Fig E2 [online]) and lack of appropriate arterial input function were recorded as an uncertain response. All responses ("yes," "no," and "uncertain") for each imaging modality were reported as proportions.

Predictive ability.-We compared the ability of multiphase CT angiography to enable prediction of both clinical outcomes vis-á-vis single-phase CT angiography and perfusion CT.

For single-phase CT angiography, a pial arterial filling score of 0-2 was considered poor; therefore, the patient was not likely to benefit from recanalization. For multiphase CT angiography, a score of 0-3 was considered poor and therefore unlikely to benefit from recanalization (Table 2). Separate logistic regression models were developed for each diagnostic tool (ie, single-phase CT angiography, multiphase CT angiography, and perfusion CT [with mismatch ratios .1.8 vs #1.8 and .3.0 vs #3.0 and infarct volume ,80 mL vs $80 mL]) as predictor variable. For each model, the ability of the individual diagnostic tool to aid in determining clinical outcome was assessed by using the area under the receiver operating characteristic curve (or C statistic) derived from the receiver operating characteristic curves of the logistic regression model. The C statistics of models were compared by using the x2 test of Gönen.[28] Since comparison of models by using receiver operating characteristic curves may result in misclassification errors, we also used Akaike information criterion (AIC) and Bayesian information criterion (BIC) to compare models.[29] These latter methods have the ability to express the probability that each model is correct when compared with the best model (ie, the one with the highest probability to minimize information loss). A model with the lowest AIC or BIC score is the best model.[29] Each of the previously mentioned analyses was restricted to patients in whom all information on the dependent variable and classifier was available. We also performed additional sensitivity analyses with the previously described models restricted to patients (a) with proximal anterior circulation occlusions, (b) who underwent revascularization therapy, and (c) who had early recanalization data.

RESULTS

A total of 147 patients were included in the present study. Mean age was 72 years 6 13.1 (standard deviation), 49.7% were male, median baseline NI- HSS was 9 (interquartile range, 13), median Alberta Stroke Program Early CT Score at unenhanced CT was 9 (interquartile range, 4), and median time from stroke symptom onset to baseline CT was 133 minutes (interquartile range, 188 minutes). Distribution of occlusions was as follows: internal carotid artery (six of 147 patients), M1 middle cerebral artery (MCA) (60 of 147 patients), M2 MCA (21 of 147 patients), posterior cerebral artery (three of 147 patients), distal occlusions (24 of 147 patients), and no occlusions (33 of 147 patients). Distribution

of pial arterial filling with single and multiphase CT angiography is shown in Figure 3. Single-phase CT angiography consistently resulted in underestimation of pial arterial filling when compared with multiphase CT angiography; thus, many patients with moderate pial arterial filling at multiphase CT angiography were labeled as having a poor score. When we used a priori thresholds for infarct and penumbra for both gray and white matter at perfusion CT, median mismatch ratio was 6.6 (range, 1.2-319.6), while mean baseline infarct volume was 18.9 mL 6 31.1. Fifty-one patients underwent intravenous thrombolysis, 24 underwent intravenous and intraarterial therapy, seven underwent intraarterial therapy alone, and 44 underwent conservative treatment. Early reperfusion data were available in 71 patients; 42 (59%) achieved reperfusion. Fifty-six (38.1%) patients achieved the primary clinical outcome (50% decrease in NIHSS over 24 hours), while 72 of 119 (60.5%) had an mRS score of 0-2 at 90 days.

Interrater Reliability

Interrater reliability for pial arterial filling with multiphase CT angiography was excellent (n = 30, k = 0.81, P , .001).

Agreement on Clinical Decision Making

Table 3 describes "yes," "no," and "uncertain" for intravenous tissue plasminogen activator and intraarterial treatment with each imaging modality. Detailed results are described in Appendix E1 (online). For intravenous tissue plasminogen activator decision making,

Table 3

Certainty in Clinical Decision Making for Intravenous Tissue Plasminogen Activator Administration and Intraarterial Therapy with Each Baseline Imaging Modality and Paradigm

	Intravenous Tissue Plasminogen Activator				Intraarterial Therapy			
Imaging Modality and Criteria	No. of Patients	Yes (%)	No (%)	Uncertain (%)	No. of Patients	Yes (%)	No (%)	Uncertain (%)
Unenhanced CT	147	89.8	7.5	2.7	147	32.6	8.8	58.5
Multiphase CT angiography and unenhanced CT	147	90.5	8.8	0.7	147	51.0	47.6	1.4
Single-phase CT angiography and unenhanced CT	147	83.0	14.3	2.7	147	44.2	51.0	4.8
Baseline infarct volume <80 mL	145	88.9	6.9	4.1	85	37.2	58.6	4.1
Mismatch ratio ≤1.8	145	92.4	3.4	4.1	85	40.7	55.2	4.1
Mismatch ratio ≤3.0	145	82.7	13.1	4.1	85	34.5	61.4	4.1

Note.—Agreement between imaging modalities for clinical decision making is described in the text.

maximal agreement (92.5%, k = 0.68) was seen between single and multiphase CT angiography. The next best agreement was between unenhanced CT and multiphase CT angiography (89.1%, k = 0.4) and then between unenhanced CT and single-phase CT angiography (85.7%, k = 0.41). Agreement for all other pairs was 70.1% or less. For intraarterial treatment decision, maximal agreement (89.8%, k = 0.8) was seen between single and multiphase CT angiography. The next best agreement was between multiphase CT angiography and perfusion CT mismatch ratio greater than 3 (72.5%, k = 0.46) and between multiphase CT angiography and perfusion CT mismatch ratio greater than 1.8 (72.1%, k = 0.45). Agreement for all other pairs was 45% or less. Figures 4-7 show various combinations of congruence or incongruence in clinical decision making between unenhanced CT, multiphase CT angiography, and perfusion CT in our data.

Figure 4

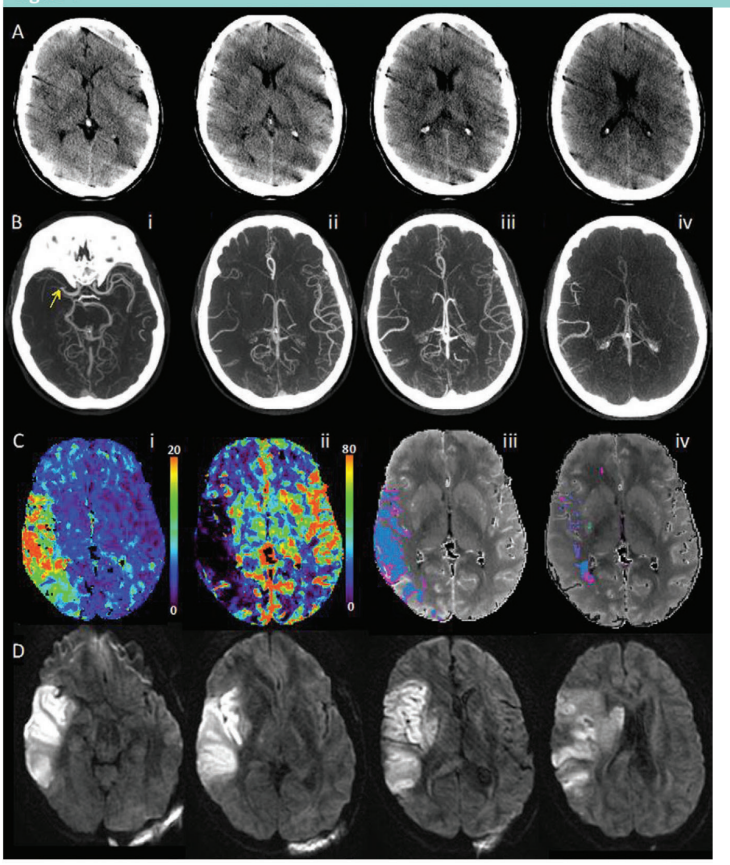

Figure 4: Multimodal CT imaging at 2 hours 51 minutes after symptom onset in a 47-year-old woman with NIHSS of 20 and right hemisphere symptoms. *A,* Unenhanced CT shows movement artifact; however, ASPECTS score was 7. *B,* A proximal right M1 MCA occlusion is seen *(i).* Multiphase CT angiography (three phases) maximum intensity projection images are shown *(ii, iii, iv).* Pial arterial filling is modest, with delay of two phases and some regions indicating minimal filling when compared with the contralateral side, thus indicating that no treatment be performed. *C,* Perfusion CT Tmax and cerebral blood flow (CBF) maps (*i, ii*). Tissue with Tmax greater than 6 seconds (pink) is superimposed onto the CT perfusion average maps for both gray and white matter (*iii* and *iv,* respectively). CBF less than 10 $mL \cdot min^{-1} \cdot 100\ g^{-1}$ and less than 7 $mL \cdot min^{-1} \cdot 100\ g^{-1}$ for gray and white, respectively, is flooded in blue on the CT perfusion average maps *(iii, iv).* CBF-defined infarct core is 100 mL. A mismatch ratio (total Tmax hypoperfusion volume/total CBF infarct volume) of 1.7 and a large infarct core indicates that no treatment should be performed. Multiphase CT angiography and perfusion CT imaging are congruent for treatment decision. *D,* Diffusion MR images at 24 hours after admission show the final infarct as hyperintense.

Figure 5

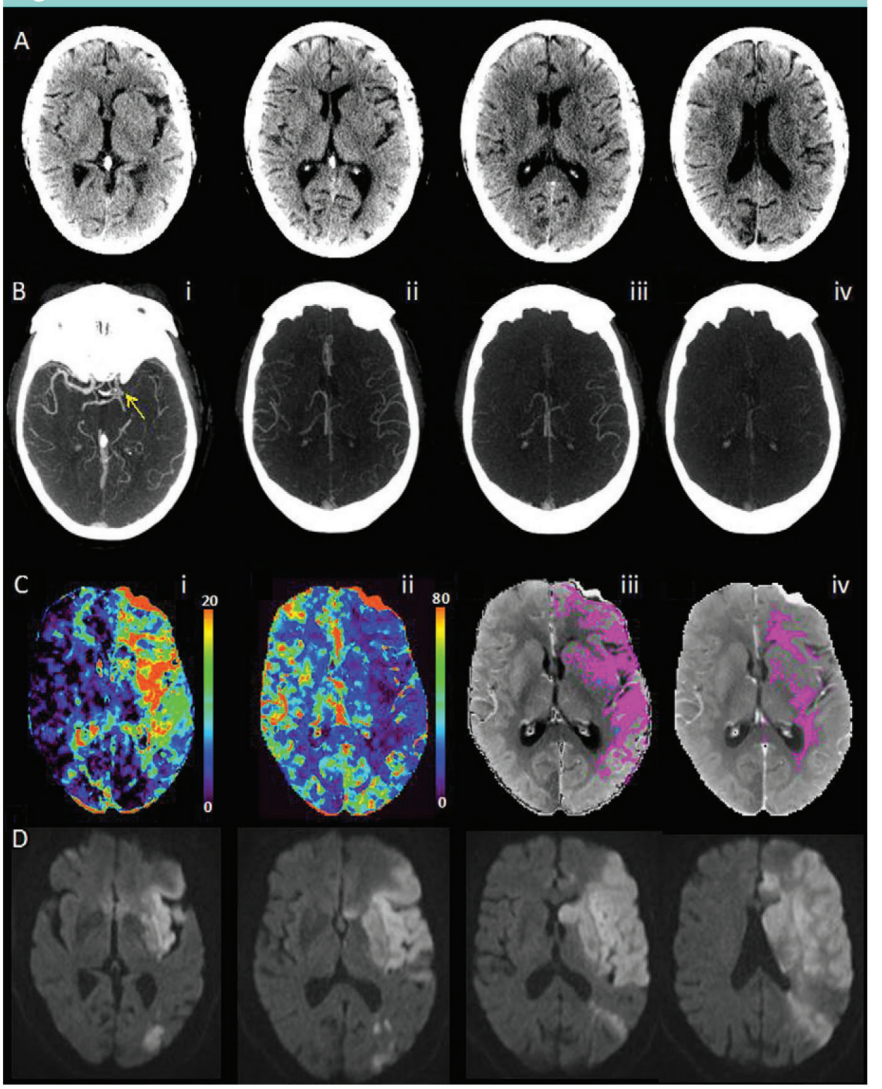

Figure 5: Multimodal CT images obtained 2 hours 18 minutes after symptom onset in an 87-year-old woman with an NIHSS of 15 and left hemisphere symptoms. *A,* Unenhanced CT ASPECTS score was 6. *B,* A proximal left M1 MCA occlusion *(i).* Multiphase CT angiography (three phases) maximum intensity projection images *(ii, iii, iv)* are indicative of one phase delay at worst, with similar extent and prominence when compared with the contralateral side. These indicate of a score of 4 and suggest the patient should undergo treatment. *C,* CT perfusion Tmax and CBF maps *(i, ii).* A CBF-defined infarct core is 1 mL (*iii*, no blue regions). A mismatch ratio of 106 and a small infarct core suggests the patient should undergo treatment. Multiphase CT angiography and perfusion CT imaging are congruent for treatment decision. *D,* MR diffusion images at 26 hours after admission show the final infarct as hyperintense. This patient did not attain recanalization with endovascular therapy.

Figure 6

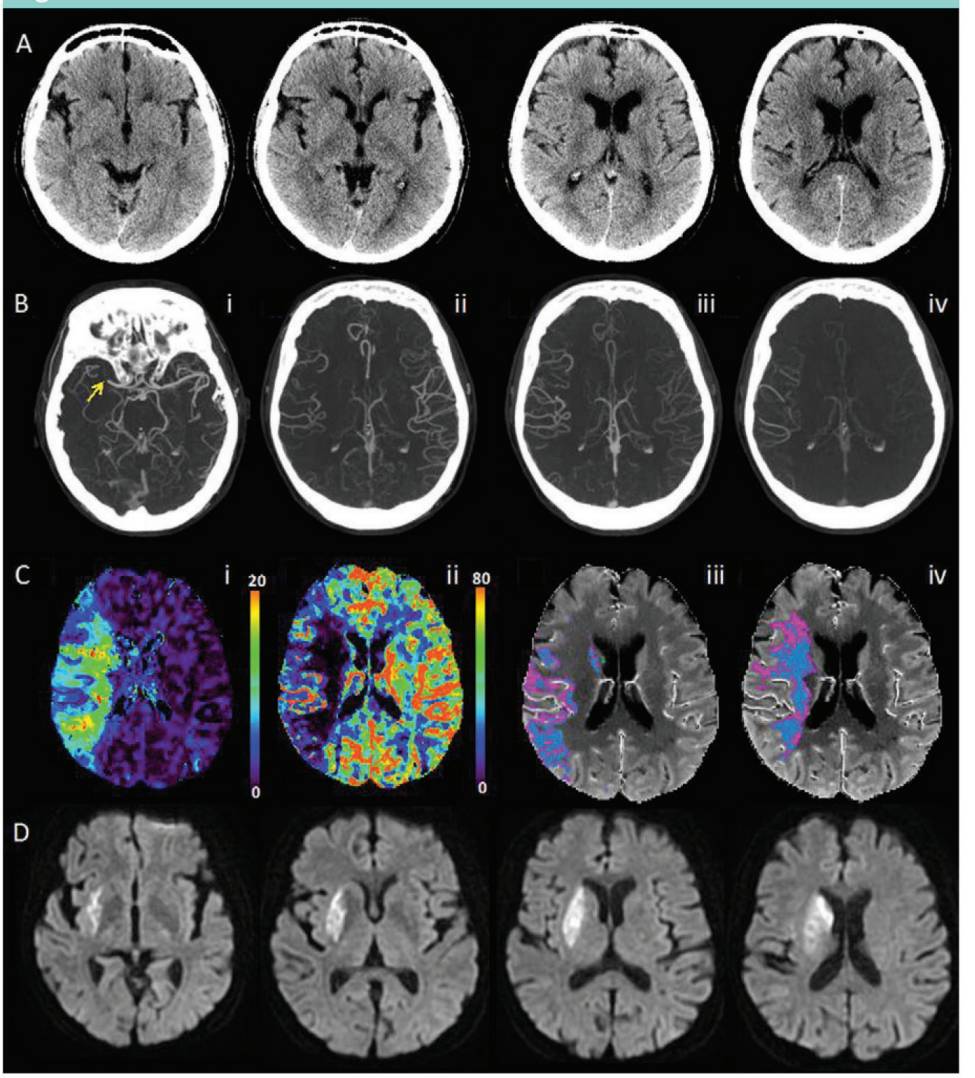

Figure 6: Multimodal CT images obtained 1 hour 28 minutes after symptom onset in a 78-year-old woman with NIHSS of 18 and right hemisphere symptoms. *A,* Unenhanced CT ASPECTS score is 8. *B,* Proximal right M1 MCA occlusion *(i).* Multiphase CT angiography (three phases) maximum intensity projection images *(ii, iii, iv)* are indicative of one phase delay, with similar extent and prominence when compared with the contralateral side. These suggest a score of 4 and that the patient should undergo treatment. *C,* CT perfusion Tmax and CBF maps *(i, ii).* A CBF-defined predicted infarct core is 113 mL (blue) and mismatch ratio (blue/pink areas) *(iii, iv)* is 1.7; this indicates the patient should not undergo treatment. Multiphase CT angiography and perfusion CT imaging are incongruent for treatment decision. *D,* MR diffusion images at 26 hours after admission show the final infarct as hyperintense. This M1 MCA clot recanalized with intraarterial therapy.

Figure 7

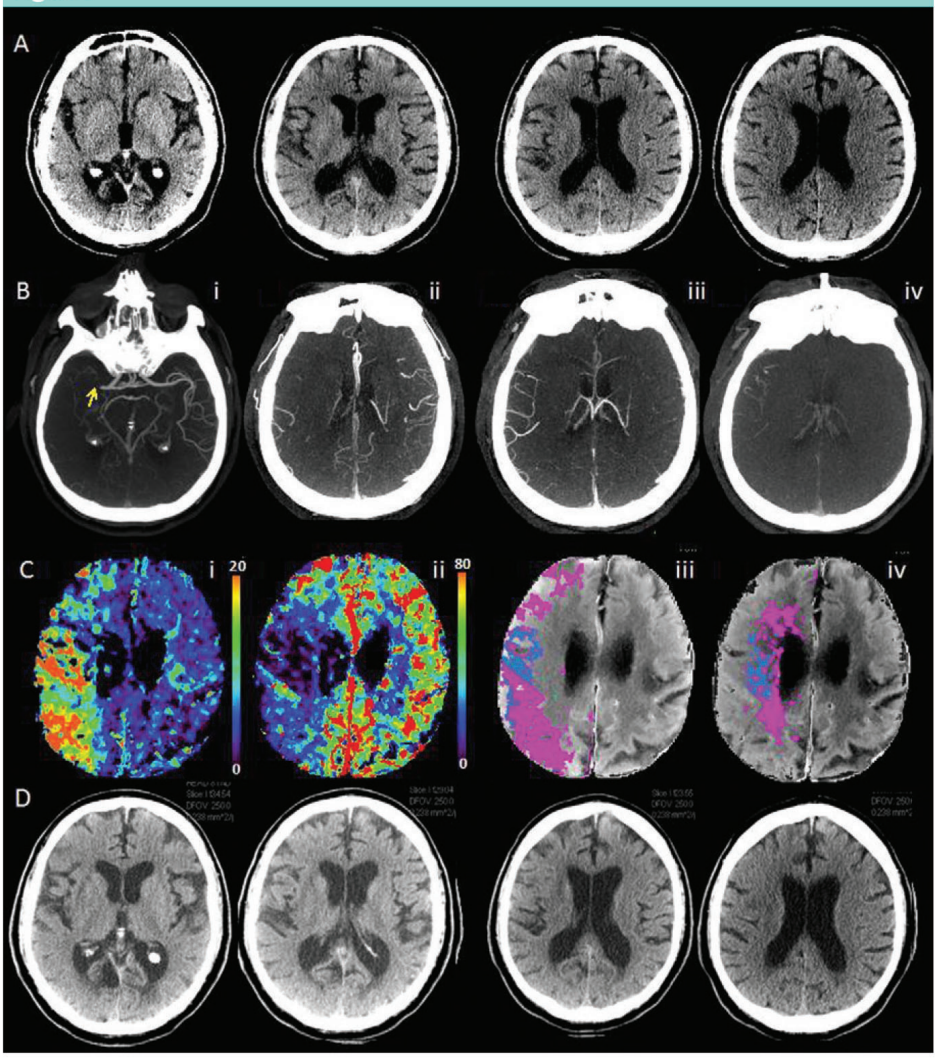

Figure 7: Multimodal CT images obtained 1 hour 32 minutes after symptom onset in a 67-year-old man with NIHSS of 17 and right hemisphere symptoms. *A,* Unenhanced CT ASPECTS score is 7. *B,* A proximal right M1 MCA occlusion extending to M2 MCA is seen *(i).* Multiphase CT angiography (three phases) maximum intensity projection images (*ii, iii,* and *iv*) are indicative of, at worst, one phase delay but with large regions having minimal pial arterial filling when compared with the contralateral side. The multiphase CT angiography score is 3, which indicates no treatment should be performed. *C,* Perfusion CT Tmax and CBF maps *(i, ii).* A CBF-defined predicted infarct core is 19 mL *(iii, iv).* A mismatch ratio of 7.1 indicates treatment should be performed. Multiphase CT angiography and CT perfusion images are incongruent for treatment decision. Fast (<60 minutes) recanalization was achieved by using endovascular thrombectomy. *D,* Unenhanced CT 3 days after admission shows the final infarct as hypointense.

Table 4

Ability of Each Imaging Modality to Discriminate Clinical Outcome (50% or More Decrease in NIHSS from Baseline to 24 Hours) Using Logistic Regression Analysis Receiver Operating Curve Analysis, AIC, and BIC

Imaging Modality and Criteria	No. of Patients	Odds Ratio	*P* Value	*C* Statistic	AIC	BIC
Multiphase CT angiography (>3 vs ≤3)	126	4.3 (1.2, 15.7)	.02	0.58	166.0	171.7
Single-phase CT angiography (>2 vs ≤2)	126	2.8 (0.75, 10.6)	.12	0.55	169.6	175.4
Baseline infarct volume (<80 mL vs ≥80 mL)	126	5.2 (1.1, 27.1)	.05	0.45	167.8	173.5
Mismatch ratio (≤1.8 vs >1.8)	126	3.2 (0.3, 36.6)	.34	0.49	171.4	177.1
Mismatch ratio (≤3 vs >3)	126	1.6 (0.6, 4.8)	.33	0.47	171.5	177.1

Note.—Data in parentheses are 95% CIs. Higher *C* statistics imply better models, whereas lower AIC and BIC values imply better models.

Predictive Ability

The C statistic for models using single-phase CT angiography, multiphase CT angiography, and perfusion CT (with mismatch ratios .1.2, .1.8, and .3.0 and infarct volume ,80 mL vs $80 mL) in determining a 50% decrease in NIHSS at 24 hours is described in Table 4. The C statistic was highest for multiphase CT angiography (x2 test for model comparison, P = .007); nonetheless, multiphase CT angiography has only modest discrimination, while the other imaging modalities fared worse. Model comparisons on the same data set with AIC and BIC are also described in Table 4. AIC suggests that multiphase CT angiography is the best imaging modality in determination of primary clinical outcome. The model with baseline infarct volume greater than or equal to 80 mL versus that with baseline infarct volume of less than 80 mL at perfusion CT is next best; it is 0.41 times as probable to minimize information loss as the model with multiphase CT angiography. Other models

Table 5

Ability of Each Imaging Modality to Discriminate Clinical Outcome (mRS 0–2 at 90 Days) Using Logistic Regression Analysis Receiver Operating Curve Analysis, AIC, and BIC

Imaging Modality and Criteria	No. of Patients	Odds Ratio	*P* Value	*C* Statistic	AIC	BIC
Multiphase CT angiography (>3 versus ≤3)	102	5.5 (1.6, 18.8)	.01	0.60	132.1	137.4
single-phase CT angiography (>2 versus ≤2)	102	3.3 (1.0, 10.7)	.05	0.57	136.4	141.7
Baseline Infarct volume <80 mL versus ≥80 mL	102	1.2 (0.25, 5.5)	.84	0.50	140.6	145.8
Mismatch ratio ≤1.8 versus >1.8	102	0.8 (0.1, 8.8)	.80	0.50	140.6	145.8
Mismatch ratio ≤3 versus >3	102	1.4 (0.4, 4.5)	.58	0.52	140.3	145.6

Note.—Data in parentheses are 95% CIs. Higher *C* statistics imply better models, whereas lower AIC and BIC values imply better models.

with diminishing probability of minimizing information loss when compared with the best model (multiphase CT angiography) are as follows: single-phase CT angiography (0.16 times); mismatch ratio greater than 1.8 (0.06 times), and mismatch ratio greater than 3 (0.061 times). Results with BIC are similar to those with AIC (Table 4). Similar results were seen when we compared models with receiver operating characteristic analysis, AIC, and BIC, with an mRS score of 0-2 at 90 days as the clinical outcome (n = 102) (Table 5).

Sensitivity Analyses

In sensitivity analyses restricted to patients with only intracranial artery, M1 MCA, or proximal M2 MCA occlusions, the C statistic was highest with multiphase CT angiography (C statistic = 0.6; 95% CI: 0.54, 0.67). In sensitivity analyses restricted to the patients who underwent revascularization therapy (intravenous tissue plasminogen activator 6 intraarterial therapy), the C statistic was again highest for multiphase CT angiography (C statistic = 0.57; 95% CI: 0.5, 0.65). Similarly, in sensitivity analyses restricted to patients with early recanalization/reperfusion data, the C statistic was highest for multiphase CT angiography (C statistic = 0.57; 95% CI: 0.46, 0.67); other imaging modalities had a lower C statistic. Recanalization or reperfusion (TICI = 2b/3), however, was the best predictor of primary clinical outcome (C statistic = 0.66; 95% CI: 0.54, 0.77) whenever those data were available.

DISCUSSION

Multiphase CT angiography is a quick and easy-to-use imaging tool in patients with AIS. Our study shows that multiphase CT angiography has good interrater reliability. It reduces uncertainty in clinical decision making and may be slightly better in the prediction of clinical outcome than currently used techniques, such as unenhanced CT, single-phase CT angiography, and perfusion CT. Other advantages include minimal additional radiation, no additional contrast material, whole-brain coverage, and no postprocessing.

There is currently no reference standard for imaging selection in patients with AIS. Perfusion CT, however, is used in many centers for patient selection. Clinical trials Echoplanar

Imaging Thrombolytic Evaluation Trial (or EPITHET) and Diffusion Weighted Imaging Evaluation for Understanding Stroke Evolution Study-2 (or DEFUSE-2) have shown that a strategy of delineating infarct core and penumbra can be used to select patients for intravenous tissue plasminogen activator or endovascular therapy 3 hours after onset of stroke symptoms[27,30] Perfusion CT, however, requires 10-20 minutes from image acquisition to interpretation and needs algorithms for postprocessing images that are vendor specific, not standardized, and therefore variable across centers. Perfusion CT also needs trained personnel to process these images.[16,31,32] In addition, image quality is affected to some extent by patient motion.[17] Additional radiation dose is also a concern.[21] By acquiring temporal information at three data points, multiphase CT angiography is conceptually similar to perfusion CT (and dynamic CT angiography that is derived from perfusion CT images).[18,19] Differences from perfusion CT are therefore in using less information and avoiding the need for postprocessing. Of note, our study shows that currently available perfusion CT thresholds for infarct or penumbra are not better than multiphase CT angiography in clinical decision making or outcome prediction. A possible explanation could be that these externally validated thresholds are not internally valid within our own data set and that we need to derive our own thresholds for infarct core and penumbra.[17] We plan to derive such thresholds. Nonetheless, the fact that neither we nor our vendors currently have validated thresholds from literature that we can apply prospectively to our data set is an inherent limitation to the widespread use of perfusion CT in the real world. However, automated perfusion-based algorithms now available are capable of providing information to clinicians in a rapid manner like multiphase CT angiography.[33]

Unenhanced CT is widely used for patient selection. Unenhanced CT, however, has moderate interrater reliability even among experts.[10-13] Single-phase CT angiography lacks temporal resolution; therefore, this modality leads to risk of mislabeling pial arterial filling when compared with multiphase CT angiography[18,19] (Fig 3). Unlike contrast-enhanced CT, multiphase CT angiography provides clinicians with three time-resolved images and therefore a more nuanced assessment of pial arterial filling in both the normal brain and the ischemic brain. An example is the ability of multiphase CT angiography to enable discrimination between a one and two phase delay whereas contrast-enhanced CT labels both the same. Finally, when compared with multiphase CT angiography, MR imaging has practical drawbacks. MR imaging takes up to 30 minutes to screen patients, perform the examination, and interpret the results.[16] Many patients do not tolerate it well, and image

quality is affected by patient motion. MR imaging also has limited availability after working hours.[34]

Our tool, multiphase CT angiography, has limitations. The presence of flow-limiting proximal stenosis and circuitous base-of-skull collaterals can result in delay in contrast material filling of the pial arteries, even in the healthy hemisphere, thus potentially leading to mislabeling of pial arterial filling status.

Even though we did not find any such case in the current study, this possibility cannot be discounted. Thus, we recommend that multiphase CT angiography images always be interpreted in conjunction with head and neck CT angiography images. Poor cardiac function can also interfere with pial arterial filling, even though our data did not show this. A protocol that includes an additional delayed fourth phase may help in such scenarios. Finally, multiphase CT angiography cannot as yet be used in patients with posterior circulation stroke, except when involving the PCA, because of poorly understood collateral hemodynamics of the posterior circulation.

In summary, we describe multiphase CT angiography, an imaging tool for clinical decision making in patients with AIS. In this article, we have shown its reliability and ability to help predict clinical outcome. Larger studies are needed to conclusively demonstrate its utility in triage and clinical decision making.

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Supplementary Appendix

CT Perfusion Postprocessing

One author (C.D.d.E., >7 years of experience) processed each study by using commercially available delay-insensitive deconvolution software (CT Perfusion 4D; GE Healthcare, Waukesha, Wis). Of note, in this study, postprocessing was performed offline in a nonacute setting. For each computed tomography (CT) perfusion study, time-density curves (TDCs) for the arterial input function (AIF) and venous output function (VOF) were obtained from the basilar artery and superior sagittal sinus, respectively. The AIF was corrected for partial volume averaging by using the VOF TDC. If these criteria were not met, we planned to reselect the best possible AIF by visually inspecting the TDC. Functional maps of cerebral blood flow (measured in milliliters per minute per 100 g] and Tmax (measured in seconds) were calculated by deconvolution of tissue TDCs and the AIF. The Tmax of the flow-scaled tissue residue function is the summation of the delay between the arrival time of contrast material at the artery and the arrival time of contrast material at the tissue region and the mean transit time of the local vasculature. Perfusion-weighted maps were created by averaging the cine perfusion CT images over the duration of the first pass of contrast material. Patient motion artifacts were corrected in the x- and y-axes by using automated software. In patients with extreme motion artifacts, time points were manually removed, if needed. The software did not allow motion correction in the z- axis (Fig 1b). All analysis on CT perfusion maps was performed by using custom software (IDL, version 6.2; RSI, Boulder, Colo). For all perfusion studies, perfusion-weighted maps were used to exclude cerebrospinal fluid and the cranium from analysis and to produce a gray and white matter anatomic mask based on the attenuation (measured in Hounsfield units) differences between the two tissue types. For each 16 × 5 mm section, the Tmax functional map was used to delineate the penumbra based on a previously reported Tmax threshold of more than 6 seconds (25,35). For both gray matter and white matter, any pixel value with a Tmax of more than 6 seconds delineates the penumbra from the benign oligemia (tissue that will die if occlusion persists). Within the perfusion lesion with Tmax of more than 6 seconds, gray and white matter infarct core volume was determined by using established absolute cerebral blood flow thresh-

olds obtained previously from perfusion CT processing and postprocessing (ie, cerebral blood flow <10 mL·min-1·100 g-1 and <7 mL·min-1·100 g-1 for gray and white matter, respectively). A mismatch ratio was defined for each patient by dividing the total Tmax perfusion lesion (penumbra and core) by the total infarct core volume.

Interrater Reliability

Interrater reliability was measured by using the unweighted *k* statistic. Our sample size calculations are based on the Stata kaputil command (http://fmwww.bc.edu/RePEc/bocode/k) and two raters with a margin of error 0.2, a standard error of 0.1, and the assumption that both raters score 40% of ratings as good.

Rules for Image Interpretation

Unenhanced CT

For intravenous tissue plasminogen activator (tPA) decision making, if unenhanced CT showed extensive early ischemic changes or the presence of subacute infarcts in the symptomatic hemisphere, such cases were considered to indicate no treatment should be performed ("no" for treatment). Moderate to minimal early ischemic changes at unenhanced CT were considered to indicate treatment should be performed ("yes" for treatment). For intra-arterial therapy decision making with unenhanced CT, the presence of a proximal hyperdense sign along with mild to moderate early ischemic changes in the presumed ischemic territory was considered to indicate treatment should be performed, whereas extensive early ischemic changes (Alberta Stroke Program Early CT Score score ≤4) or large subacute infarcts were considered to indicate no treatment should be performed. Absence of any hyperdense sign was considered an "uncertain" finding for treatment, as the patient's symptoms could still be explained by small clots (single or multiple) blocking sufficient blood supply to the brain. Severe motion artifacts resulted in uninterpretable and thus uncertain images.

Single- and Multiphase CT Angiography

For intravenous tPA decision making with multiphase CT angiography, we considered a pial arterial filling score greater than 3 to indicate presence of salvageable brain and a "yes" for treatment; a score of 0–3 was considered a "no" for treatment. For single-phase CT angiography, the corresponding threshold indicating presence of salvageable brain

was a pial arterial filling score greater than 2 (Table 2). For IA decision making, presence of a proximal occlusion safely accessible by using current endovascular techniques along with presence of salvageable brain as defined previously is considered a "yes" for treatment; distal occlusions with or without salvageable brain and no evident occlusions are considered a "no" for treatment. Motion artifacts, poor-quality images, or large chronic ipsilesional infarcts impairing assessment of pial arterial filling resulted in "uncertainty" for treatment. Each of these responses was also recorded after we assessed unenhanced CT images, as happens in real life.

Perfusion CT

For interpretation of single- and multiphase CT angiograms, the readers were not blinded to unenhanced CT findings; this was to stimulate real-life conditions. Perfusion CT images were interpreted with the readers blinded to CT angiograms for intravenous tPA decision making and informed by CT angiography at the site of occlusion for intra-arterial decision making. At perfusion CT, a patient was considered a candidate for intravenous tPA ("yes") if there was presence of salvageable brain or absence of a large baseline infarct. A patient was considered for intra-arterial therapy ("yes") if there was presence of salvageable brain or absence of large baseline infarct and the patient had a proximal occlusion (internal carotid artery or M1 middle cerebral artery).

Results

Unenhanced CT

For intravenous tPA decision, a "yes" response was recorded in 132 of 147 patients, a "no" response was recorded in 11, and "uncertainty" was recorded in only four (2.7%). Uncertainty was due to motion artifacts in all four patients. For intra-arterial decision making, a "yes" response was recorded in 48 of 147 patients, a "no" response was recorded in 13, and "uncertainty" was recorded in 86 (58.5%). Uncertainty was due to absence of hyperdense sign (n = 79), motion artifact (n = 4), chronic large ipsilesional infarct (n = 2), and large ipsilesional arachnoid cyst (n = 1).

Single-Phase CT Angiography

The readers were uncertain about pial arterial filling in 12 (8.2%) of 147 patients. This uncertainty was primarily due to poor-quality images as a result of very early arterial weight-

ing (n = 6), severe motion artifact (n = 4), and large chronic ipsilesional infarct (n = 2). When unenhanced CT image interpretation was added to single-phase CT angiography for intravenous tPA decision making as it happens in the real world, a "yes" response was recorded in 122 of 147 patients, a "no" response was recorded in 21, and "uncertainty" was recorded in only four (2.7%). In these four patients, neither pial arterial filling nor early ischemic changes could be evaluated with any certainty. For intra-arterial decision making using unenhanced CT and single- phase CT angiography, a "yes" response was recorded in 65 of 147 patients, a "no" response was recorded in 75, and "uncertainty" was recorded in seven (4.8%).

Multiphase CT Angiography

The readers were uncertain about pial arterial filling in seven (4.8%) of 147 patients. This uncertainty was due to severe motion artifact (n = 4) and large chronic ipsilesional infarct (n = 3). With concurrent use of unenhanced CT for intravenous tPA decision making as it happens in the real world, a "yes" response was recorded in 133 of 147 patients, a "no" response was recorded in 13, and "uncertainty" was recorded in only one (0.7%) patient. For intra-arterial decision making using unenhanced CT and multiphase CT angiography, a "yes" response was recorded in 75 of 147 patients, a "no" response was recorded in 70, and "uncertainty" was recorded in two (1.4%) patients.

Perfusion CT

Mismatch ratio and baseline infarct volume could be measured with certainty in 117 of 145 patients (perfusion images were missing in two patients). In 22 of 145 patients, no Tmax lesion was detected. In these 22 patients with no Tmax lesions, 18 had no arterial occlusion, while four had evident intracranial occlusion on multiphase CT angiograms. Analysis of perfusion CT was not possible, even after motion correction in another six of 145 patients (motion artifact, n = 4; improper acquisition, n = 2). With all these patients included, uncertainty about intravenous tPA clinical decision making with perfusion CT was noted in 28 (19.3%) of 145 patients.

Since patients are included in the study only when the admitting physician has a degree of clinical certainty that stroke mimics cannot explain the patient's symptoms, absence of a perfusion lesion could be construed as being due to limited brain coverage or small is-

chemic lesions, including lacunes, thus reducing uncertainty about intravenous tPA clinical decision making with perfusion CT to only six (4.1%) of 145 patients. Similarly, for intra-arterial decision making with perfusion CT, analysis of perfusion CT was not possible in six of 145 patients (motion artifact, n = 4; improper acquisition, n = 2), thus creating uncertainty about intra-arterial clinical decision making in 4.1% of patients.

Figure E1:

Flow diagram shows imaging evaluations performed as part of testing clinical properties of multiphase CT angiography. *IV* = intravenous, *mCTA* = multiphase CT angiography, *NCCT* = unenhanced CT, *PCT* = perfusion CT, *sCTA* = single-phase CT angiography

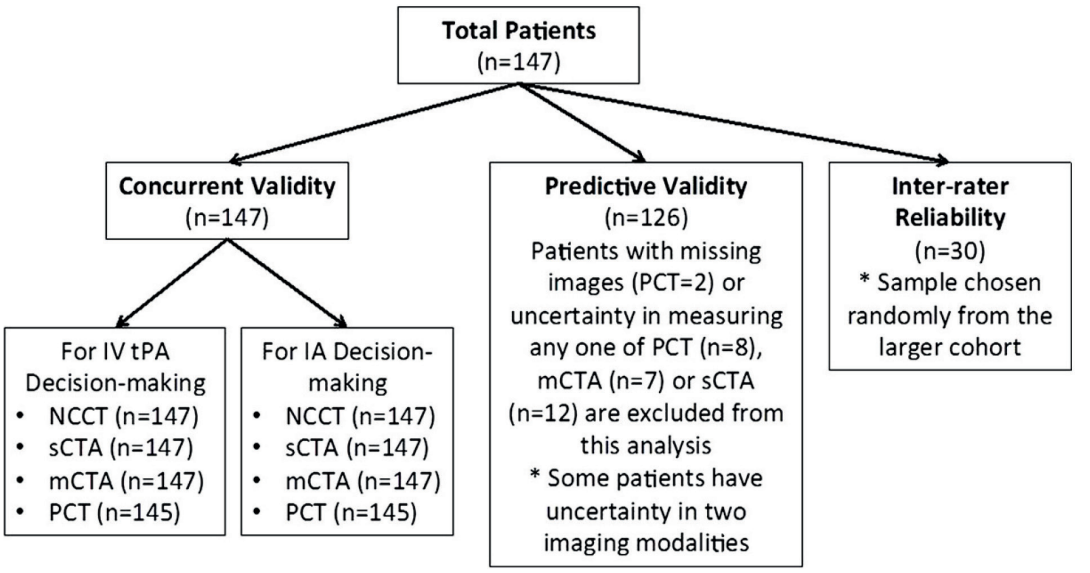
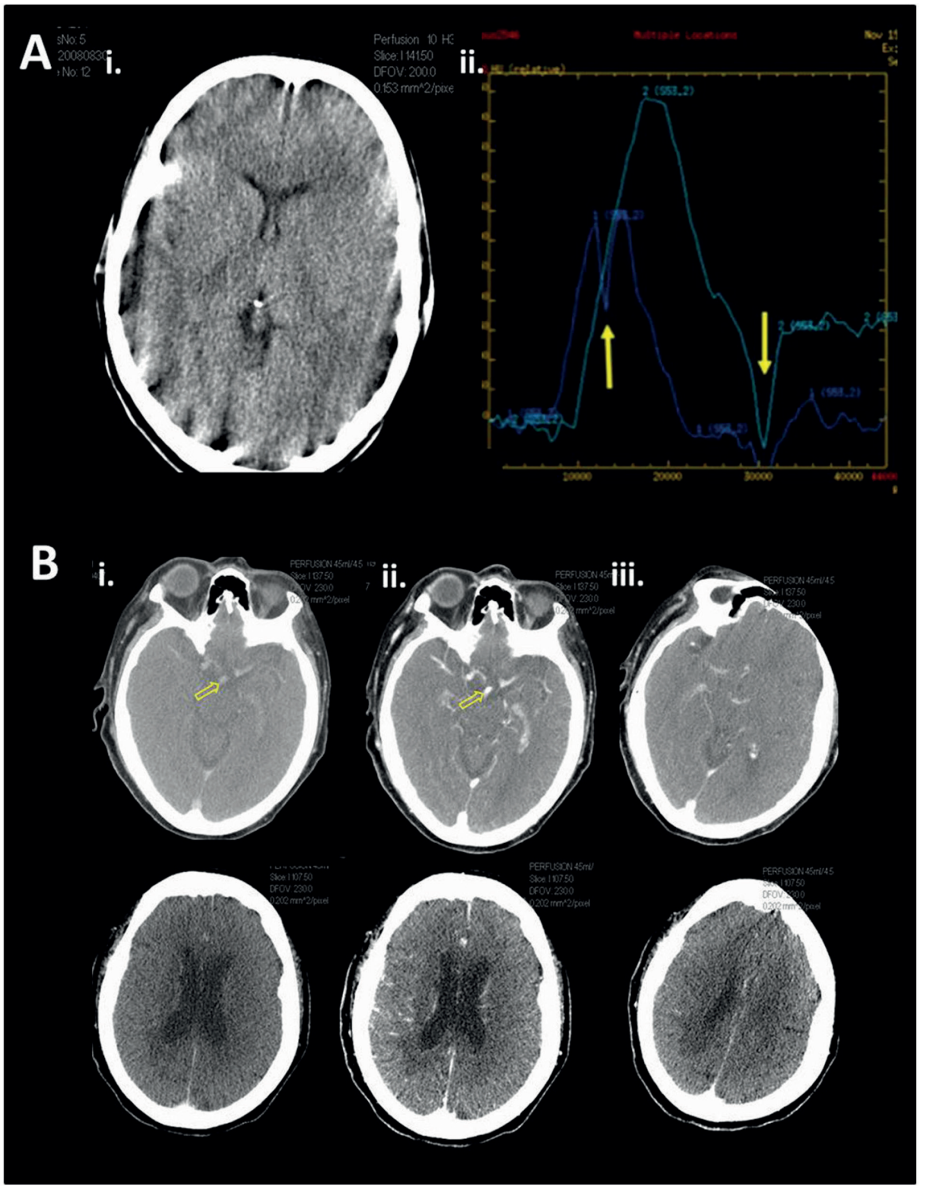


Figure E2:

A, Dynamic contrast material–enhanced CT image shows movement of the patient's head during acquisition caused significant artifacts *(i).* The arterial and venous TDCs were significantly affected and exhibited large fluctuations (yellow arrows) *(ii). B,* Cine perfusion CT images (two levels) from same section location obtained during CT contrast material injection over 66 seconds. The basilar artery (yellow arrow), eye orbits, and lateral ventricles are visible at the beginning of the scan *(i, ii)* but are no longer visible later in the scan *(iii)* due in part to patient motion in the craniocaudal direction (z-axis).



CHAPTER 4.4

Regional Comparison Of Multiphase CT Angiography And CT Perfusion For Prediction Of Tissue Fate In Ischemic Stroke

Based upon:
Regional Comparison of Multiphase Computed Tomographic Angiography and Computed Tomographic Perfusion for Prediction of Tissue Fate in Ischemic Stroke
Christopher D. d'Esterre, Anurag Trivedi, Pooneh Pordeli, Mari Boesen, Shivanand Patil, Seong Hwan Ahn, Mohamed Najm, Enrico Fainardi, Jai Jai Shiva Shankar, Marta Rubiera, Mohammed A. Almekhlafi, Jennifer Mandzia, Alexander V. Khaw, Philip Barber, Shelagh Coutts, Michael D. Hill, Andrew M. Demchuk, Tolulope Sajobi, Nils D. Forkert, Mayank Goyal, Ting-Yim Lee, Bijoy K. Menon
Stroke. 2017;48:939-945.

ABSTRACT

Background and Purpose

Within different brain regions, we determine the comparative value of multiphase computed tomographic angiography (mCTA) and computed tomographic perfusion (CTP) in predicting follow-up infarction.

Methods

Patients with M1-middle cerebral artery occlusions were prospectively included in this multicenter study. Regional analysis was performed for each patient within Alberta Stroke Program Early CT Score regions M2 to M6. Regional pial vessel filling was assessed on mCTA in 3 ways: (1) Washout of contrast within pial vessels; (2) Extent of maximal pial vessel enhancement compared with contralateral hemisphere; (3) Delay in maximal pial vessel enhancement compared with contralateral hemisphere. Cerebral blood flow, cerebral blood volume, and Tmax data were extracted within these Alberta Stroke Program Early CT Score regions. Twenty-four- to 36-hour magnetic resonance imaging/CT was assessed for infarct in each Alberta Stroke Program Early CT Score region (defined as >20% infarction within that region). Mixed effects logistic regression models were used to compare mCTA and CTP parameters when predicting brain infarction. Area under the receiver operating characteristics was used to assess discriminative value of statistical models.

Results

Seventy-seven patients were included. mCTA parameter washout and CTP parameter Tmax were significantly associated with follow-up infarction in all models ($P<0.05$). The area under the receiver operating characteristic for mCTA models ranged from 92% to 94% and was not different compared with all CTP models ($P>0.05$). Mean Tmax and cerebral blood volume values were significantly different between each washout score ($P<0.01$) and each delay score category ($P<0.01$). Mean Tmax, cerebral blood flow, and cerebral blood volume values were significantly different between each extent score category ($P<0.05$).

Conclusion

Similar to CTP, multiphase CTA can be used to predict tissue fate regionally in acute ischemic stroke patients.

Multiphase computed tomographic angiography (mCTA) and computed tomographic perfusion (CTP) have been used for patient selection in recent clinical trials and are used in clinical routine as a result.[1-3] CTP generates quantitative functional maps of regional brain hemodynamics and perfusion, including collateral and microvascular hemodynamic efficiency,[4,5] whereas mCTA depicts whole-brain time-resolved images of pial arteries and veins beyond an occlusion, while informing on thrombus location/size and extracranial vessel patency and tortuosity.[5,6] A perceived advantage of CTP over multiphase CTA has been an inability to use the latter tool to predict fate of ischemic tissue regionally. To address this issue, we systematically examine mCTA parameters of delay in maximal pial vessel enhancement compared with contralateral hemisphere, washout of contrast within pial vessels, and extent of maximal pial vessel enhancement compared with contralateral hemisphere in their ability to predict tissue fate regionally. We compare these parameters to well-established parameters of cerebral blood flow, blood volume, and Tmax on CTP.

METHODS

Patients

Data are from the Prove-IT study, a prospective, multicenter study that acquired acute multimodal CT imaging (mCTA and CTP) at baseline among ischemic stroke patients.5 All patients in this study have been published in previous studies by the authors.[5,7,8] Local ethics review committees approved the study. Only patients with known symptom onset time and complete middle cerebral artery-M1 segment occlusion at baseline were included for this analysis.

Imaging Protocols

At admission, all patients had a noncontrast CT scan, head/neck multiphase CTA, and CTP.[5]

Multiphase CTA

Time-resolved cerebral angiograms of the brain vasculature were generated following the injection of 80 mL of contrast agent injected at a rate of 5 mL/s followed by a saline flush of 50 mL at 6 mL/s. For the first phase, the aortic arch-to-vertex helical scan was timed to be in the peak arterial phase of normal brain by triggering the scan based on bolus tracking. This first phase acquisition was 7 seconds in length. The second phase was acquired after a delay of 4 seconds allowing for table repositioning to the skull base. Scan duration for each additional phase is 3.4 seconds. Thick-section axial maximum intensity projections at 24 mm thickness and 4 mm intervals were reconstructed.

CT Perfusion

Forty-five milliliter of CT contrast agent was power injected at 4.5 mL/s followed by a saline flush of 40 mL at 6 mL/s. Sections of 8 cm thickness were acquired at 5 mm slice thickness. Scanning began after a delay of 5 seconds from contrast injection in up to 2 phases (scanning intervals): first phase every 2.8 seconds for 60 seconds (in 30 patients) and an additional second phase every 15 seconds for 90 seconds (in 47 patients). One author processed each study using commercially available delay-insensitive deconvolution

software (CT Perfusion 4D, GE Healthcare, Waukesha, WI). For each study, the arterial input function was manually selected from the basilar artery or internal carotid artery using a 2 voxel×2 voxel (in-slice) region of interest. Absolute maps of cerebral blood flow (CBF; mL·min-1·(100 g)-1], cerebral blood volume (CBV; mL·(100 g)-1], and Tmax (seconds) were calculated by deconvolution of tissue time-density curves and the arterial input function using a delay-insensitive algorithm (CT Perfusion 4D, GE Healthcare).7 Average maps were created by averaging the dynamic CTP images over the duration of the first pass (66 seconds) of contrast. In-plane patient motion was minimized using automated software (CT Perfusion 4D), and volumes were manually removed, as needed, by visual inspection of the cine series and time density curve.

Image Analysis

Regional analysis was performed for each patient within 5 Alberta Stroke Program Early CT Score (ASPECTS) regions, M2 to M6, by consensus of 2 readers who were blinded to all other clinical and imaging information. The M1 region was not included as pial vessel filling is difficult to interpret in this area of the brain, and there are also beam-hardening artifacts caused by the subjacent sphenoid bone.

Multiphase Computed Tomographic Angiography

Pial vessels were assessed in each ASPECTS region using these 3 parameters: (1) washout of contrast agent within pial vessels; (2) extent of maximal pial vessel enhancement compared with contralateral hemisphere; (3) delay in maximal pial vessel enhancement compared with contralateral hemisphere (Figure 1). All parameters were scored on a 3-point scale, where 1=poor, 2=intermediate, and 3=good (ie, higher score means better collaterals). Each parameter was scored as follows:

1. Washout of contrast agent within pial vessels. Washout was assessed by comparing pial vessel enhancement on the ipsilesional side across phases II and III and scored as follows: 1=no washout of contrast agent, that is, no difference in pial vessel enhancement between the second and third phases; 2=intermediate washout, that is, decrease in pial vessel enhancement in the third phase as compared with the second phase; and 3=complete washout, that is, no luminal contrast in the pial vessel enhancement on the third phase.

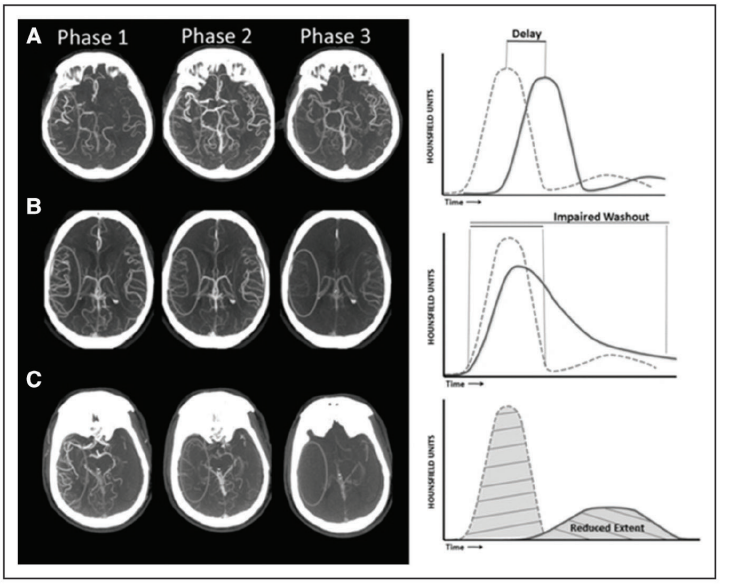


Figure 1. Admission multiphase computed tomographic angiography (mCTA) profiles for (**A**–**C**) 3 patients with L-middle cerebral artery-M1 occlusions, and corresponding hypothetical time–density curves for pial vessel enhancement. Contralateral hemisphere is outlined in blue for all patients and used as reference to ipsilateral enhancement. Delay was assessed by comparing the maxima appearance of CT contrast in the pial vessels in the ischemic region to maxima appearance within the same region within the normal hemisphere. Washout was assessed by comparing the pial vessel enhancement on the third phase mCTA compared with the second phase within each hemisphere. Extent was assessed by comparing the number of pial vessels in a particular ischemic region with the corresponding contralateral hemisphere in all phases of the mCTA acquisition.

2. Extent of pial vessel enhancement compared with contralateral hemisphere. Extent was assessed by comparing visually the maximal number of pial vessels in a particular ischemic region across all phases of the mCTA acquisition when compared with the corresponding contralateral hemisphere region. 1=0% to 50% pial vessels compared with contralateral region; 2=50% to 99% pial vessels compared with the contralateral side; and 3=number of pial vessels indistinguishable from the corresponding contralateral hemisphere region.

3. Delay in maximal pial vessel enhancement across all phases compared with contralateral hemisphere. Delay was assessed by comparing the maximal appearance of CT contrast in the pial vessels in each ipsilesional ischemic region to maximal pial vessel enhancement in the corresponding contralateral hemisphere region and scored as follows: 1=2-phase delay; 2=1-phase delay; and 3=no delay.

Six regions had no contrast filling of pial vessels in all 3 phases. In these regions with 0% pial vessel enhancement, washout and delay could not be scored.

Computed Tomographic Perfusion

Within each ASPECTS region, a gray and white matter tissue mask was manually segmented using the CTP-average image based on individual Hounsfield Uni thresholds. This tissue mask was applied to the CBF, CBV, and Tmax functional maps. Regional gray and white matter perfusion values were extracted from each ASPECTS region, removing any large vessels.[9]

Recanalization/Reperfusion

The last run of the digital subtraction angiography post endovascular treatment was assessed for reperfusion in each of the ASPECTS regions (M2-M6), respectively, using a previously published template for regional assessment of angiographic images.[10] The presence of capillary blush in each ASPECTS region was considered as evidence of reperfusion. A minority of patients (11/77) with either no recanalization (no change in baseline thrombus) or complete recanalization (no thrombus in any pial artery) on repeat CT angiography Circle of Willis done 2 to 4 hours from baseline imaging were also included in this analysis.

Final Tissue Fate

Twenty-four to 36-hour magnetic resonance diffusion weighted imaging (preferably) or noncontrast CT was assessed to assess extent of infarct in each of the 5 ASPECT regions (M2-M6). Greater than 20% infarction within an ASPECTS region as assessed by 2 experts by consensus was classified as an infarct positive region.

Statistical Analysis

We used a mixed effect logistic regression analysis to study the impact of mCTA and CTP parameters on follow-up infarction while adjusting for patients' clinical and demographic characteristics, and considering the patients and their brain regions (nested within each patient) as random effects variables. The regression models were independently developed for mCTA and CTP modalities separately. The mCTA models were as follows: All imaging parameters adjusted for recanalization/reperfusion and demographic/clinical variables (age, sex, and baseline National Institutes of Health Stroke Scale [NIHSS]; model-1A), adjusted for demographic/clinical variables only (model-2A), adjusted

for reperfusion only (model-3A), and only mCTA imaging parameters (model-4A). CTP models were as follows: All imaging parameters adjusted for recanalization/ reperfusion and demographic/clinical variables (age, sex, and baseline NIHSS; model-1B), adjusted for demographic/clinical variables only (model-2B), adjusted for recanalization/reperfusion only (model-3B), and only CTP imaging parameters (model-4B). The six regions with 0% pial vessel enhancement did not have any scores for washout and delay and were therefore excluded by default from regression analyses. The effect of each variable was estimated using odds ratios and 95% confidence intervals. Receiver operator characteristic curves were plotted and area under the receiver operator characteristic curve along with 95% confidence intervals were reported for each model. Differences in the area under the receiver operating characteristics of the predictive models for mCTA and CTP parameters were compared using Delong's method.[11] The relationship between mCTA parameters with CTP parameters was assessed using analysis of variance. Reliability between 2 raters in assessing mCTA parameters washout, extent, and delay at the regional level was assessed using unweighted Fleiss's κ. Statistical significance was assessed at $\alpha=0.05$. All analyses were performed using R (version 3.2.1).

Table 1. Demographic, Clinical and Imaging Characteristics of Patients Included in the Study (N=77 Patients and n=385 ASPECTS Regions)

Variables	Central Tendency				
Age, y [mean (SD)]	70.1 (14.3)				
Sex (% female)	54				
Baseline ASPECTS [median (IQR)]	7 (6–9)				
Onset to CT time, m [mean (SD)]	227.9 (258.6)				
Recanalization (modified TICI 2b/3), %	81				
Baseline NIHSS [median (IQR)]	18 (15–23)				
24 h NIHSS [median (IQR)]	10 (4–18)				
	Imaging characteristics				
	M2	M3	M4	M5	M6
Multiphase CTA parameters, N (%)					
Washout					
1=none	26 (35)	7 (9)	0 (0)	14 (18)	5 (6)
2=intermediate	48 (61)	50 (65)	21 (27)	46 (60)	36 (47)
3=complete	3 (4)	20 (26)	56 (73)	17 (22)	36 (47)
Extent					
1=poor	11 (12)	13 (17)	7 (9)	9 (12)	5 (6)
2=intermediate	40 (52)	30 (39)	26 (34)	36 (46)	31 (40)
3=good	26 (36)	34 (44)	44 (57)	32 (42)	41 (54)
Delay					
1=2 phase	7 (9)	3 (4)	0 (0)	6 (7)	3 (4)
2=1 phase	53 (69)	39 (51)	34 (44)	39 (51)	30 (39)
3=none	17 (22)	35 (45)	43 (56)	32 (42)	44 (57)
CT perfusion parameters, mean±SD					
Tmax, s	14.7±6.2	12.6±4.9	11.3±5.7	13.7±6.3	11.7±4.9
Cerebral blood flow, $mL \cdot min^{-1} \cdot (100\ g)^{-1}$	15.2±9.6	14.8±7.1	16.9±8.6	14.6±7.7	15.8±7.2
Cerebral blood volume, $mL \cdot (100\ g)^{-1}$	3.9±1.8	3.3±1.3	3.3±1.4	3.5±1.3	3.4±1.4

ASPECTS indicates Alberta Stroke Program Early CT Score; CTA, computed tomographic angiography; and IQR, interquartile range.

RESULTS

The demographic, clinical, and imaging characteristics of participants are summarized in Table 1. Of the 77 study participants, 42 (54%) were female. The mean age was 70.1 (SD ±14.3) years, with 72% of the patients being 65 years or older. Median NIHSS score was 18 (interquartile range 15- 23). Mean onset to CT time was 227.9 (SD ±258.6) minutes. Median baseline ASPECTS was 7 (interquartile range 6-9). Follow-up infarction was assessed using magnetic resonance imaging in 45 of 77 (58.4%) patients, whereas the rest

Table 2. Odds Ratio (95% CI) for Demographic, Clinical, and mCTA Parameters Associated With Follow-Up Brain Infarction*

Predictors	Model-1A	Model-2A	Model-3A	Model-4A
	Odds Ratio (95% CI)			
Recanalization/reperfusion	0.69 (0.26–1.84)	…	0.55 (0.21–1.47)	…
Demographics/clinical characteristics				
Age	1.90† (0.99–3.64)	1.87† (1.10–3.19)	…	…
Sex	0.89 (0.26–2.98)	0.56 (0.20–1.60)	…	…
NIHSS (baseline)	1.81 (0.94–3.48)	2.07† (1.19–3.62)	…	…
Onset to imaging time	0.74 (0.33–1.61)	1.14 (0.62–2.09)	…	…
Multiphase CTA parameters				
Extent=1 (reference)	1	1	1	1
Extent=2	0.58 (0.10–3.30)	0.79 (0.17–3.71)	0.53 (0.09–3.07)	0.86 (0.18–4.08)
Extent=3	0.28 (0.05–1.73)	0.47 (0.09–2.32)	0.25 (0.04–1.55)	0.47 (0.09–2,36)
Washout=1 (reference)	1	1	1	1
Washout=2	0.26† (0.08–0.81)	0.29† (0.10–0.84)	0.21† (0.07–0.65)	0.23† (0.08–0.68)
Washout=3	0.06† (0.01–0.25)	0.08† (0.02–0.30)	0.05† (0.01–0.20)	0.06† (0.01–0.24)
Delay=1 (reference)	1	1	1	1
Delay=2	0.22 (0.01–5.48)	0.17 (0.01–2.98)	0.24 (0.01–6.94)	0.15 (0.01–3.19)
Delay=3	0.68 (0.02–18.83)	0.48 (0.02–9.59)	0.71 (0.02–22.94)	0.41 (0.02–9.40)
AUC, % (95% CI)	93 (90–96)	92 (90–95)	94 (91–96)	93 (91–96)

AUC indicates area under the receiver operator characteristic curve; CI, confidence interval; CTA, computed tomographic angiography; mCTA, multiphase CTA; and NIHSS, National Institutes of Health Stroke Scale.

*Six regions with 0% pial enhancement were excluded from analysis.

†Significant variable with $P<0.05$ significance level.

were assessed on CT. All 6 regions with 0% pial vessel enhancement developed follow-up infarction.

Tables 2 and 3 describe the results for the mixed effect logistic regression analysis for the mCTA and CTP models, respectively. Washout parameter on mCTA was significantly associated with follow-up infarction in all mCTA models (P<0.05). The Tmax parameter was significantly associated with follow-up infarction in all CTP models (P<0.05). The area under the receiver operating characteristics for mCTA models ranged between 92% and 94%, whereas all CTP models had an area under the receiver operating characteristics between 90% and 92%. The addition of recanalization/reperfusion and clinical parameters did not significantly affect the discriminative value of the models. There was no statistically significant difference between mCTA and CTP models (all P values >0.05). The relationship between mCTA parameters and CTP parameters are shown using box plots

Table 3. Odds Ratio (95% CI) for Demographic, Clinical, and CTP Parameters Associated With Follow-Up Brain Infarction

Predictors	Model-1B	Model-2B	Model-3B	Model-4B
	Odds Ratio (95% CI)			
Reperfusion	0.81 (0.32–2.07)	…	0.47 (0.20–1.14)	…
Demographics/clinical characteristics				
Age	1.64 (0.92–2.96)	1.62* (1.03–2.55)	…	…
Sex	0.53 (0.16–1.74)	0.60 (0.24–1.51)	…	…
NIHSS (baseline)	1.33 (0.74–2.42)	1.63* (0.74–2.41)	…	…
Onset to CT time	0.86 (0.48–1.53)	1.10 (1.01–2.63)	…	…
CTP parameters				
Tmax	3.85* (1.75–8.44)	3.40* (1.71–6.76)	3.72* (1.72–8.06)	3.51* (1.78–6.97)
CBF	2.01 (0.90–4.50)	2.24* (1.12–4.50)	1.78 (0.80–3.98)	2.08* (1.03–4.17)
CBV	0.69 (0.37–1.30)	0.74 (0.42–1.28)	0.80 (0.43–1.52)	0.81 (0.46–1.42)
AUC, % (95% CI)	91 (87–94)	90 (87–93)	92 (88–95)	91 (88–94)

AUC indicates area under the receiver operator characteristic curve; CBF, cerebral blood flow; CBV, cerebral blood volume; CI, confidence interval; CT, computed tomographic; CTP, CT perfusion; and NIHSS, National Institutes of Health Stroke Scale.
*Significant variable with *P*<0.05 significance level.

(Figure 2). The mean Tmax and CBV values were significantly different between each washout score (P<0.01) and each delay score (P<0.01), respectively. The mean Tmax, CBF, and CBV values were significantly different between each extent score (P<0.05). Washout grade 1 on mCTA corresponds to a Tmax value of around 15 seconds, whereas

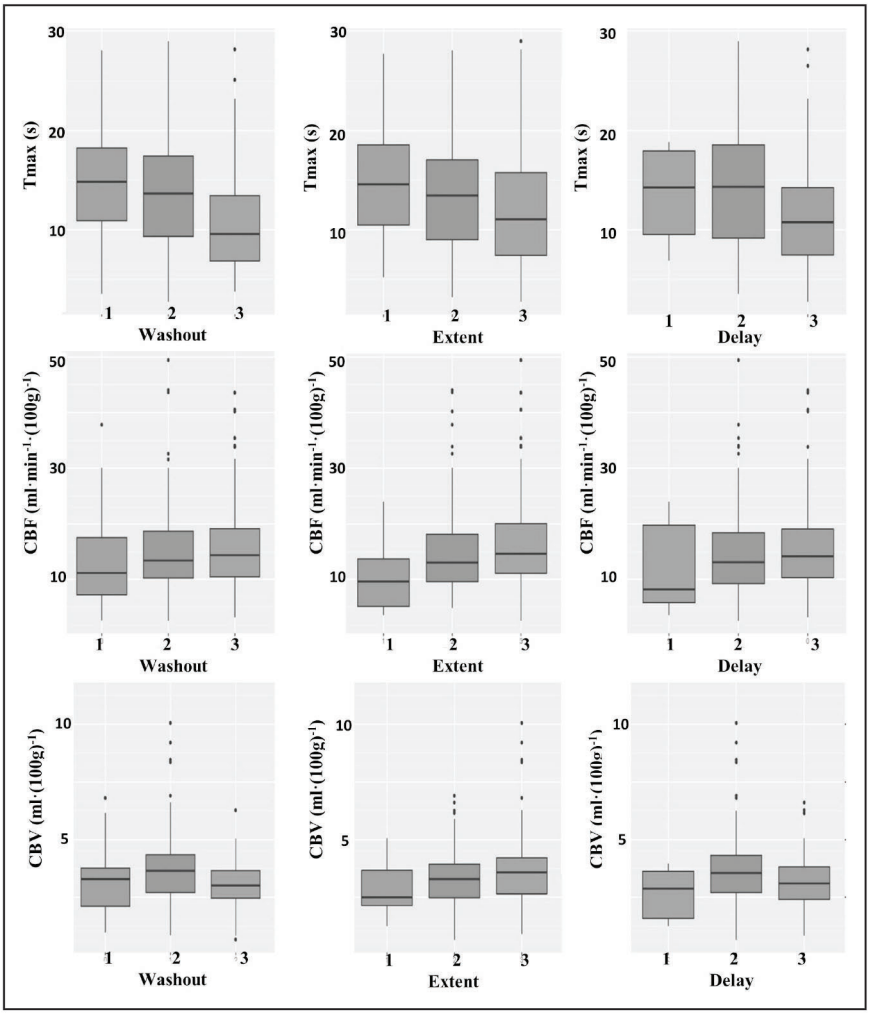


Figure 2. Box plots for the relationship between individual multiphase computed tomographic angiography parameters: washout, extent, and delay respectively, and individual computed tomographic perfusion parameters: Tmax (s), cerebral blood flow (CBF; mL·min·1·(100 g)$^{-1}$), and cerebral blood volume (CBV; mL·(100 g)$^{-1}$).

grade 3 corresponds to a Tmax value of 10 seconds. A 2-phase delay on mCTA corresponds to a Tmax of around 14 seconds, whereas no delay corresponds to a Tmax of around 10 seconds. Comparative mCTA and CTP parameter values across all parameters are shown in Figure 2 and in Table I in the online-only Data Supplement. Interrater reliability for the mCTA parameters was highest for washout (κ 0.89; P<0.01) followed by delay (κ 0.75; P<0.01) and extent (0.60; P<0.01).

DISCUSSION

In this analysis, we show that imaging parameters on multiphase CTA are predictive of follow-up infarction regionally in patients with acute ischemic stroke. We also find that mCTA and CTP modalities have similar accuracy in predicting follow-up infarction when using the ASPECTS template and that the mCTA imaging parameters of washout, extent, and delay have comparable values of Tmax, CBF, and CBV on CTP.

The multiphase CTA imaging modality is used to assess pial vessel filling and collateral status in patients with acute ischemic stroke and was successfully used as an imaging selection tool in the ESCAPE trial.[1] Because anterior cerebral artery to middle cerebral artery collaterals are likely different from posterior cerebral artery (posterior cerebral artery-middle cerebral artery) collaterals, the technique has been adapted in the past to assess collateral status and consequent tissue fate in these 2 vascular territories differently.[12] Nonetheless, the ability of multiphase CTA to predict tissue fate in smaller ischemic regions of the brain was as yet unexplored. We recently showed that hang up of contrast within pial vessels on mCTA was more reliable than single phase CTA in detecting distal intracranial occlusions.[6] In the current article, we sought to analyze in detail all available spatial and temporal information in a multiphase CT angiogram using imaging parameters like degree of washout, extent of filling, and delay in filling of contrast within pial arteries over time. Conceptually, these mCTA imaging parameters are very similar to the CTP parameters of transit time delay, blood volume, and blood flow (Figure 1).

Our results show that the imaging parameter washout on mCTA correlates with follow-up infarction in acute ischemic stroke patients. Washout is a measure of the local

perfusion pressure (inversely proportional to mean transit time) at the region. Prolonged washout would signify an ischemic region to which collateral supply is also poor, that is, severe ischemia. Interestingly, the CTP measure that best correlated with follow-up infarction in our analysis was also a measure that is the summation of T0 (difference in contrast appearance time in the artery and region) and mean transit time (a surrogate marker of local perfusion pressure), that is, Tmax.[7] The mCTA parameters delay and extent were not independently associated with follow-infarction in our analysis in all models when adjusting for washout. Of note however, all 6 regions with 0% pial vessel enhancement (poor extent) went on to develop infarction on follow-up. Similarly, although CTP parameters CBF (significant in models 2B and 4B alone) and CBV were not independently associated with follow-up infarction in all models when adjusting for Tmax, this may be because of collinearity with Tmax and our approach of estimating mean values of CTP parameters within ASPECTS regions rather than at a voxel level.

The regional assessment approach is conceptually all that may be required for acute decision making. It may not be necessary to know exact volumes for clinical decision making, more so because of the inherent measurement uncertainty. Although on average, poor clinical outcome is observed with predicted ischemic core volumes of 70 mL or greater, regional assessment of pial vessel filling may be equally useful.[13-15] Our analysis suggests that regions with no pial vessel enhancement are likely to be infarcted on follow-up imaging. Our analysis also shows that mCTA parameters like washout and delay correlate with CTP parameters like Tmax and CBF (Figure 2). Significantly impaired washout or a 2-phase delay in pial vessel filling in ASPECTS regions is likely suggestive of a Tmax >14 to 16 seconds within that same ASPECTS region, whereas quick washout of contrast or no delay in filling of pial vessels when compared with the contralateral side may suggest a regional Tmax of around 8 to 10 seconds (Figure 3). Assessment of mCTA pial vessel filling could therefore provide surrogate regional measures of ischemia status and at risk brain tissue over the time it takes for reperfusion to be achieved.

The mCTA imaging modality has limitations. The presence of poor cardiac output or flow limiting proximal stenosis can cause delay and dispersion in pial vessel contrast filling, potentially confounding measurements that are based on comparison to contralesional normal side. Delay-insensitive deconvolution algorithms in use with CTP potentially correct for some of these problems. The spatial resolution of the mCTA imaging modality

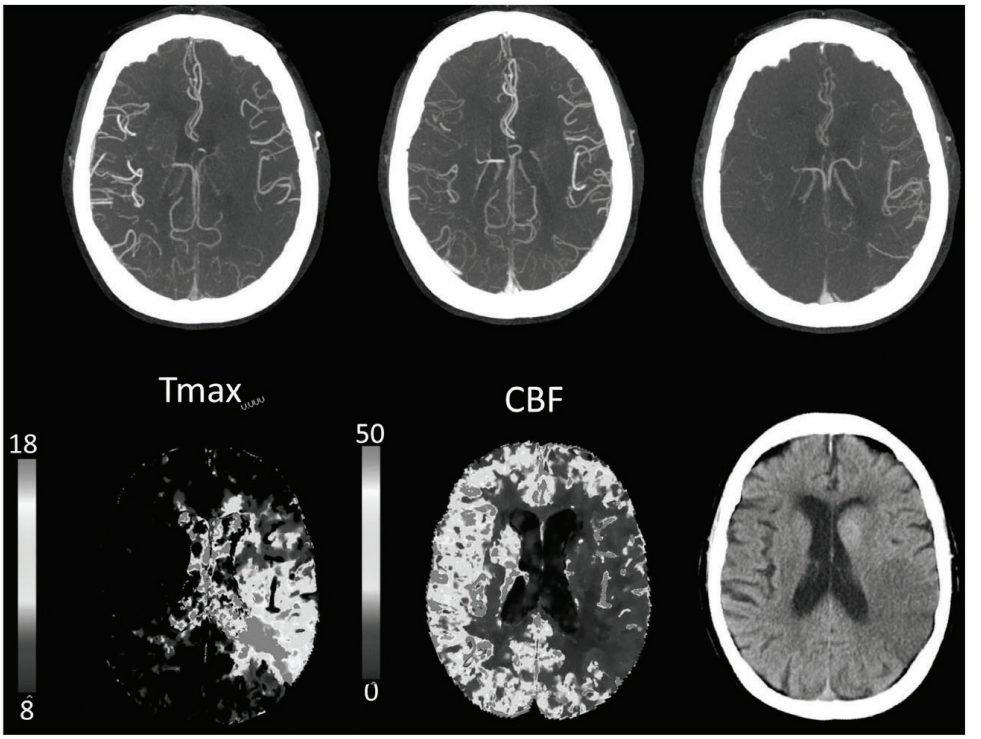


Figure 3. Multiphase computed tomographic angiography (mCTA; 3 phases) maximum intensity projection images and computed tomographic perfusion (CTP) functional maps performed at 2h 57 min post symptom onset for a patient with baseline NIHSS of 13 and left middle cerebral artery M1 segment occlusion. The multiphase CTA scoring within M4-M6 is congruent with the CTP Tmax profile: the M4 region shows no delay and good washout of contrast filling within pial vessels on mCTA with Tmax≈8-10 s; the M5 region shows 1-phase delay and poor washout on mCTA with Tmax of ≈16 s; the M6 region shows 2-phase delay and reduced extent with Tmax of ≈20 s. Recanalization occurred 96 min post CTP. Follow-up noncontrast CT shows that M5 and M6 regions went on to infarction. Tmax=seconds, cerebral blood flow (CBF)=mL·min-1·(100 g)$^{-1}$.

is still limited when compared with CT perfusion, especially when trying to predict tissue fate where bone artifact occurs such as the posterior circulation and M1 ASPECTS region, isolated white or deep gray matter ischemia and smaller brain regions than the size of an average ASPECTS region. We limited our sample to middle cerebral artery-M1 occlusions to account for the effect of early recanalization/reperfusion on our analysis. Future study would include assessing the ability of the mCTA imaging parameters individually and together in predicting regional tissue fate in all patients with acute ischemic stroke (including those with more distal occlusions).

CONCLUSIONS

In summary, our analysis shows that the mCTA imaging modality compares well with CTP in ability to predict ischemic tissue fate in ASPECTS regions in patients with major disabling ischemic strokes.

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Supplementary Appendix

Supplemental Table I. The relationship between individual multi-phase CTA parameters Washout, Extent, and Delay respectively, and individual CT perfusion parameters: Tmax (s) CBF ($ml \cdot min^{-1} \cdot (100g)^{-1}$) and CBV ($ml \cdot (100g)^{-1}$).

	Washout = 1	**Washout = 2**	**Washout = 3**
Tmax	Mean= 14.55511 Std= 5.488056 Median= 14.8555 IQR= 7.344	Mean= 13.80929 Std= 5.9275 Median= 13.65 IQR= 8.091625	Mean= 10.65667 Std= 4.868693 Median= 9.4544 IQR= 6.579275
CBV	Mean= 3.211273 Std= 1.328878 Median= 3.283525 IQR= 1.662863	Mean= 3.780927 Std= 1.705632 Median= 3.6526 IQR= 1.64375	Mean= 2.993526 Std= 1.030032 Median= 3.0035 IQR= 1.19745
CBF	Mean= 12.903280 Std= 7.804781 Median= 11.161350 IQR= 10.289650	Mean= 15.019148 Std= 7.537569 Median= 13.397600 IQR= 8.419700	Mean= 16.417319 Std= 8.573300 Median= 14.558025 IQR= 8.703400

	Extent = 1	**Extent = 2**	**Extent = 3**
Tmax	Mean= 15.604075 Std= 6.793808 Median= 14.597725 IQR= 8.065075	Mean= 13.190076 Std= 5.683898 Median= 13.447450 IQR= 8.043400	Mean= 12.053282 Std= 5.440430 Median= 11.052575 IQR= 8.342812
CBV	Mean= 2.881314 Std= 1.066064 Median= 2.498925 IQR= 1.522938	Mean= 3.312502 Std= 1.209276 Median= 3.294350 IQR= 1.461400	Mean= 3.634395 Std= 1.753410 Median= 3.573925 IQR= 1.555188

CBF	Mean= 11.006532 Std= 6.857300 Median= 9.644100 IQR= 8.508900	Mean= 14.680405 Std= 7.626666 Median= 13.050000 IQR= 8.510100	Mean= 16.372761 Std= 8.273691 Median= 14.621700 IQR= 8.900100

	Delay = 1	**Delay = 2**	**Delay = 3**
Tmax	Mean= 13.560333 Std= 5.198227 Median= 14.268775 IQR= 8.390612	Mean= 14.154174 Std= 6.235494 Median= 14.116600 IQR= 9.492475	Mean= 11.481586 Std= 4.871097 Median= 10.766550 IQR= 6.777900
CBV	Mean= 2.666475 Std= 1.204763 Median= 2.875000 IQR= 2.044537	Mean= 3.742651 Std= 1.728529 Median= 3.557925 IQR= 1.627050	Mean= 3.144198 Std= 1.148614 Median= 3.100000 IQR= 1.411475
CBF	Mean= 12.090317 Std= 9.056744 Median= 8.195950 IQR= 13.953375	Mean= 14.674766 Std= 7.839999 Median= 13.169700 IQR= 9.071213	Mean= 15.841417 Std= 8.096871 Median= 14.150000 IQR= 8.734450

CHAPTER 4.5

Imaging Features And Safety And Efficacy Of Endovascular Stroke Treatment: A Meta-Analysis Of Individual Patient-Level Data

Based upon:
Imaging Features and Safety and Efficacy of Endovascular Stroke Treatment: A Meta-Analysis of Individual Patient-Level Data
Luis San Román, Bijoy K Menon, Jordi Blasco, María Hernández-Pérez, Antoni Dávalos, Charles B L M Majoie, Bruce CV Campbell, Francis Guillemin, Hester Lingsma, René Anxionnat, Jonathan Epstein, Jeffrey L Saver, Henk Marquering, John HWong, Demetrius Lopes, Gernot Reimann, Hubert Desal, Diederik W J Dippel, Shelagh Coutts, Richard du Mesnil de Rochemont, Dileep Yavagal, Jean Christophe Ferre, Yvo BW E M Roos, David S Liebeskind, Robert Lenthall, Carlos Molina, Fahad S Al Ajlan, Vivek Reddy, Dar Dowlatshahi, Sourour Nader-Antoine, Catherine Oppenheim, Alim P Mitha, Stephen M Davis, Christian Weimar, Robert J van Oostenbrugge, Erik Cobo, Timothy J Kleinig, Geoffrey A Donnan, Aad van der Lugt, Andrew M Demchuk, Olvert A Berkhemer, Anna M M Boers, Gary A Ford, Keith W Muir, B Scott Brown, Tudor Jovin, Wim H van Zwam, Peter J Mitchell, Michael D Hill, Phil White, Serge Bracard, Mayank Goyal, on behalf of the HERMES collaborators
Lancet Neurol 2018; 17: 895-904

ABSTRACT

Background

Evidence regarding whether imaging can be used effectively to select patients for endovascular thrombectomy (EVT) is scarce. We aimed to investigate the association between baseline imaging features and safety and efficacy of EVT in acute ischaemic stroke caused by anterior large-vessel occlusion.

Methods

In this meta-analysis of individual patient-level data, the HERMES collaboration identified in PubMed seven randomised trials in endovascular stroke that compared EVT with standard medical therapy, published between Jan 1, 2010, and Oct 31, 2017. Only trials that required vessel imaging to identify patients with proximal anterior circulation ischaemic stroke and that used predominantly stent retrievers or second-generation neurothrombectomy devices in the EVT group were included. Risk of bias was assessed with the Cochrane handbook methodology. Central investigators, masked to clinical information other than stroke side, categorised baseline imaging features of ischaemic change with the Alberta Stroke Program Early CT Score (ASPECTS) or according to involvement of more than 33% of middle cerebral artery territory, and by thrombus volume, hyperdensity, and collateral status. The primary endpoint was neurological functional disability scored on the modified Rankin Scale (mRS) score at 90 days after randomisation. Safety outcomes included symptomatic intracranial haemorrhage, parenchymal haematoma type 2 within 5 days of randomisation, and mortality within 90 days. For the primary analysis, we used mixed-methods ordinal logistic regression adjusted for age, sex, National Institutes of Health Stroke Scale score at admission, intravenous alteplase, and time from onset to randomisation, and we used interaction terms to test whether imaging categorisation at baseline modifies the association between treatment and outcome. This meta-analysis was prospectively designed by the HERMES executive committee but has not been registered.

Findings

Among 1764 pooled patients, 871 were allocated to the EVT group and 893 to the control group. Risk of bias was low except in the THRACE study, which used unblinded assessment of outcomes 90 days after randomisation and MRI predominantly as the primary baseline imaging tool. The overall treatment effect favoured EVT (adjusted common odds ratio [cOR] for a shift towards better outcome on the mRS 2·00, 95% CI 1·69-2·38; p<0·0001). EVT achieved better outcomes at 90 days than standard

medical therapy alone across a broad range of baseline imaging categories. Mortality at 90 days (14·7% vs 17·3%, p=0·15), symptomatic intracranial haemorrhage (3·8% vs 3·5%, p=0·90), and parenchymal haematoma type 2 (5·6% vs 4·8%, p=0·52) did not differ between the EVT and control groups. No treatment effect modification by baseline imaging features was noted for mortality at 90 days and parenchymal haematoma type 2. Among patients with ASPECTS 0-4, symptomatic intracranial haemorrhage was seen in ten (19%) of 52 patients in the EVT group versus three (5%) of 66 patients in the control group (adjusted cOR 3·94, 95% CI 0·94-16·49; $p_{interaction}$=0·025), and among patients with more than 33% involvement of middle cerebral artery territory, symptomatic intracranial haemorrhage was observed in 15 (14%) of 108 patients in the EVT group versus four (4%) of 113 patients in the control group (4·17, 1·30-13·44, $p_{interaction}$=0·012).

Interpretations

EVT achieves better outcomes at 90 days than standard medical therapy across a broad range of baseline imaging categories, including infarcts affecting more than 33% of middle cerebral artery territory or ASPECTS less than 6, although in these patients the risk of symptomatic intracranial haemorrhage was higher in the EVT group than the control group. This analysis provides preliminary evidence for potential use of EVT in patients with large infarcts at baseline.

Funding

Medtronic.

Randomised clinical trials from the past 3 years have established the safety and efficacy of endovascular thrombectomy (EVT) in the treatment of patients with acute ischaemic stroke and proximal anterior circulation occlusion.[1-8] Because the clinical benefit observed in these trials was time dependent, the need for fast and efficient patient selection is well recognised.[9] Imaging is widely used to determine prognosis and to select patients for EVT.[10-12] After the results of five trials were reported in 2015, the new American Heart Association guidelines[13] recommended EVT as standard of care (level I, class A evidence) in patients with a baseline non-contrast Alberta Stroke Program Early CT Score (ASPECTS) between 6 and 10.

Imaging features are strong predictors of clinical outcome.[10] Large infarcts at baseline, large thrombi in proximal arteries, and poor collateral circulation identified with imaging are associated with overall lower likelihood of functional independence and increased risk of intracranial haemorrhage after reperfusion therapies.14-19 However, evidence regarding whether these imaging features are useful for selecting patients for EVT is scarce. This patient-level meta-analysis by the highly effective reperfusion evaluated in multiple endovascular stroke trials (HERMES) collaboration aims to determine safety and efficacy of EVT compared with standard medical therapy, by baseline imaging features.

RESEARCH IN CONTEXT

Evidence Before The Study

Randomised trials from the past 3 years have shown the efficacy of endovascular thrombectomy (EVT) in patients with acute ischaemic stroke and proximal anterior circulation occlusion. In February, 2016, the highly effective reperfusion evaluated in multiple endovascular stroke trials (HERMES) collaboration published a pooled analysis of individual patient-level data of the first five randomised trials of EVT. It confirmed the benefit of EVT across a wide range of clinical subgroups and reported on the effect of the Alberta Stroke Program Early CT Score (ASPECTS) and site of vessel occlusion as assessed by each individual trial. However, evidence regarding use of imaging in the selection of patients for EVT is scarce.

Added Value Of This Study

To our knowledge, this is the first individual patient-level meta-analysis of imaging data obtained through single core laboratory analysis from all seven randomised endovascular stroke trials listed in PubMed (published between Jan 1, 2010, and Oct 31, 2017), which compared EVT with standard medical therapy in patients with acute ischaemic stroke and anterior circulation large-vessel occlusion. *Trials* requiring imaging to identify patients with anterior circulation ischaemic stroke and using second-generation neurothrombectomy devices in the EVT group were included. This unique dataset is unlikely to be replicated in the future, since randomised trials of thrombectomy for large-vessel occlusion stroke in the patient population studied by these trials are no longer considered ethically justifiable. This meta-analysis provides new evidence that patients with a broad range of baseline imaging characteristics, including those with large infarcts (ie, ASPECTS <6 or involvement of >33% of middle cerebral artery territory), poor collateral circulation, and any clot burden score, might benefit from EVT.

Implications Of All The Available Evidence

Current guidelines by the American Heart Association recommend EVT for patients with an ASPECTS of 6 or more. This analysis provides evidence to support further investigation of the use of EVT for patients with large infarcts at baseline (ASPECTS as low as 3).

METHODS

Search Strategy and Selection Criteria

In this individual patient-level meta-analysis, we searched PubMed for randomised trials published between Jan 1, 2010, and Oct 31, 2017, which compared EVT predominantly done with stent retrievers with standard care in patients with anterior circulation ischaemic stroke. The PubMed search string was ((“randomized controlled trial”[Publication Type]) AND ((thrombectomy [Title/ Abstract]) OR (clot retrieval [Title/Abstract]) OR intraarterial[Title/Abstract]) AND (stroke[Title/Abstract]) AND (“2010/01/01”[Date-Publication]: “2017/10/31”[Date- Publication])).

The HERMES collaboration pooled patient-level demographic, clinical, and imaging data, as well as functional and radiological outcomes from seven randomised trials: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT, THRACE, and PISTE (appendix).[1-7] All of these trials required vessel imaging to identify patients with anterior circulation ischaemic stroke and used predominantly stent retrievers or second-generation neurothrombectomy devices in the EVT groups. All participants provided written informed consent according to each trial protocol (appendix), and each study was approved by the local ethics board. The methodological design for this patient-level pooling has been previously described.[8]

Data analysis

Differences in patient population, sampling frame, and operational definitions of intervention (EVT) and control were assessed before collating all data at a patient level (appendix). Baseline images included information available either on CT or on MRI. All imaging studies were de-identified at the HERMES central coordinating centre. The imaging datasets were then read by independent HERMES core laboratories for baseline CT or MRI, baseline CT angiography (CTA), MRI angiography (MRA), follow-up CT or MRI, and conventional angiography. Readers were masked to all clinical information, except side of stroke.

Imaging in acute ischaemic stroke is used to identify extent of early ischaemic change and location and density of thrombi. We assessed the following five prespecified baseline imaging features. First, ASPECTS defined on CT or magnetic resonance diffusion-weighted imaging (MRDWI)-a widely used ordinal scale that measures the extent of ischaemia in the middle cerebral artery territory (from score 0 in complete infarction to 10 for no infarction).[20] An ASPECTS region was considered as involved on DWI if the lesion occupied more than 30% of the respective region, and on CT if any signs of ischaemia were visible on at least two consecutive cuts of the ten standardised regions of the middle cerebral artery territory. ASPECTS categories were evaluated independently by experts masked to all clinical and imaging information except stroke side. Any disagreement was resolved by consensus. Trichotomised ASPECTS agreement between two raters (JB and LSR, since they read the majority of the scans) assessed in 30 patients with weighted $\varkappa$ was good ($\varkappa$ 0·89, 95% CI 0·81-0·99).

Second, infarcts were categorised as occupying more than or less than 33% of the middle cerebral artery territory, as determined on CT or MR-DWI, according to Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS)/CT Summit criteria.[21]

Third, thrombus location identified on CTA or MRA was classified as that in the intracranial internal carotid artery, proximal M1 middle cerebral artery segment, distal M1 segment, or M2 segment. Tandem occlusion was defined as a thrombus in the extracranial internal carotid artery along with an intracranial (internal carotid artery, M1 segment, and M2 segment) thrombus.[22]

Fourth, collateral circulation distal to an intracranial thrombus was evaluated on multiphase CTA, single-phase CTA, or contrast-enhanced MRA and classified according to a previously published prespecified collateral grade category (grade 0-1 was poor, grade 2 was intermediate, and grade 3 was good collateral circulation).[19]

Finally, thrombus density on imaging was assessed with the hyperdense artery sign on CT[23] and thrombus volume on CTA, analysed with the clot burden score.[24]

Data for number of patients assessed for each imaging variable at baseline and reasons for exclusion are described in the appendix. Patients were excluded from further analyses if images were unavailable from the primary trial or were of poor quality.

Anonymised individual participant data are available in VISTA, an open access registry.

The primary endpoint was neurological functional disability scored on the modified Rankin scale (mRS) 90 days after randomisation, with categories 5 (severe disability) and 6 (death) collapsed into a single category. Primary results are reported as adjusted treatment effects using common odds ratios (cORs) with 95% CIs (indicating the odds that the intervention would lead to improvement of 1 point on the mRS in a shift analysis). Secondary efficacy outcomes were functional independence (mRS 0-2) at 90 days, excellent functional outcome (mRS 0-1) at 90 days, and substantial neurological improvement (defined as neurological improvement of 8 or more points on the National Institute of

Health Stroke Scale [NIHSS] or an NIHSS score of 0-1 24 h after stroke). Secondary results are reported as ORs with 95% CIs. Risk of bias in the individual studies was assessed with the Cochrane handbook methodology. Safety outcomes included intracranial haemorrhage defined as both symptomatic intracranial haemorrhage (defined by each trial) and parenchymal haematoma type 2 (blood clot occupying >30% of the infarcted territory with substantial mass effect) within 5 days of randomisation, and mortality within 90 days.

All analyses were based on the intention-to-treat population. Unless otherwise stated, all reported analyses were prespecified in the statistical analysis plan (appendix). To account for between-trial differences when pooling patient-level data, mixed-effects modelling was used for all analyses, with fixed effects for parameters of interest and "trial" and an interaction term between "trial" and "treatment" as random effects variables in all models.[8] Ordinal logistic regression models included fixed effects (age, sex, NIHSS score at admission, intravenous alteplase use, and time from onset to randomisation) and multiplicative interaction terms to test whether prespecified baseline imaging features modified the effect of treatment allocation on predefined outcomes. ASPECTS were trichotomised as 0-4, 5-7, and 8-10 for the primary analysis. Furthermore, as prespecified in the statistical analysis plan, an attempt was made to analyse treatment effect across each ASPECTS to identify an ASPECTS below which endovascular treatment might be considered futile or potentially harmful.[13] Sensitivity analyses were done according to the primary imaging modality (CT or MRI) used at baseline. Missing data (n=21) for the primary outcome were imputed as per methods prespecified in each of the trials. All statistical analyses were done with SAS, version 9.2. This meta-analysis was prospectively designed by the HERMES executive committee but not registered.

Role of the funding source

An unrestricted grant was provided to the University of Calgary (Calgary, AB, Canada) by Medtronic. The funder of the study had no role in study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the paper for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

RESULTS

We obtained data from 1764 randomised participants, of whom 871 were assigned to receive EVT and 893 to receive standard medical treatment (control group). Prerandomisation brain imaging features were evaluated in 1388 patients on CT and in 364 patients on MRI (appendix). Clinical characteristics and imaging features at baseline were balanced between the two treatment groups, but treatment with intravenous alteplase was more common in the control group (table 1). Risk of bias was low except in the THRACE study,[2] which used unblinded assessment of outcomes 90 days after randomisation and MRI predominantly as the primary baseline imaging tool.

	Endovascular thrombectomy group (n=871)	Control group (n=893)
Age, years	67·4 (57·0–76·0)	67·8 (58·0–76·0)
Sex		
Female	412 (47%)	421/891 (47%)
Male	459/871 (53%)	470/891 (53%)
NIHSS	17 (14–20)	17 (13–21)
Onset to randomisation, min	181 (141–241)	184 (140–250)
Intravenous alteplase	763/871 (88%)	809/893 (91%)
ASPECTS	8 (7–9)	8 (7–9)
Clot burden score	4 (3–6)	4 (3–6)
>33% involvement of middle cerebral artery territory	114/860 (13%)	119/876 (14%)
Hyperdense vessel sign	356/687 (52%)	330/701 (47%)
Thrombus location		
Internal carotid artery	215/818 (26%)	227/828 (27%)
Proximal M1 segment of middle cerebral artery	315/818 (39%)	327/828 (39%)
Distal M1 segment of middle cerebral artery	221/818 (27%)	210/828 (25%)
M2 segment of middle cerebral artery	67/818 (8%)	64/828 (8%)
Collateral circulation grade		
0	6/639 (1%)	8/651 (1%)
1	91/639 (14%)	108/651 (17%)
2	283/639 (44%)	275/651 (42%)
3	259/639 (41%)	260/651 (40%)

Data are median (IQR), n (%), and n/N (%). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score.

Table 1: **Baseline clinical and imaging variables by treatment groups**

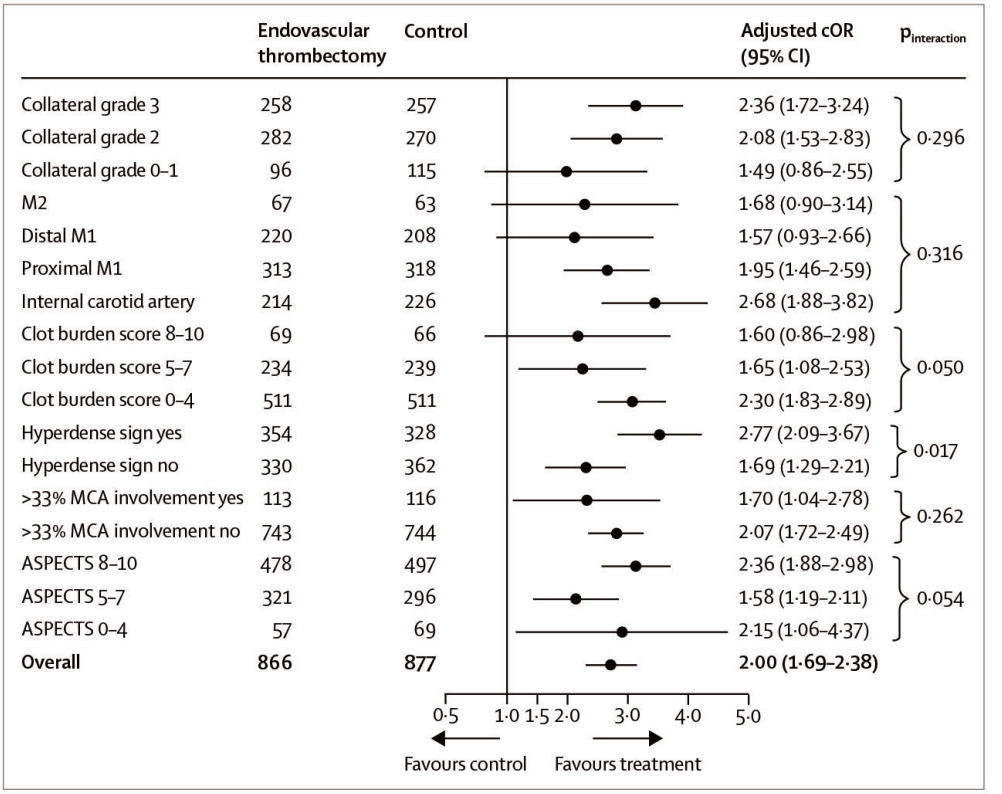

Figure 1: **Forest plot of endovascular treatment effect on primary outcome (modified Rankin Scale shift at 90 days), by baseline imaging variable categories**
cOR=common odds ratio. M1=M1 segment of MCA. M2=M2 segment of MCA. MCA=middle cerebral artery. ASPECTS=Alberta Stroke Program Early CT Score.

Treatment with EVT was associated with reduced disability at 90 days (adjusted cOR for a shift in direction towards a better functional outcome on the mRS 2·00, 95% CI 1·69-2·38; pinteraction<0·0001; figure 1). Distribution of 90-day mRS by treatment group and baseline imaging features are shown in the appendix. A treatment effect favouring EVT over control was observed in a broad range of prespecified imaging strata (figure 1). The treatment effect favoured EVT over standard treatment across all three categories of ASPECTS (0-4, 5-7, and 8-10; pinteraction=0·054; figure 1). Treatment effects favouring EVT over control were observed in both the CT and the MRI subgroups (appendix). An exploratory analysis was done that combined individual ASPECTS into categories (6-10 vs 3-5 and 0-2), informed by prespecified analyses of treatment effect by individual

baseline ASPECTS and by potential direction of treatment effect across each individual ASPECTS that suggested that point estimates for treatment effect probably favoured EVT for each individual ASPECTS category except 0-2. In this analysis, significant treatment effects favouring EVT were seen in patients with baseline ASPECTS 6-10 and 3-5. The point estimate of treatment effect (cOR) was less than 1 in the ASPECTS 0-2 group (n=37); however, no significant interaction for treatment effect size was noted across the three exploratory ASPECTS categories (6-10, 3-5, and 0-2; pinteraction=0 ·30; figure 2).

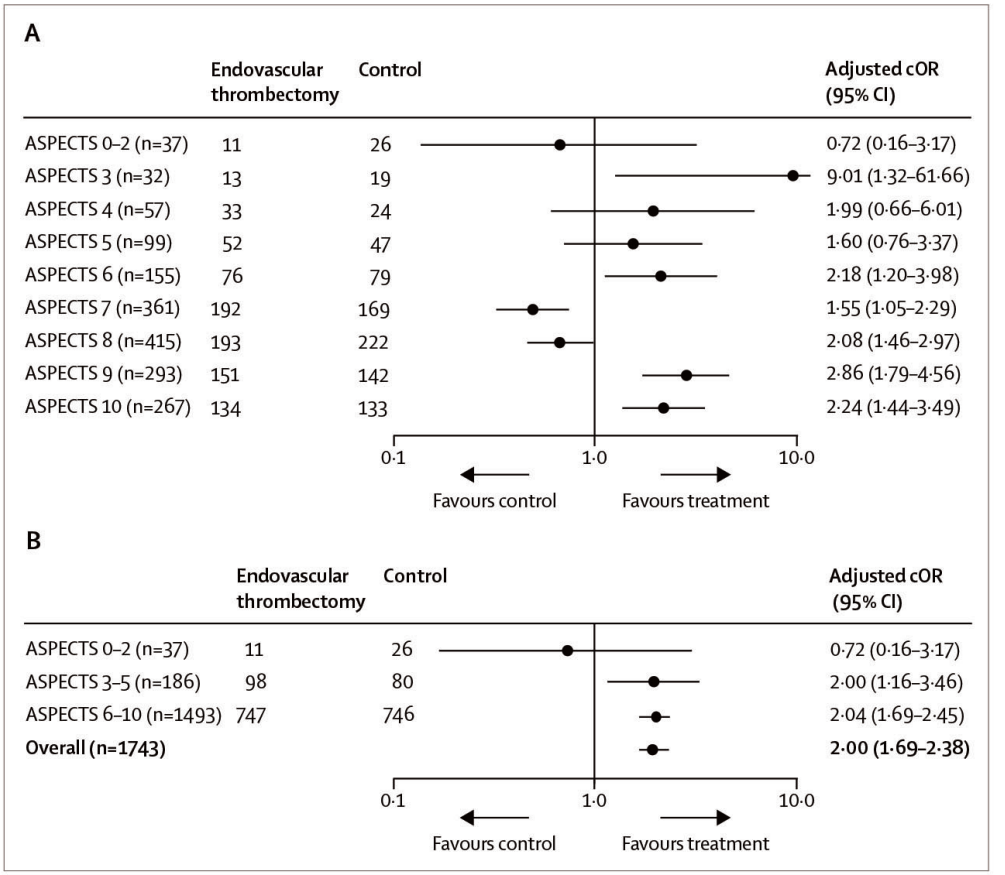

Figure 2: **Forest plot of endovascular treatment effect on primary outcome (modified Rankin Scale shift at 90 days), by ASPECTS**

(A) Endovascular treatment effect by individual baseline ASPECTS on primary outcome. There was no statistical evidence of heterogeneity across ASPECTS categories for the association between treatment and primary outcome. (B) Exploratory analysis informed by prespecified analyses of treatment effect by individual baseline ASPECTS and combines individual ASPECTS into categories (6–10 *vs* 3–5 and 0–2). ASPECTS=Alberta Stroke Program Early CT Score. cOR=common odds ratio.

	Modified Rankin Scale 0–2 at 90 days				Modified Rankin Scale 0–1 at 90 days				Substantial neurological improvement at 24 h*				NIHSS 0–2 at 24 h			
	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value
All participants (n=1743)	414/866 (48%)	268/877 (31%)	2·32 (1·87–2·87)	NA	254/866 (29%)	146/877 (17%)	2·29 (1·74–3·01)	NA	416/841 (49%)	204/857 (24%)	3·20 (2·59–3·96)	NA	167/835 (20%)	79/853 (9%)	2·91 (2·13–3·96)	NA
ASPECTS 0–4, 5–7, and 8–10	..	..	..	0·308	..	..	..	0·251	..	..	..	0·516	..	..	..	0·557
0–4 (n=126)	14/57 (25%)	10/69 (14%)	2·72 (0·89–8·33)	..	9/57 (16%)	4/69 (6%)	9·10 (0·96–86·76)	..	16/51 (31%)	7/65 (11%)	4·62 (1·61–13·25)	..	1/50 (2%)	1/64 (2%)	0·05 (0·00–266·93)	..
5–7 (n=615)	140/321 (44%)	87/296 (29%)	2·07 (1·43–2·99)	..	73/321 (23%)	47/296 (16%)	1·61 (1·04–2·48)	..	137/313 (44%)	56/288 (19%)	3·34 (2·28–4·88)	..	43/312 (14%)	19/287 (7%)	2·68 (1·47–4·91)	..
8–10 (n=975)	257/478 (54%)	169/497 (34%)	2·56 (1·93–3·40)	..	170/478 (36%)	94/497 (19%)	2·64 (1·89–3·68)	..	260/469 (55%)	141/492 (29%)	3·19 (2·42–4·20)	..	121/465 (26%)	59/490 (12%)	3·06 (2·12–4·42)	..
ASPECTS 0–2, 3–5, and 6–10	..	..	..	0·695	..	..	..	0·879	..	..	..	0·756	..	..	..	0·864
0–2 (n=37)	0/11 (0%)	3/26 (12%)	0·00 (0·00–5·81)	..	0/11 (0%)	0/26 (0%)	NA	..	1/10 (10%)	3/24 (13%)	0·63 (0·03–14·11)	..	0/10 (0%)	0/24 (0%)	NA	..
3–5 (n=186)	30/98 (31%)	14/90 (16%)	4·27 (1·62–11·25)	..	16/98 (16%)	8/90 (9%)	2·76 (0·86–8·86)	..	25/89 (28%)	7/85 (8%)	5·53 (2·06–14·84)	..	6/88 (7%)	3/84 (4%)	1·70 (0·32–9·15)	..
6–10 (n=1493)	381/747 (51%)	249/746 (33%)	2·29 (1·83–2·88)	..	236/747 (32%)	137/746 (18%)	2·25 (1·69–2·99)	..	387/734 (53%)	194/736 (26%)	3·16 (2·53–3·95)	..	159/729 (22%)	76/733 (10%)	2·88 (2·09–3·95)	..
>33% involvement of middle cerebral artery territory	..	..	..	0·495	..	..	..	0·962	..	..	..	0·359	..	..	..	0·458
No (n=1487)	380/743 (51%)	245/744 (33%)	2·38 (1·89–2·98)	..	235/743 (32%)	136/744 (18%)	2·27 (1·70–3·03)	..	383/730 (52%)	193/734 (26%)	3·13 (2·50–3·91)	..	161/725 (22%)	76/731 (10%)	2·93 (2·14–4·02)	..
Yes (n=229)	31/113 (27%)	21/116 (18%)	2·23 (1·07–4·65)	..	17/113 (15%)	9/116 (8%)	3·16 (1·08–9·24)	..	30/103 (29%)	11/111 (10%)	4·74 (2·12–10·62)	..	4/102 (4%)	3/110 (3%)	0·08 (0·00–215·24)	..
Hyperdense sign	..	..	..	0·034	..	..	..	0·997	..	..	..	0·416	..	..	..	0·962
No (n=692)	151/330 (46%)	112/362 (31%)	1·95 (1·39–2·70)	..	93/330 (28%)	50/362 (14%)	2·40 (1·65–3·50)	..	158/326 (48%)	82/359 (23%)	4·59 (1·65–12·23)	..	60/324 (19%)	32/357 (9%)	2·83 (1·71–4·70)	..
Yes (n=682)	165/354 (47%)	78/328 (24%)	3·20 (2·26–4·53)	..	98/354 (28%)	46/328 (14%)	2·47 (1·70–3·60)	..	171/341 (50%)	71/318 (22%)	3·67 (2·58–5·20)	..	71/339 (21%)	29/318 (9%)	3·03 (1·83–5·02)	..

(Table 2 continues on next page)

	Modified Rankin Scale 0–2 at 90 days				Modified Rankin Scale 0–1 at 90 days				Substantial neurological improvement at 24 h*				NIHSS 0–2 at 24 h			
	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value	Endovascular thrombectomy group	Control group	Adjusted odds ratio (95% CI)	p value
(Continued from previous page)																
Clot burden score	..	..	..	0·038	..	..	..	0·244	..	..	..	0·082	..	..	..	0·042
0–4 (n=1026)	212/511 (41%)	118/511 (23%)	2·84 (2·07–3·90)	..	123/511 (24%)	61/511 (12%)	2·69 (1·79–4·05)	..	236/495 (47%)	100/501 (20%)	3·61 (2·71–4·81)	..	82/490 (17%)	31/499 (6%)	4·14 (2·56–6·68)	..
5–7 (n=475)	134/234 (57%)	108/239 (45%)	1·77 (1·19–2·64)	..	91/234 (39%)	61/239 (26%)	1·94 (1·17–3·19)	..	120/229 (52%)	80/237 (34%)	2·41 (1·59–3·64)	..	57/228 (25%)	39/236 (17%)	1·82 (1·11–2·96)	..
8–10 (n=135)	40/69 (58%)	27/66 (41%)	2·31 (1·06–5·04)	..	25/69 (36%)	15/66 (23%)	2·30 (0·72–7·30)	..	33/69 (48%)	14/64 (22%)	3·77 (1·64–8·64)	..	18/69 (26%)	6/64 (9%)	3·70 (1·21–11·30)	..
Occlusion location	..	..	..	0·249	..	..	..	0·909	..	..	..	0·242	..	..	..	0·416
Internal carotid artery (n=440)	71/214 (33%)	35/226 (15%)	2·91 (1·79–4·73)	..	38/214 (18%)	19/226 (8%)	2·26 (1·23–4·15)	..	87/206 (42%)	33/218 (15%)	3·87 (2·41–6·21)	..	19/205 (9%)	8/218 (4%)	3·05 (1·23–7·60)	..
Proximal M1 segment of middle cerebral artery (n=631)	147/313 (47%)	92/318 (29%)	2·63 (1·76–3·93)	..	87/313 (28%)	49/318 (15%)	2·42 (1·43–4·09)	..	156/305 (51%)	78/317 (25%)	3·18 (2·25–4·50)	..	66/301 (22%)	27/315 (9%)	3·81 (2·23–6·51)	..
Distal M1 segment of middle cerebral artery (n=428)	129/220 (59%)	100/208 (48%)	1·67 (1·10–2·54)	..	89/220 (40%)	55/208 (26%)	2·00 (1·16–3·43)	..	113/215 (53%)	71/205 (35%)	2·29 (1·46–3·59)	..	54/214 (25%)	35/204 (17%)	1·84 (1·09–3·12)	..
M2 segment of middle cerebral artery (n=130)	39/67 (58%)	25/63 (40%)	2·35 (1·07–5·14)	..	25/67 (37%)	13/63 (21%)	2·49 (0·80–7·75)	..	32/67 (48%)	11/61 (18%)	4·73 (2·00–11·21)	..	18/67 (27%)	5/61 (8%)	4·38 (1·39–13·82)	..
Collateral grade	..	..	..	0·402	..	..	..	0·623	..	..	..	0·145	..	..	..	0·975
0–1 (n=211)	26/96 (27%)	16/115 (14%)	1·80 (0·69–4·71)	..	15/96 (16%)	6/115 (5%)	4·05 (1·03–15·91)	..	29/91 (32%)	19/104 (18%)	2·18 (1·04–4·55)	..	10/89 (11%)	3/103 (3%)	3·47 (0·48–25·12)	..
2 (n=552)	124/282 (44%)	77/270 (29%)	2·49 (1·68–3·69)	..	78/282 (28%)	38/270 (14%)	2·90 (1·80–4·69)	..	131/277 (47%)	65/273 (24%)	3·01 (2·07–4·39)	..	56/275 (20%)	24/273 (9%)	3·92 (2·20–6·99)	..
3 (n=515)	143/258 (55%)	86/257 (33%)	2·63 (1·80–3·84)	..	86/258 (33%)	46/257 (18%)	2·25 (1·47–3·45)	..	144/256 (56%)	59/253 (23%)	4·30 (2·89–6·40)	..	56/256 (22%)	24/253 (9%)	2·95 (1·71–5·10)	..

Data are n/N (%). NIHSS=National Institutes of Health Stroke Scale. ASPECTS=Alberta Stroke Program Early CT Score. NA=not applicable. *Defined as neurological improvement of ≥8 points in the NIHSS or a NIHSS 0–1 24 h after stroke.

Table 2: **Endovascular treatment effect on secondary outcomes by baseline imaging variable categories**

A beneficial effect of EVT over control was seen across all imaging features for most prespecified secondary outcomes (table 2). A significant interaction between treatment effect and clot burden score was found for functional independence and substantial neurological recovery at 24 h (patients with more extensive thrombus at baseline probably benefit more with EVT); however, point estimates for treatment effect favoured EVT across all strata.

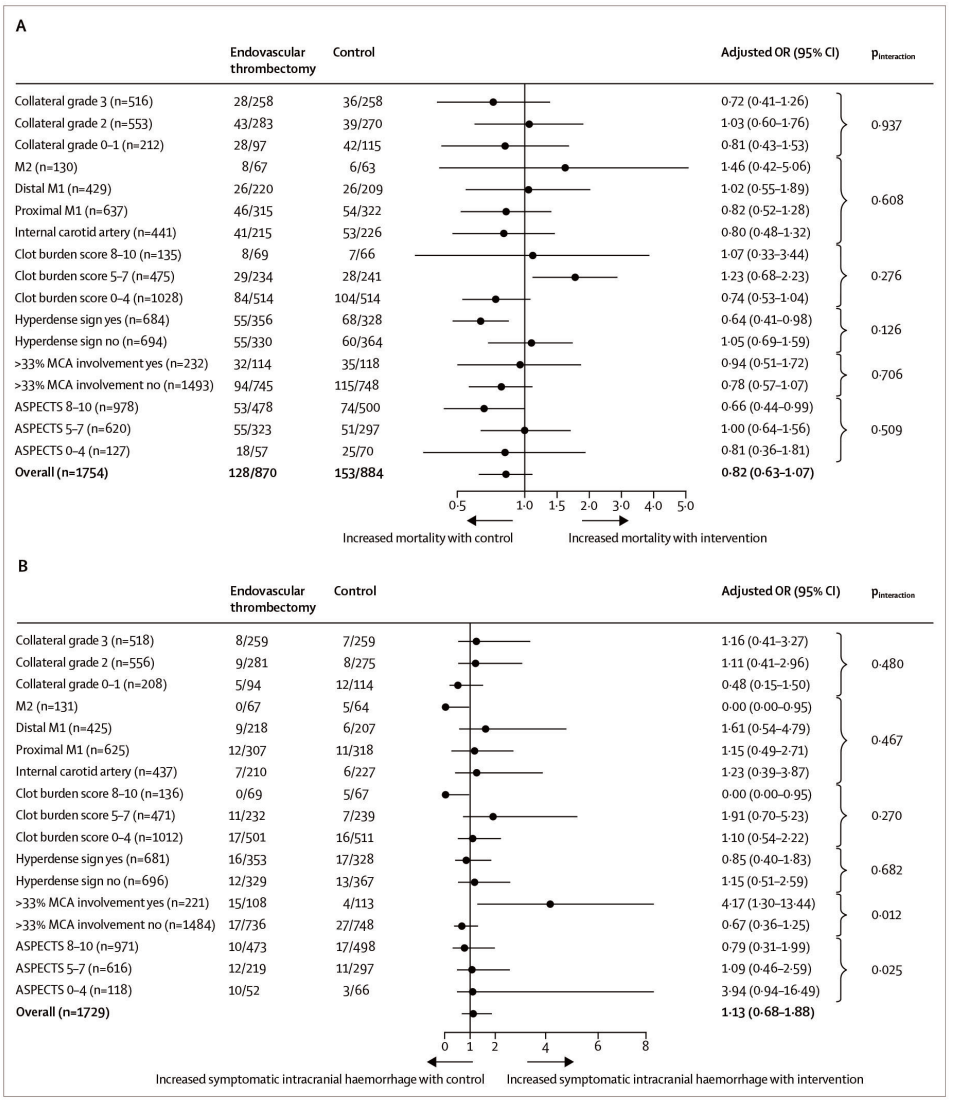

Figure 3: **Forest plot of endovascular treatment effect on safety outcomes (mortality at 90 days and symptomatic intracranial haemorrhage incidence), by baseline imaging variable categories**
OR=odds ratio. M1=M1 segment of MCA. M2=M2 segment of MCA. MCA=middle cerebral artery. ASPECTS=Alberta Stroke Program Early CT Score.

In the analysis of safety outcomes, mortality at 90 days (14·7% vs 17·3%, p=0·15), symptomatic intracranial haemorrhage (3·8% vs 3·5%, p=0·90), and parenchymal haematoma type 2 (5·6% vs 4·8%, p=0·52) did not differ between the EVT and control groups. We noted no treatment effect modification by baseline imaging features for mortality at 90 days (figure 3A) and parenchymal haematoma type 2 (appendix). When considering intracranial haemorrhage, results were inconsistent. EVT was associated with a higher risk of symptomatic intracranial haemorrhage in the ASPECTS 0-4 subgroup than in other ASPECTS subgroups (adjusted cOR 3·94, 95% CI 0·94-16·49; pinteraction=0·025; figure 3B) and in patients with baseline early ischaemic change in more than 33% of middle cerebral artery territory than in those without (4·17, 1·30-13·44; pinteraction=0·012; figure 3B), but not when the outcome was purely radiological using parenchymal haematoma type 2 (appendix). Among patients with ASPECTS 0-4, symptomatic intracranial haemorrhage was observed in ten (19%) of 52 patients in the EVT group versus three (5%) of 66 in the control group (unadjusted p=0·016; table 3). Similarly, symptomatic intracranial haemorrhage was observed in 15 (14%) of 108 patients in the EVT group versus four (4%) of 113 patients in the control group among patients with baseline early ischaemic change in more than 33% of middle cerebral artery territory (unadjusted p=0·0075; table 3).

DISCUSSION

Our patient-level meta-analysis lends support to a benefit of EVT for acute ischaemic stroke across a broad range of imaging subgroups. Our results add to previous work from the HERMES collaboration that showed benefit of EVT across a broad range of clinical subgroups.8 Our analysis is larger than this previous work (seven trials instead of five and 1764 patients instead of 1287), uses more rigorous imaging analysis (HERMES core laboratory uniform rereading of all scans from all trials), and analyses key imaging subgroups not previously assessed. Our results suggest that EVT might not be futile in patients with large (ASPECTS <6 or more than 33% involvement of middle cerebral artery territory) infarcts identified on baseline imaging, at least among patients otherwise deemed eligible to participate in the component clinical trials of the collaboration. Our findings are in line

	Endovascular thrombectomy group	Control group	Unadjusted odds ratio (95% CI)	Unadjusted p value	Unadjusted $p_{interaction}$ value
Baseline ASPECTS 0–4, 5–7, and 8–10	..	..	..	..	0·026
0–4	10/52 (19%)	3/66 (5%)	5·00 (1·30–19·25)	0·016	..
5–7	12/319 (4%)	11/297 (4%)	1·02 (0·44–2·34)	1	..
8–10	10/473 (2%)	17/498 (3%)	0·61 (0·28–1·35)	0·245	..
Baseline ASPECTS 0–2, 3–5, and 6–10	..	..	..	..	0·0084
0–2	1/9 (11%)	1/24 (4%)	2·88 (0·16–51·53)	0·477	..
3–5	14/95 (15%)	3/87 (3%)	4·84 (1·27–27·03)	0·010	..
6–10	17/740 (2%)	27/750 (4%)	0·63 (0·32–1·21)	0·168	..
>33% involvement of middle cerebral artery territory	..	..	..	..	0·0019
No	17/736 (2%)	27/748 (4%)	0·63 (0·34, 1·17)	0·168	..
Yes	15/108 (14%)	4/113 (4%)	4·40 (1·41–13·70)	0·0075	..
Hyperdense sign	..	..	..	..	0·865
No	12/360 (3%)	14/401 (4%)	0·95 (0·43–2·09)	1	..
Yes	16/353 (5%)	17/328 (5%)	0·87 (0·43–1·75)	0·724	..
Clot burden score	..	..	..	..	0·063
8–10	0/69 (0)	5/67 (8%)	0·00 (0·00–0·95)	0·027	..
5–7	11/233 (5%)	7/240 (3%)	1·65 (0·63–4·33)	0·344	..
0–4	17/503 (3%)	16/513 (3%)	1·09 (0·54–2·18)	0·861	..
Occlusion location	..	..	..	..	0·154
Internal carotid artery	7/210 (3%)	6/227 (3%)	1·27 (0·42–3.84)	0·781	..
Proximal M1 segment of middle cerebral artery	12/307 (4%)	11/318 (4%)	1·14 (0·49–2·61)	0·834	..
Distal M1 segment of middle cerebral artery	9/218 (4%)	6/207 (3%)	1·44 (0·50–4·13)	0·603	..
M2 segment of middle cerebral artery	0/67 (0)	5/64 (8%)	0·00 (0·00–0·96)	0·026	..
Collateral grade	..	..	..	..	0·443
3	8/259 (3%)	7/259 (3%)	1·15 (0·41–3·21)	1	..
2	9/281 (3%)	8/275 (3%)	1·10 (0·42–2·91)	1	..
0–1	5/94 (5%)	12/114 (11%)	0·48 (0·16–1·41)	0·209	..

Data are n/N (%). ASPECTS=Alberta Stroke Program Early CT Score.

***Table 3*: Symptomatic intracranial haemorrhage by treatment and baseline imaging variable categories**

with CT perfusion-based studies derived from the same cohort of patients, which were also not able to identify baseline ischaemic core volumes associated with treatment futility.[25] EVT is offered to patients with acute ischaemic stroke when there is a target artery occlusion and what is presumed to be salvageable brain beyond that occlusion, based on interpretation of various imaging methods.[26] Thrombus in proximal intracranial arterial segments such as in the internal carotid artery and M1 segment of the middle cerebral

artery are more easily reached by current EVT than thrombus in more distal arterial segments.[10] Proximal intracranial arterial segment thrombi are also larger in volume (greater clot burden) than more distal thrombi. Therefore, unlike EVT, intravenous alteplase is less likely to recanalise proximal thrombi early than thrombi in distal arterial segments.[27] Moreover, patients with thrombi in proximal intracranial arterial segments are likely to have a greater amount of brain tissue at risk than patients with more distal thrombi. Imaging is also used to identify the extent of irreversibly injured brain tissue beyond target artery occlusion. Patients with a large extent of irreversible brain injury are less likely to have brain tissue that is salvageable with EVT.[10,14,16] Both ASPECTS and the 33% of the middle cerebral artery rule inform the extent of probable irreversible brain injury on CT or MRI.[20,23] Our analysis suggested relative treatment benefit with EVT across all ASPECTS categories and in patients with brain infarcts occupying more than 33% of the ischaemic middle cerebral artery territory. The effect size by ASPECTS categories was, however, graded, with larger effect sizes noted in patients with higher ASPECTS. Despite evidence of treatment benefit, the prognosis for patients with a low ASPECTS remains poor, with few achieving independent outcomes. We also noted a significant benefit with EVT even in patients with baseline ASPECTS 3-5, an ASPECTS category that until now might have been considered as indicative of treatment futility.[13] Faster and better reperfusion techniques available since the HERMES trials could magnify potential benefit from EVT in these patients.[28] The number of patients with ASPECTS 0 (n=12), 1 (n=13), and 2 (n=12) in our analyses was very small; this imaging subgroup was the only one for which the point estimate for treatment effect did not favour EVT. Ongoing clinical trials, such as TENSION (NCT03094715) and IN EXTREMIS, are likely to provide more evidentiary support for or against the net benefit of thrombectomy in patients with ASPECTS less than 6 and with a large ischaemic core at baseline.

Patients with good collateral circulation status beyond target arterial occlusion are more likely to have salvageable brain tissue than are patients with poorer collaterals.[29] CTA (or MRA) is often used to identify patients with poor collateral circulation. The technique therefore complements CT and MRI by identifying patients with a large extent of irreversibly injured brain tissue. The ESCAPE trial[4] used collateral circulation status to exclude patients with poor collaterals; other trials such as SWIFT PRIME[7] and EXTEND-IA[3] used CT perfusion or MR perfusion. These techniques are based on the same principle of blood flow imaging that collateral assessments are based on for selecting patients for

those trials.[3,4,7] Like ASPECTS and the 33% middle cerebral artery rule on CT and MRI, our analyses suggest benefit with EVT across all strata of collateral circulation status; however, patients with poor collaterals are less likely to benefit from EVT than those with better collaterals. Assessment of poor collateral circulation with dynamic angiographic techniques (rather than the single-phase CTA or MRA used in most patients in our analyses) could help to better identify patients who are unlikely to benefit with EVT.[30]

Finally, imaging is used to determine risk with treatment. Our analyses suggest that symptomatic intracranial haemorrhage is four times more common in patients with ASPECTS 0-4 and hypodensity where more than 33% of the ischaemic middle cerebral artery territory is involved. This increase in symptomatic intracranial haemorrhage with EVT was not affected by age, baseline stroke severity, or intravenous alteplase use. A net beneficial effect of EVT was, however, still seen in these patients.

Our study has limitations. Since five of the seven HERMES trials used baseline imaging criteria to exclude patients who were likely to have large infarcts, we had relatively few patients with such imaging signatures in our analyses. Our results are reasonably consistent across both CT and MRI, and the sensitivity analyses suggest similar effects but could not confirm a significant benefit of thrombectomy in patients with largest baseline infarcts when assessed separately by either CT or MR-DWI. Confirmatory randomised trials are in progress (TENSION and IN EXTREMIS) in patients with ASPECTS less than

No statistical adjustment for multiple comparisons was included. The central re-analysis of images in this study might not reflect the quality of on-site assessments. In clinical practice, patients are treated on the basis of investigator reads, not expert consensus reads. There was heterogeneity in the use of imaging tools, techniques, and scanners in our study.[10] This heterogeneity is, however, reflective of real-world practice.

In summary, in the first individual patient-level metaanalysis analysing the usefulness of baseline imaging in patients eligible for EVT, we found limited evidence of heterogeneity of treatment effect across imaging sub-groups. Our analysis provides some evidence to suggest that the estimated treatment effect for EVT should be weighted in conjunction with other predictors of outcome when deciding whether to offer therapy to patients with large baseline infarcts.

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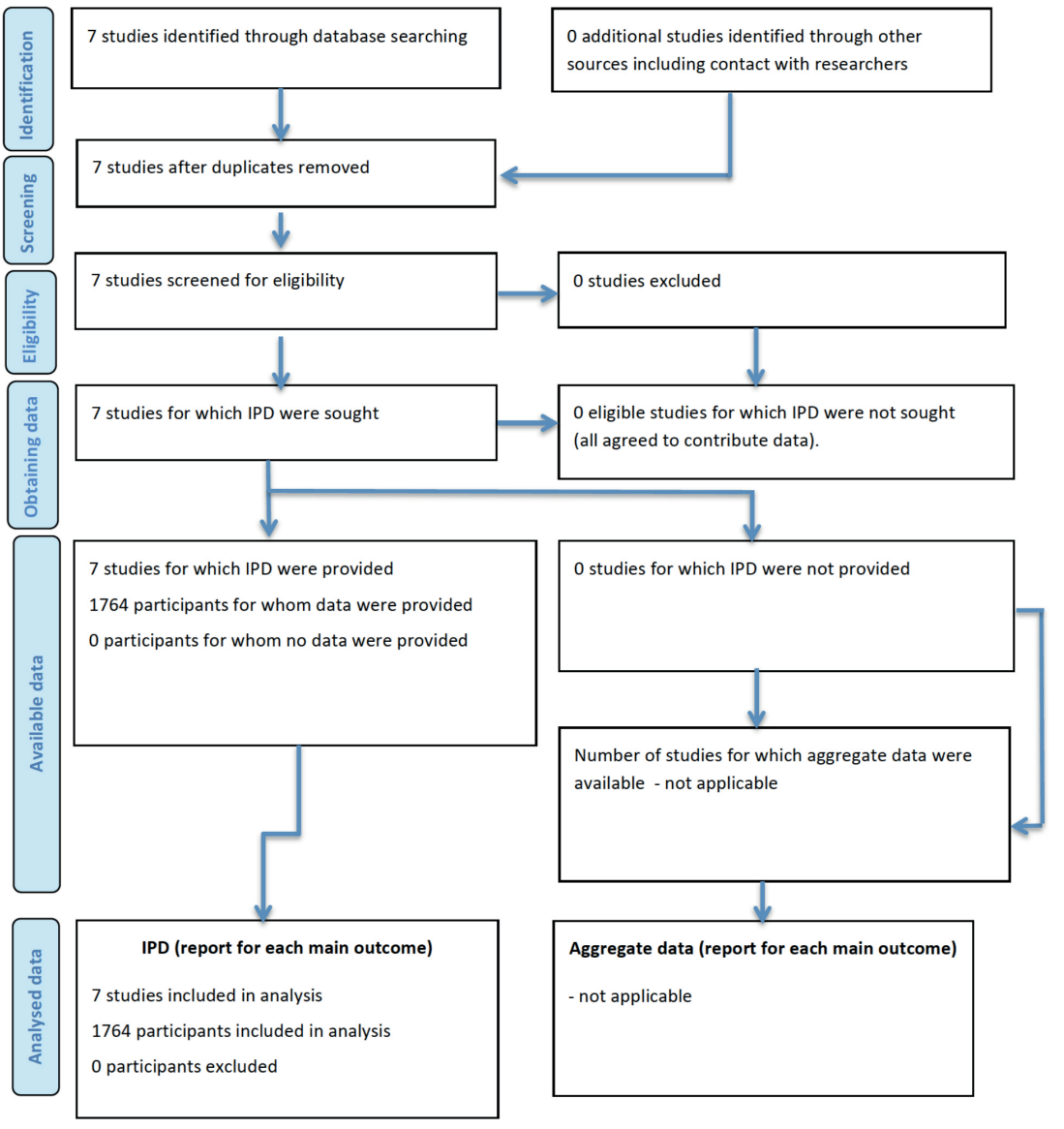
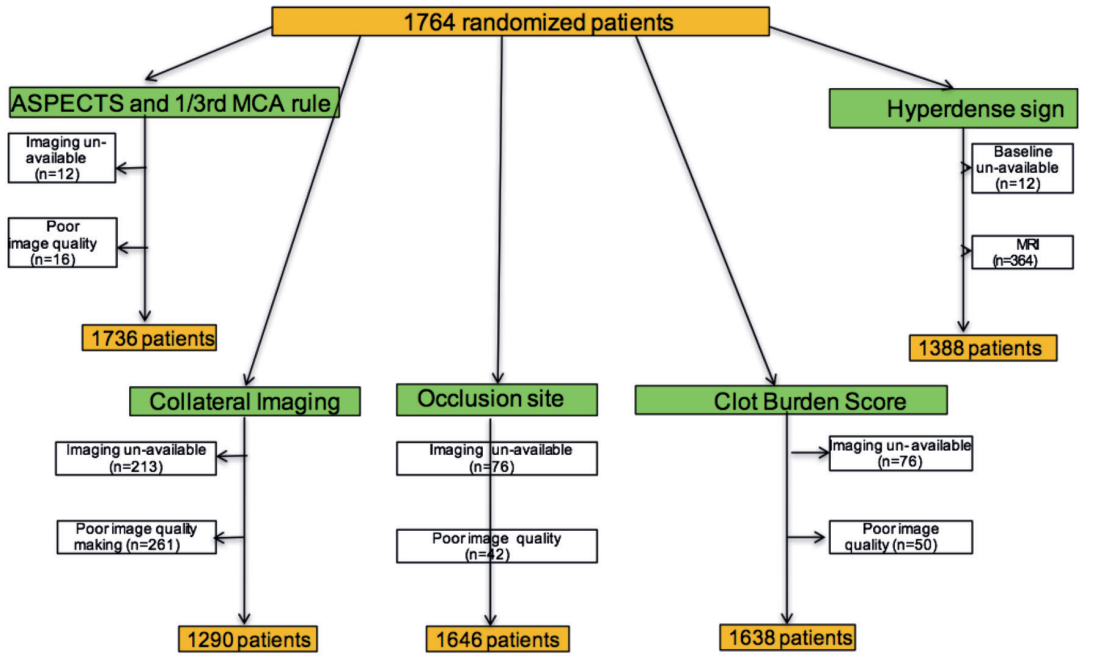
Supplementary Appendix

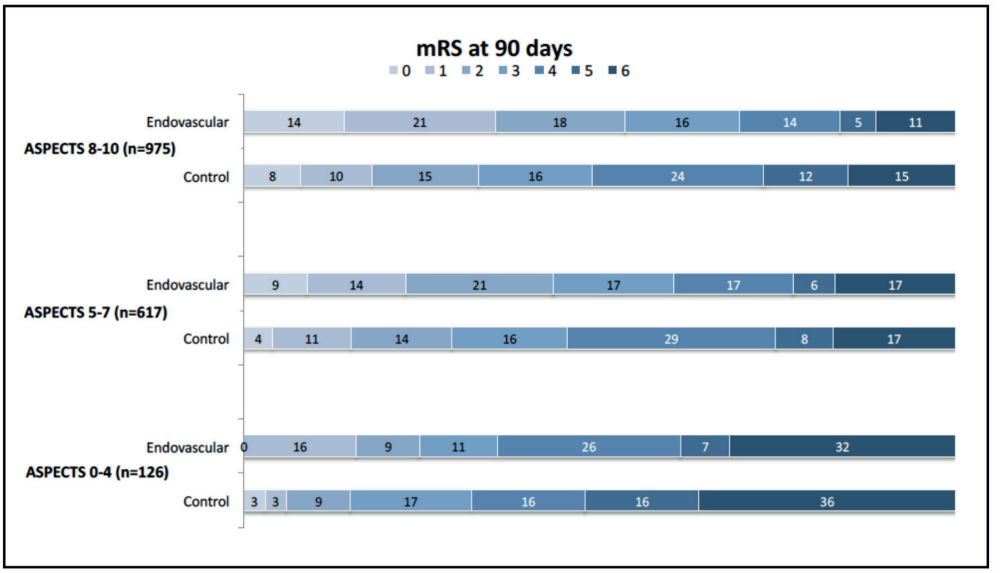
eFigure 1: PRISMA IPD flow diagram illustrating study selection.



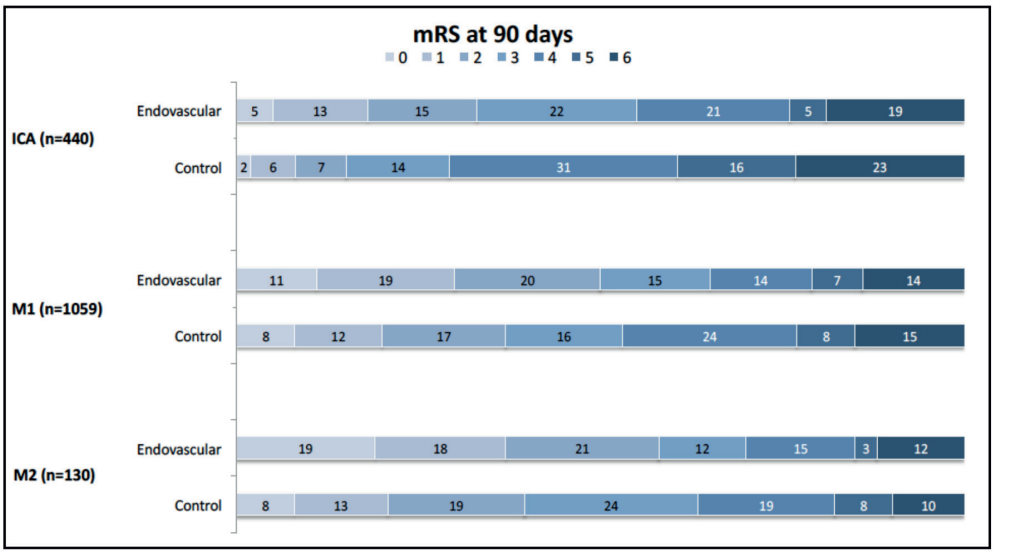
eFigure 2: Flow chart describing number of patients assessed for imaging variable at baseline and reasons for exclusion. Missing patients were not included in the different analysis of each imaging variable.



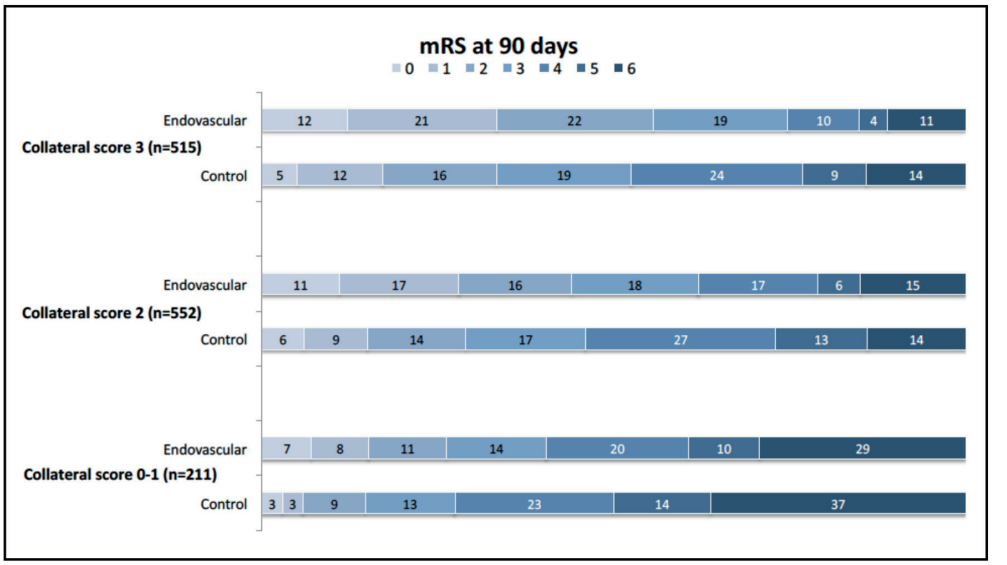
eFigure 3: Distribution of modified Rankin Scale at 90 days stratified by ASPECTS categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).



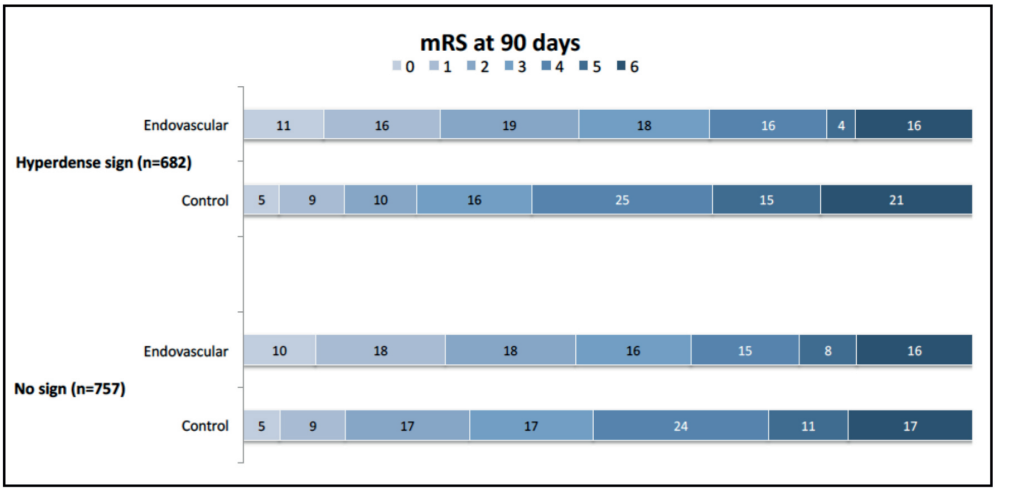
eFigure 4: Distribution of modified Rankin Scale at 90 days stratified by thrombus location in the endovascular and control groups (numbers within the horizontal bars represent percentages).



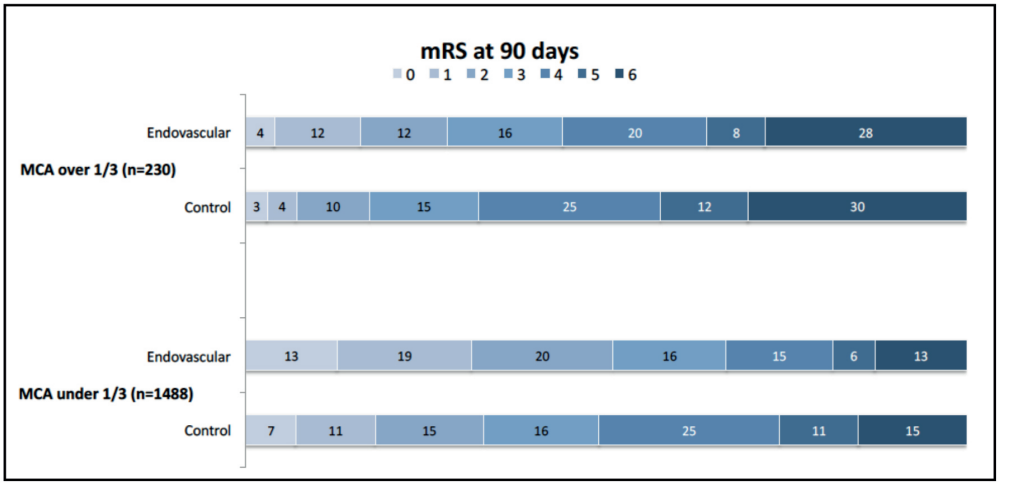
eFigure 5: Distribution of modified Rankin Scale at 90 days stratified by collateral circulation score categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).



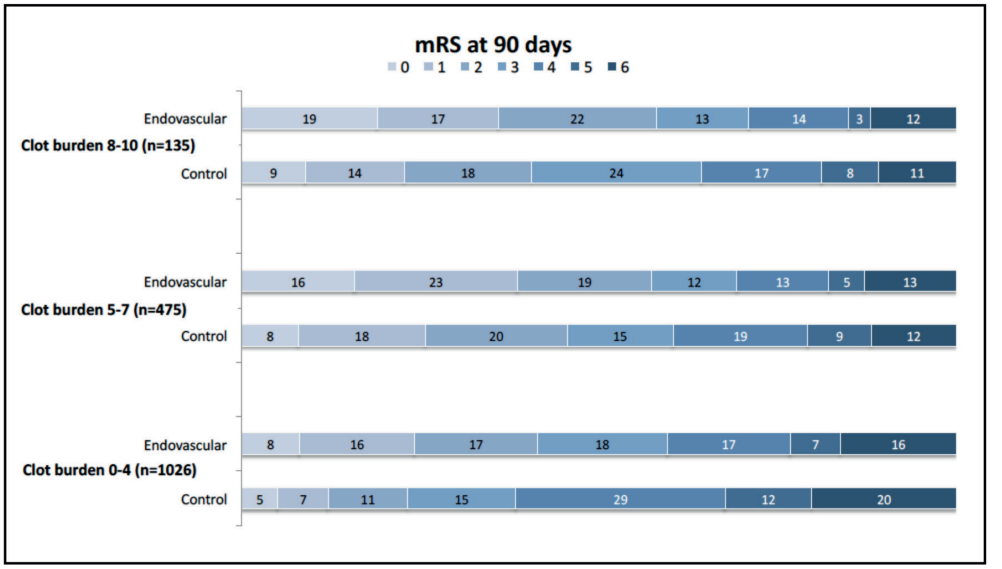
eFigure 6: Distribution of modified Rankin Scale at 90 days stratified by presence or absence of hyperdense sign on CT in the endovascular and control groups (numbers within the horizontal bars represent percentages).



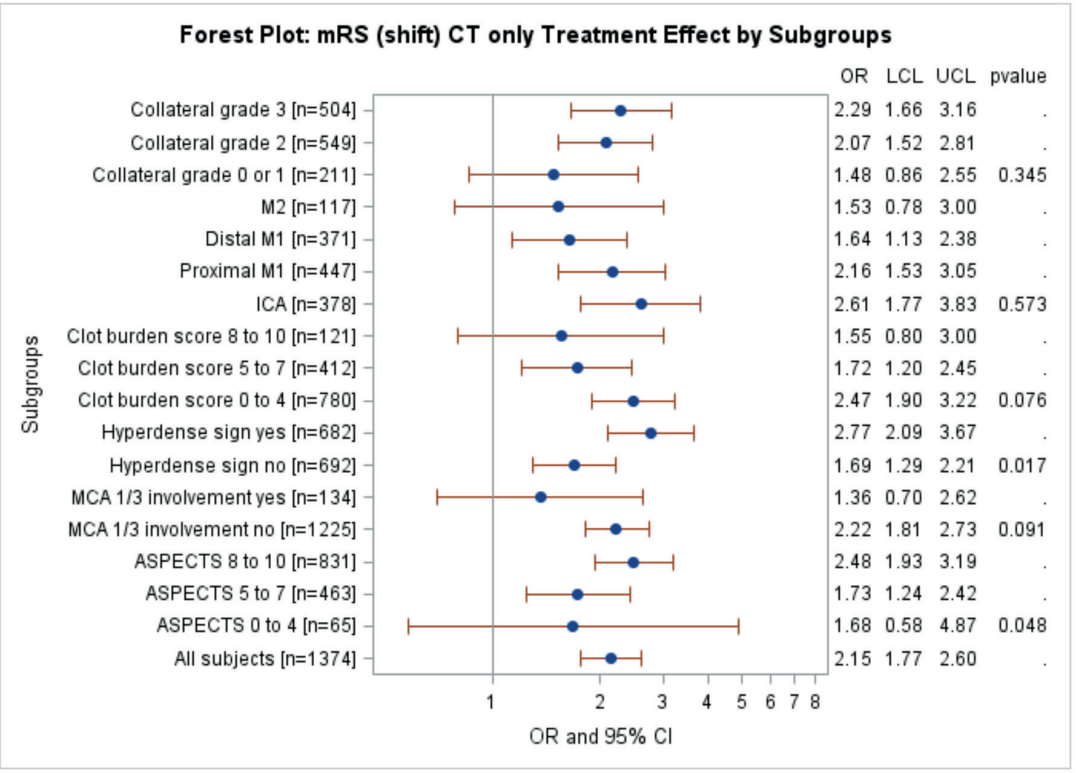
eFigure 7: Distribution of modified Rankin Scale at 90 days stratified by presence or absence of early ischemic changes in 1/3rd of MCA territory in the endovascular and control groups (numbers within the horizontal bars represent percentages).

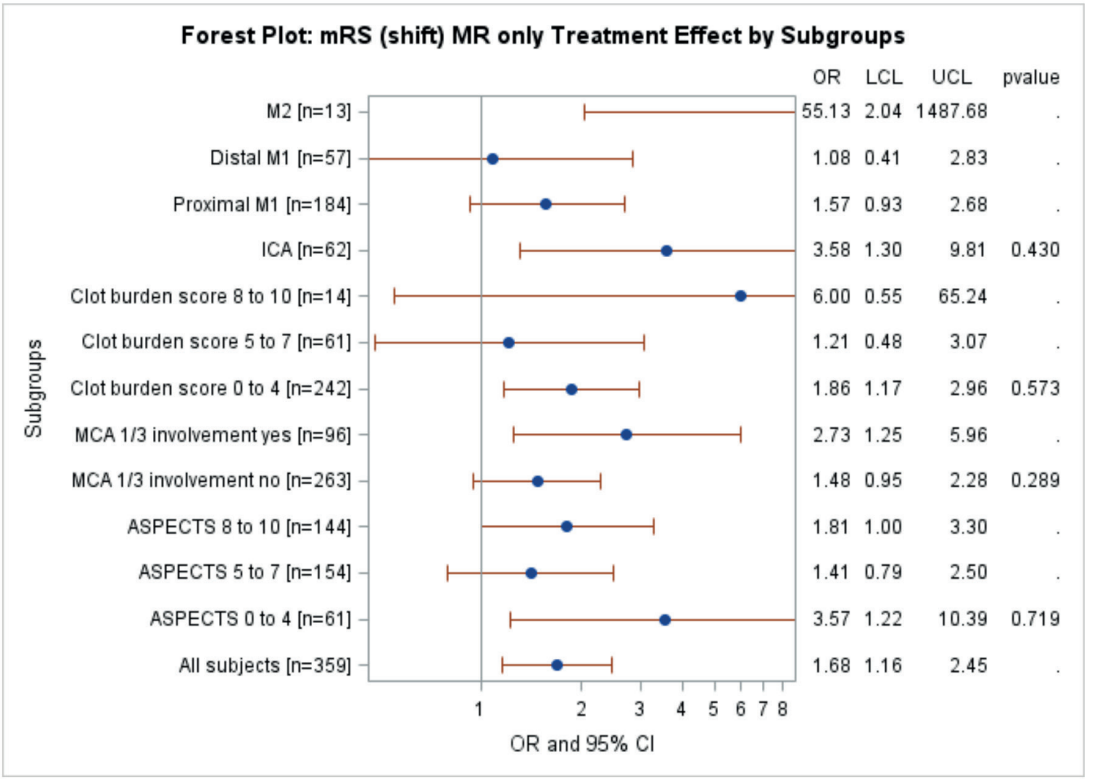


eFigure 8: Distribution of modified Rankin Scale at 90 days stratified by clot burden score categories in the endovascular and control groups (numbers within the horizontal bars represent percentages).

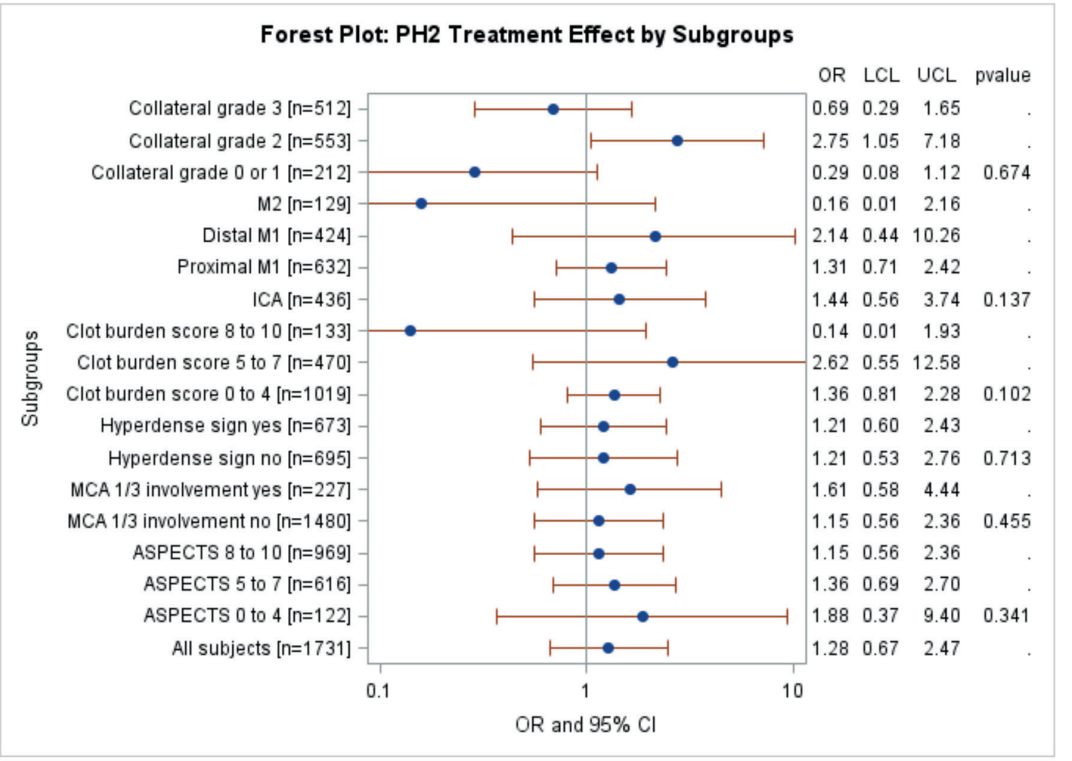


eFigure 9: Endovascular treatment effect by baseline imaging variable categories on primary outcome (mRS at 90 days) stratified by imaging modality (CT vs. MRI). Treatment effect is assessed through the common odds ratio for mRS shift.




Forest Plot: mRS (shift) MR only Treatment Effect by Subgroups
OR LCL UCL pvalue
M2 [n=13] 55.13 2.04 1487.68 .
Distal M1 [n=57] 1.08 0.41 2.83 .
Proximal M1 [n=184] 1.57 0.93 2.68 .
ICA [n=62] 3.58 1.30 9.81 0.430
Clot burden score 8 to 10 [n=14] 6.00 0.55 65.24 .
Clot burden score 5 to 7 [n=61] 1.21 0.48 3.07 .
Clot burden score 0 to 4 [n=242] 1.86 1.17 2.96 0.573
MCA 1/3 involvement yes [n=96] 2.73 1.25 5.96 .
MCA 1/3 involvement no [n=263] 1.48 0.95 2.28 0.289
ASPECTS 8 to 10 [n=144] 1.81 1.00 3.30 .
ASPECTS 5 to 7 [n=154] 1.41 0.79 2.50 .
ASPECTS 0 to 4 [n=61] 3.57 1.22 10.39 0.719
All subjects [n=359] 1.68 1.16 2.45 .
Subgroups
1 2 3 4 5 6 7 8
OR and 95% CI

eFigure 10: Endovascular treatment effect by baseline imaging variable categories on imaging safety outcome, namely, Parenchymal Hemorrhage Type 2. Treatment effect is assessed through the common odds ratio for mRS shift.



eTable 1: Qualitative assessment of between-trial differences in population, sampling frame and operational definitions of treatment groups.

	MR CLEAN	ESCAPE	EXTEND IA	SWIFT PRIME	REVASCAT	THRACE	PISTE
Population							
Continent	Europe	North America, Europe, East Asia	Oceania	North America and Europe	Europe	Europe	Europe
Country	Netherlands	Multiple	Australia and New Zealand	Multiple	Spain	France	United Kingdom
Sampling Frame							
Imaging Criteria							
Modality	NCCT/CTA	NCCT/CTA *CTP optional	NCCT/CTA/ CTP *MRI optional	NCCT/CTA/ CTP *MRI optional	NCCT/CTA *CTP optional	MRI or NCCT/CTA	NCCT/CTA
Occlusion Site	ICA M1 M2	ICA M1	ICA M1 M2	ICA M1	ICA M1	ICA M1	ICA M1
Ischaemic Core Definition	Not used	ASPECTS 6-10 Good Collaterals	CTP mismatch and ischemic core <70mL	CTP and NCCT ASPECTS criteria (modified protocol)	ASPECTS 6-10	Not used	ASPECTS 6-10
Clinical Criteria							
Age (years)	≥18	≥18	≥18	18-85 (later amended to 18-80)	18-80 (later amended to allow 81-85 if ASPECTS> 8)	18-80	≥18
Baseline Stroke Severity	NIHSS ≥2	NIHSS ≥6	No limit	NIHSS 8-29	NIHSS ≥6	NIHSS 10-25	NIHSS ≥6
Time to randomization	6 hours	12 hours	6 hours	6 hours	8 hours	5 hours	6 hours
Definition of sICH	Any ICH and ≥4-point increase NIHSS	Any ICH judged to cause ≥2-point increase NIHSS	PH2/SAH + ≥4-point increase NIHSS	Any PH/ SAH/IVH + ≥4-point increase NIHSS	PH2 + ≥4 point increase NIHSS	Any ICH and ≥4-point increase NIHSS	PH2 + ≥4 point increase NIHSS

Control Group							
	Standard care	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients	Standard care	Standard care in IV alteplase eligible patients	Standard care in IV alteplase eligible patients
Intervention Group							
Wait for response to IV alteplase	No	No	No	No	Yes	No	No
Pre-specified time metrics	No	Yes	No	Yes	Yes	No	No
Type of Devices	Any	Any	Solitaire	Solitaire	Solitaire	Any	Any

NCCT, Non contrast CT; CTA, CT angiography; CTP, CT Perfusion; MRI, Magnetic Resonance Imaging; ICA, Internal Carotid Artery; MCA, Middle Cerebral Artery; ASPECTS, Alberta Stroke Program Early CT Score; PH, Parenchymal Hemorrhage; SAH, Subarachnoid hemorrhage; IVH, Intra-ventricular Hemorrhage; NIHSS, National Institute of Health Stroke Scale; IV, intravenous.

eTable 2: Endovascular treatment effect in patients with large ischemic core at baseline defined post-hoc using different ASPECTS scores on CT and/or MRI.

Large extent of early ischemic change at baseline*	**common Odds Ratio**	**95% Confidence Interval**	**p-value**
ASPECTS 0 to 4 [n=126]	2.15	1.06 - 4.37	0.036
ASPECTS 0 to 4 CT or 0 to 3 MR [n=105]	1.9	0.86 - 4.2	0.12
ASPECTS 0 to 4 CT or 0 to 2 MR [n=89]	1.38	0.58 - 3.29	0.47
ASPECTS 0 to 4 CT only [n=65]	1.68	0.58 - 4.87	0.34

*Post-hoc definitions of large early ischemic change extent combining using different ASPECTS cut-points for CT and MRI. Statistical significance is only obtained once all CT/MR data are used for ASPECTS 0-4. Since most MRI data are from one study (THRACE), we are not confident that one can reliably distinguish MRI specific effect from a trial specific effect, especially among subgroups of this size.

eTable 3: sICH numbers in patients who underwent EVT stratified by reperfusion status (mTICI>=2b or not) and ASPECTS categories 0-4.

mTICI<2b				mTICI>=2b			
ASPECTS	sICH			ASPECTS	sICH		
	No	Yes	Total		No	Yes	Total
0	1	0	1	**0**	0	1	1
1	1	0	1	**1**	0	0	0
2	2	0	2	**2**	3	0	3
3	7	2	9	**3**	2	0	2
4	1	4	5	**4**	21	2	23
Total	12	6	18	**Total**	26	3	29

CHAPTER 5

Optimizing Systems Of Care

5.1 - Drip And Ship Versus Direct To Comprehensive Stroke Center; Conditional Probability Modeling

5.2 - Drip 'N Ship Versus Mothership For Endovascular Treatment Modeling The Best Transportation Options For Optimal Outcomes

CHAPTER 5.1

Drip And Ship Versus Direct To Comprehensive Stroke Center; Conditional Probability Modeling

Based upon:

Drip and Ship Versus Direct to Comprehensive Stroke Center

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The outcome of ischemic stroke is related to the volume of brain that is infarcted, and the volume of infarction is directly related to the time to reperfusion.1 In an anterior circulation, large-vessel ischemic stroke 1.9 million neurons are lost every minute.2 Treatment efficacy is dependent on time to treatment initiation. Acute ischemic stroke is treated medically with the administration of intravenous alteplase. Recent results of several randomized trials established the efficacy of endovascular treatment in ischemic stroke.3-8

The facilities and expertise needed for endovascular procedures are only available at endovascular capable centers (ECCs), which are typically tertiary care hospitals. Medical treatment with alteplase is more widely available. This creates 2 options for prehospital destination decision-making for suspected stroke: (1) transport the patient directly to the nearest ECC to receive alteplase and, if appropriate, immediate endovascular therapy even though this might mean bypassing a closer non-ECC (nECC; mothership model); or (2) transport the patient to the nearest nECC to receive alteplase and then transfer the patient to the nearest ECC for endovascular therapy (drip and ship model). There are advantages and disadvantages to each of these options, and it is currently unknown which of these options will lead to the highest probability of good outcome for the patient. The RACECAT trial in Barcelona, Spain, is planned to directly address this question (NCT02795962). Herein, we propose a methodology for addressing this problem using statistical probability modeling and suggest a candidate model for evaluation.

BUILDING THE MODEL

Assumptions

We make several assumptions in the development of the prediction models (Table I in the online-only Data Supplement). First, these models apply when there is uncertainty on which transport and treatment decision to choose. Second, the nECC is the closest treatment center to the location of stroke occurrence. If an ECC is the closest treatment center, we assume that the patient should be transported directly to the ECC because all treatment options are available at the ECC. Third, this discussion assumes that there is

only 1 decision-making point (at the scene) and that decision is always followed. Fourth, this does not apply to found down or strokeon-awakening patients because it is not possible to account for the time between stroke onset and first medical contact. Fifth, we assume that the probability of successful reperfusion with alteplase therapy varies linearly with time but has an upper limit.[9,10] We assume that the probability of successful reperfusion with endovascular therapy is time invariant. Although we know that this is untrue, the variation with time is probably small.[11] Sixth, we assume that all patients with occlusions are eligible for alteplase, and all patients with large-vessel occlusion (LVO) are eligible for endovascular therapy. And last, we assume that for patients with LVOs, reperfusion is only achieved through treatment, something which is known to be ≈95% true in the first 1 to 2 hours after stroke onset.[7,12]

Conditional Probabilities

A variety of conditional probabilities are considered (Table II in the online-only Data Supplement). We have approached the problem physiologically, considering the probability of achieving reperfusion with each given treatment strategy in combination with the probability of good outcome as a function of time to reperfusion and including the possibility of good outcome without reperfusion. The components of this model are shown in the Table.

Table. Mothership and Drip and Ship Models

Model	Conditional Probabilities	Time Considerations	Conditional Probability Estimates
Mothership	*P*(good outcome|mothership model)=*P*(reperfusion|EVT)·*P*(good outcome|reperfusion at ϕ mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)	*P*(good outcome|mothership model)=*P*(reperfusion|EVT)·*P*(good outcome|reperfusion at 30+Z+C+30 mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)	*P*(good outcome|mothership model)=0.74·[0.75-0.0006(30+Z+C+30)]+0.26·0.30
Drip and Ship	*P*(good outcome|drip and ship model)=*P*(early reperfusion|alteplase)·*P*(good outcome|reperfusion at ϕ mins)+*P*(no early reperfusion|alteplase) ·[*P*(reperfusion|EVT)·*P*(good outcome|reperfusion at ϕ mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)]	*P*(good outcome|drip and ship model)=*P*(early reperfusion|alteplase)·*P*(good outcome|reperfusion at 30+X+A+70 mins)+*P*(no early reperfusion|alteplase) ·[*P*(reperfusion|EVT)·*P*(good outcome|reperfusion at 30+X+A+B+Y+C+30 mins)+*P*(no reperfusion|EVT)·*P*(good outcome|no reperfusion)]	*P*(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+A+B+70)]+0.82·[0.74·[0.75-0.0006(30+X+A+B+Y+C+30)]+0.26·0.30

EVT indicates endovascular therapy. A indicates the time from the patient's arrival at the nonendovascular capable centre (nECC) to the administration of alteplase. B is the time from alteplase administration to leaving for the endovascular capable centre (ECC). C is the time from the patients arrival at the ECC to the beginning of the endovascular procedure. X is the transportation time from the patient to the nECC. Y is the transportation time from the nECC to the ECC. Z is the transportation time from the patient to the ECC.

Time Considerations

The time from stroke onset to treatment initiation is vital.[2] Figure 1 displays the parameterization of the times involved in transportation and treatment. We assume time A (door-to-needle time) equals 60 minutes, and time B (alteplase bolus to departure for ECC time) equals 15 minutes. Time C (door-to-arterial access time) is assumed to be 90 minutes in the mothership scenario, and 50 minutes in the drip and ship scenario as treatment times has been shown to be faster at the ECC because of prenotification in the drip and ship case.[13]

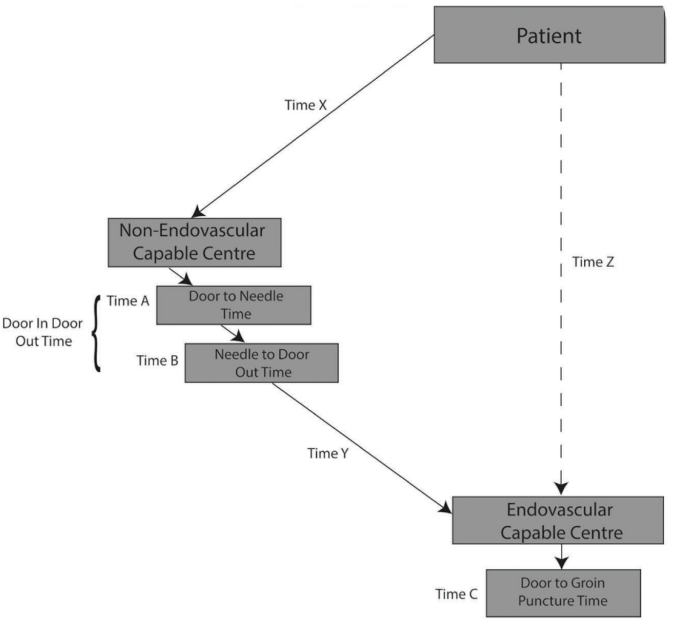

Figure 1. Transportation time framework. The dashed line represents the mothership model, the solid lines represent the drip and ship model. Time X is the transportation time from the patient to the nonendovascular capable center (nECC). Time Y is the transportation time from the nECC to the endovascular capable center (ECC). Time Z is the transportation time from the patient to the ECC. Time A is the time from the patient's arrival at the nECC to the administration of alteplase, and time B is the time from alteplase administration to leaving the nECC. Time C is the time from the patient's arrival at the ECC to the beginning of the endovascular procedure.

We assume that first reperfusion is achieved 30 minutes into the endovascular procedure. For alteplase, the time of reperfusion is harder to define. We define early reperfusion as 70 minutes post treatment initiation because angiography studies have shown that 1.6% of internal carotid artery, 23.9% of M1 (M1 segment of the middle cerebral artery), and 38.9% of M2 (M2 segment of the middle cerebral artery) occlusions were recanalized at first angiography post alteplase administration (median 70 minutes).[14] Also, this is a relevant time point when considering interfacility transportation. When the nECC and ECC

are close together (ie, closer than the duration of the alteplase infusion), we adjust the rate of reperfusion to vary linearly with time (Table III in the online-only Data Supplement). A constant 30 minutes has been added to represent the average time from first medical contact to ambulance arrival and ambulance scene time.

Estimating the Conditional Probabilities with Existing Data

We used data from the ESCAPE trial (Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke)[7] to estimate the time-dependent probability of good outcome given reperfusion. The probability of good outcome given successful reperfusion decreases by 0.0006 for every minute delay.[1] Because the time of reperfusion for patients receiving alteplase is unknown, we assume that the same rate of decay applies.

The probability of achieving reperfusion given endovascular therapy was estimated from the ESCAPE trial at 0.74.[7] The probability of early reperfusion given alteplase therapy varies by occlusion location. The prevalence of LVO with a positive Los Angeles Motor Scale (LAMS) screen (score of 4-5) is 62%, and occlusion locations are estimated at 28% internal carotid artery, 65% M1, and 5% M2.15 These data are combined with the above early reperfusion proportions to estimate that overall 18% of patients with a proven LVO will achieve early reperfusion with intravenous alteplase. In the cases where the time of early reperfusion needed to be adjusted to <70 minutes, this probability was also adjusted. In preclinical studies, it has been shown that clot dissolution rates progress linearly in the early treatment phase; therefore, these probabilities were adjusted linearly (Table III in the online-only Data Supplement).[9,10] The probability of good outcome given no reperfusion was estimated from the ESCAPE trial to be 0.30.[7] The models with these calculated probabilities are shown in the Table.

Example Scenarios

Using the above model (base model: model A), we have created example scenarios where the patient is closer to the nECC than the ECC at stroke onset, with varying times between the nECC and ECC-time Y; 10 (Figure I in the online-only Data Supplement), 20 (Figure 2), 30 (Figure 3), 45 (Figure II in the online-only Data Supplement), 90 (Figure 4), 120 (Figure 5), and 180 minutes (Figure III in the online-only Data Supplement). Distances are represented as travel times as the crow flies. For real-world use, the nECC/ECC can

be plotted on a map and road network analyses used to create catchment areas for the drip and ship and mothership models. As these models are displayed in terms of travel times (and not physical distance), both ground and air transport modalities can be considered.

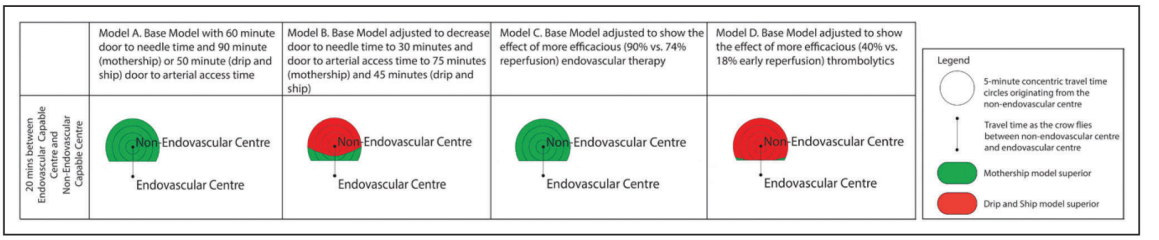

Figure 2. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 20 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74 and *P*(early reperfusion|alteplase)=0.18 (adjusted for short travel times) and shows that the mothership option is most effective. In model B, door-to-needle time is 30 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the drip and ship model is the most effective strategy if the patient is close to the nECC or would have to drive past the nECC. Model C assumes *P*(reperfusion|endovascular therapy)=0.90 and shows that the mothership approach is the superior option. Model D assumes a novel intravenous thrombolytic agent where *P*(early reperfusion|thrombolysis)=0.40 (adjusted for shorter travel times) and shows that the drip and ship option is superior.

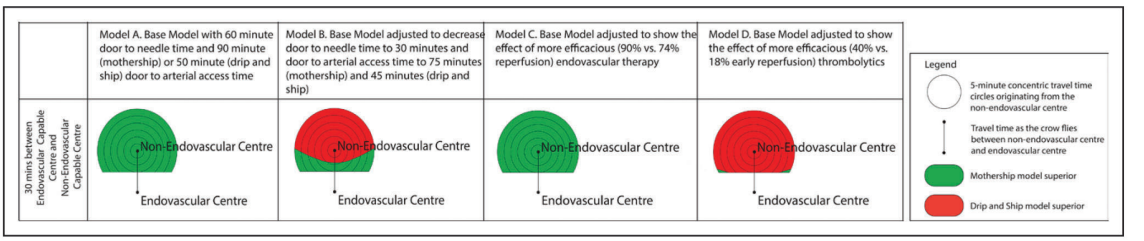

Figure 3. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 30 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74, and *P*(early reperfusion|alteplase)=0.18 (adjusted for short travel times). Model A shows that the mothership model is the most effective strategy. In model B, door-to-needle time is 30 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the drip and ship model now becomes an effective option when the patient is close to the nECC or would have to drive past the nECC. Model C assumes *P*(reperfusion|endovascular therapy)=0.90 and shows that the mothership approach is always the superior option. Model D assumes a novel intravenous thrombolytic agent with *P*(early reperfusion|thrombolysis)=0.40 (adjusted for shorter travel times) and shows that the drip and ship approach is superior in almost all scenarios.

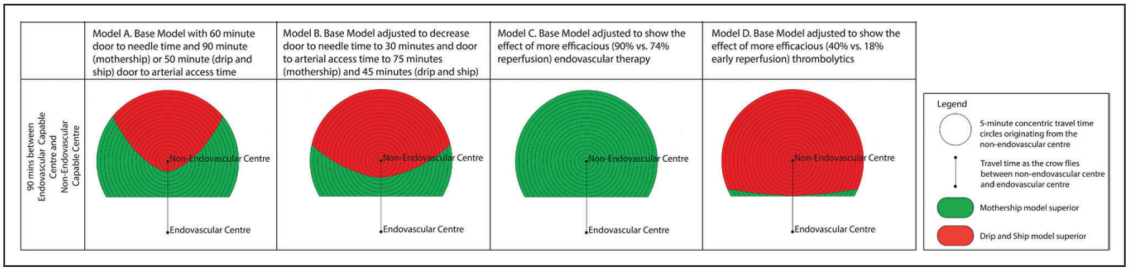

Figure 4. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 90 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74, and *P*(early reperfusion|alteplase)=0.18. Model A shows that the drip and ship model is the most effective option if the patient is close to the nECC or would have to drive past the nECC. In model B, door-to-needle time is 30 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the area where the drip and ship model is the most effective option has increased. Model C assumes *P*(reperfusion|endovascular therapy) and shows that the mothership approach is always the superior option. Model D assumes a novel intravenous thrombolytic agent with *P*(early reperfusion|thrombolysis)=0.40 and shows that the drip and ship approach is superior in almost all scenarios.

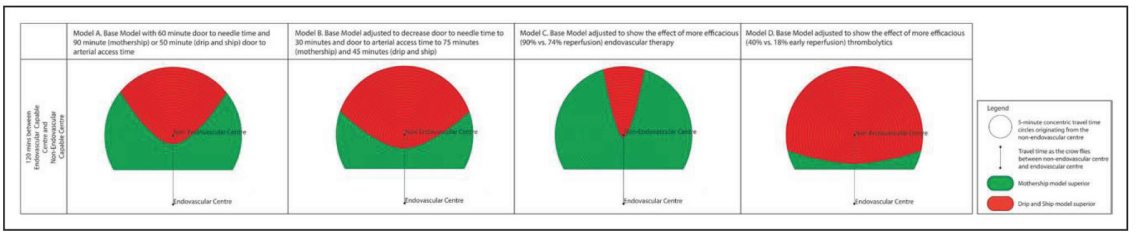

Figure 5. Optimization of the use of the drip and ship vs mothership models when the endovascular capable center (ECC) and non-ECC (nECC) are 120 min apart. Red indicates regions where the drip and ship approach is more favorable; green indicates regions where the mothership approach is more favorable. Model A assumes a door-to-needle time of 60 min, door-to-arterial access time of 90 min for mothership, and 50 min for drip and ship, *P*(reperfusion|endovascular therapy)=0.74, and *P*(early reperfusion|alteplase)=0.18. Model A shows that the drip and ship model is the most effective option when the patient is close to the nECC or would have to travel past the nECC. In model B, door-to-needle time is 30 min, and door-to-arterial access is 75 min (mothership) and 45 min (drip and ship). Here, the area where the drip and ship model is the most effective option has increased. Model C assumes *P*(reperfusion|endovascular therapy)=0.90 and shows that the mothership model is always the superior option. Model D assumes a novel intravenous thrombolytic agent with *P*(early reperfusion|thrombolysis)=0.40 and shows that the drip and ship approach is superior in almost all scenarios.

Model A (base model) shows that the mothership model is superior when the time between the nECC and ECC is between 10 and 30 minutes. The drip and ship model becomes a superior option when the patient is close to the nECC (or would have to travel past the nECC), and the time between the nECC and ECC is 45 minutes or longer (model A in Figures 2 through 5; Figures I through III in the online-only Data Supplement). These models can be used to show how altering parameters could change decision-making (Table IV in the online-only Data Supplement). Model B shows the effect of faster

treatment times; door-to-needle times are decreased to 30 minutes and door-to-arterial access times are decreased to 75 minutes for patients (mothership) and 45 minutes (drip and ship). Model B shows that faster systems of care make the drip and ship model a more favorable option when the patient is close to the nECC or would have to travel past the nECC (model B in Figures 2 through 5; Figures I through III in the online-only Data Supplement).

Models C and D show the effect of more efficacious treatments. In model C, the probability of reperfusion given endovascular therapy is increased to 0.90 (from 0.74). New techniques in endovascular therapy and new catheters may improve technical efficacy. Here, the mothership option is always superior unless the distance between the nECC and ECC is ≥120 minutes (and the patient is close to the nECC or would have to be transported past the nECC; model C in Figures 2 through 5 and Figures I through III in the online-only Data Supplement). Model D simulates more efficacious medical thrombolytic therapies; initial data suggest that tenecteplase may be more effective than alteplase, and alternate approaches are being developed.[16] In this model, the probability of early reperfusion given thrombolytic therapy is increased to 0.40 (from 0.18), using the same methodology described above, this is adjusted for the shorter times between nECC and ECC (Table III in the online-only Data Supplement). This model shows that the drip and ship method is favorable in nearly all scenarios (model D in Figures 2 through 5; Figures I through III in the online-only Data Supplement). Both models C and D demonstrate that prehospital destination decision-making is highly dependent on the efficacy of reperfusion treatments. This implies that as treatments incrementally improve the best destination hospital triage systems may have to adapt to new treatment realities.[17]

Considering All Patient Diagnoses

This model applies to patients with large-vessel ischemic strokes; however, prehospital healthcare providers do not have access to imaging making a definitive diagnosis impossible in the field. The LAMS, a 3-item tool (scores range from 0-5 with higher scores indicating more severe symptoms), is a fast and an effective way to identify patients with a probable large-vessel ischemic stroke.[15] The probability that a patient has a large artery occlusion given that they have an ischemic stroke diagnosis and a LAMS score of 4 or 5 is 0.62.[15] In the FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium), which enrolled suspected stroke patients in the field, among patients with an LAMS score

of 4 or 5, 70% had an acute ischemic stroke, 28% had an intracranial hemorrhage, and 2% were stroke mimics (J. Saver, personal communication, 2015). Combining these 2 estimates if the patient has an LAMS score of 4 or 5 in the field, the joint probability of having an acute ischemic stroke, which is a LVO, is 0.43, and the joint probability for non-LVO ischemic stroke is 0.27. The use of technology such as video conferencing could improve the detection of large-vessel ischemic stroke in the field and impact these probabilities.

The drip and ship versus mothership decision may not apply to patients who are not candidates for endovascular therapy (nonlarge-vessel ischemic stroke, intracranial hemorrhage, or stroke). Non-LVOs and stroke mimics make up roughly half of these patients. These patients can be adequately treated at either an nECC or an ECC, so they should be transported to the nearest stroke center, which under the above assumptions is an nECC. This makes the drip and ship model the most appropriate for stroke mimics and stroke because of small-vessel occlusions. Intracranial hemorrhage makes up the other half of these patients, and although these patients may require intensive care treatment at a comprehensive stroke center, there is currently no evidence that emergency treatment within minutes is beneficial.[18-20] Thus, it remains uncertain if they should be transported directly to an ECC or if they are best initially treated and stabilized at an nECC. If it is assumed that all hemorrhage patients should be transported directly to an ECC, the outcome of above models is not affected. However, if it is assumed that hemorrhage patients would benefit from stabilization at an nECC, the area where the drip and ship model is more favorable will increase when considering all patients with LAMS score of 4 to 5.

DISCUSSION

These models represent an explicit way of conceptualizing the problem of prehospital stroke triage. For real-world application, there are many other factors to consider. Age, stroke severity, comorbidities, premorbid functional status, and the patient's wishes will impact decision-making. Practical considerations such as capacity at the ECC, weather conditions, and redundancy in ambulance systems when an ambulance has to travel outside of its jurisdiction are additionally relevant.

These models assumed an average door-to-needle time of 60 minutes for all hospitals. This is based on the Get With The Guidelines: Target Stroke Initiative data that report a median door-to-needle time of 67 minutes.[21] However, on the basis of this modeling, it is abundantly clear that the door-to-needle time at the nECC must be reduced to an average of 30 minutes for the drip and ship model to be viable. We have assumed the door-to-needle time to be the same at the nECC and the ECC; however, door-to-needle times are related to the both volume of ischemic stroke admissions and alteplase utilization.[22] It is highly likely that ECCs will have lower door-to-needle times than nECCs. In addition, nECCs may be more vulnerable to slow workflow during nonbusiness hours or weekends because of limited staffing. Slower treatment times at the nECC only tilt the scales in favor of the mothership model. Similarly, if the ECCs were to have slower treatment times, the area where the drip and ship model is more favorable would increase.

In most urban and suburban areas where hospitals are geographically close together, the mothership model is always superior to the drip and ship model when transport times between the nECC and ECC are short. The American Heart Association policy on interactions within stroke systems recommend that emergency medical services not bypass a closer nECC in favor of an ECC if such a diversion would add >15 to 20 minutes of transport time.[23] The results of these models show that these recommendations may be too conservative. Hence, it is imperative that these data be systematically collected in each jurisdiction and applied locally so that data-driven policy change may occur.

There are many factors that contribute to transportation time besides distance. Other factors such as ambulance response time, ambulance scene time, traffic, weather, and ambulance availability among other things will contribute to transport time. When considering all of these factors, the relationship between time and distance may not be linear, and as such the concentric time circles shown in Figures 2 through 5 and Figures I through III in the online-only Data Supplement may not correspond to concentric distance circles. These models only consider patient outcomes in decision-making. Given the expenses associated with both alteplase and endovascular therapy and long transports by ground or helicopter, these models should be supplemented with both real-world data and an economic analysis.

Notable limitations include all probabilities presented were generated from randomized

controlled trials, representing a highly selected patient population. Enrolled patients had known vessel occlusions and were deemed good candidates for endovascular therapy using imaging selection. These probabilities do not represent all patients seen in the field by first responders, and the probabilities of good outcome, with or without reperfusion, are likely an overestimate. We assumed that all patients with LVOs are eligible for both alteplase and endovascular therapy. However, patients who have longer transport times may be outside the 4.5-hour alteplase treatment time window by the time they reach an ECC (in the mothership model); this should be considered when transport times are long. Yet, a proportion of patients will be technically ineligible for endovascular therapy because of anatomy or unfavorable imaging profiles. Further data on the proportion of patients who become ineligible for endovascular therapy during the onset-to-imaging epoch[24] are needed. The border zones between the drip and ship and mothership models in Figures 2 through 5 and Figures I through III in the online-only Data Supplement are represented as sharp edges, as this is simply a threshold effect where one probability becomes superior to the other. The differences in probabilities close to this border are small; thus, in real-world application, these boundaries would be gray areas and likely would be highly sensitive to changes in model components.

CONCLUSIONS AND FUTURE DIRECTIONS

These conditional probability models provide a framework for evaluation. Real-world data, including interval times, reperfusion rates, and patient outcomes, are needed to assess model application in a given geographic locale. The models assess the problem of acute stroke triage from a population-based perspective and should be thought of as candidate models for evaluation using real-world ischemic stroke patient data. New technology, such as the mobile stroke unit, consisting of an ambulance equipped with a computed tomographic scanner, point-of-care laboratory, and specialized prehospital stroke team, could additionally change these models.[25-27] This early imaging capability is critical to improve on screening tests, such as the LAMS score, that have only moderately good accuracy in identifying large-vessel ischemic strokes (81% sensitivity and 89% specificity).[15] Alteplase can be administered in the mobile stroke unit while on route to hospital

giving patients much faster access to medical treatment. While this is a new and resource intensive, treatment option, it does have the potential to greatly streamline the drip and ship treatment option by eliminating the need to stop at an nECC to receive alteplase.

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Supplementary Appendix

Drip 'N Ship vs. Direct to Comprehensive Stroke Centre: Conditional Probability Modeling

Supplemental Tables:

Supplemental Figures:

Supplemental References

Table I. Model Assumptions

Model Assumption	Rationale
1. There is true uncertainty regarding which transport and treatment decision to make	This model would not be needed in cases where the most favourable treatment option was certain.
2. The nECC is the closest treatment centre to the patient	If the ECC was the closest treatment centre the patient should be transported directly to the ECC as all treatment options are available here.
3. There is only one decision making point (at the scene) and this decision is never reneged upon	While we acknowledge bad weather, traffic, road closures, and hospital capacity may cause an ambulance to divert to another centre on route this cannot be accounted for in these models at this time.
4. This model does not apply to "found down" or stroke-on-awakening patients	It is impossible to account for the time between stroke onset and first medical contact if the stroke is not witnessed
5. Relationship between probability of successful reperfusion and time a. The probability of successful reperfusion with alteplase therapy varies linearly with time, but is capped at a maximum rate b. The probability of successful reperfusion with endovascular therapy is time invariant	a. In both in vitro and in vivo studies clot dissolution rates with alteplase have been shown to progress linearly in the initial treatment phase[1,2] b. While, we know that this is not strictly true, the variation with time is probably relatively small[3] and without robust data on the change in effectiveness over time we cannot account for this variation.
6. All patients with occlusions are eligible for alteplase and all patients with large vessel occlusions are eligible for endovascular therapy	This is an extension of Assumption 1, in order for there to be true uncertainty patients must be eligible for either treatment option.
7. For patients with large vessel occlusions reperfusion is only achieved through treatment (i.e. no spontaneous reperfusion)	This is known to be true in 95% of cases in the first 1-2 hours after stroke onset.[4,5]

nECC: non-endovascular capable centre (primary stroke centre); ECC: endovascular capable centre (comprehensive stroke centre)

Table II. Model Baseline and Sensitivity Analysis Values

Model Component	Base Values	Values Used in Sensitivity Analyses	Rationale
1. Door to Needle Time	60 minutes	30 minutes	60 minutes was chosen as the base case for door to needle time as it reflective of the median door to needle time found in the Target Stroke initiative (median = 67 minutes, 41% DTN less than 60 mins)[6] as well as the upper quartiles in the other studies.[7-9] However, as we move forward with ischemic stroke treatment door to needle times of 30 minutes should be the standard.[10] Median door to needle times of close to or below 30 minutes have been reported in several centres around the world.[7-9]
2. Door in Door Out Time	75 minutes (60 minute DTN)	45 minutes (30 minute DTN)	Assuming a door-to-needle time of 60 minutes, a door-in-door-out time of 75 minutes is estimated to be an appropriate target. This is the target time for the QuICR project in Alberta, and this the target time for STEMI care.
3. Door to Arterial Access	90 mins (mothership) 50 mins (drip and ship)	75 mins (mothership) 45 mins (drip and ship)	Among a group of patients who had a median door to needle time of 60 minutes who presented at the ECC in ESCAPE the median door to arterial access time was approximately 90 minutes.[4] This was adjusted to be 45% faster in the drip and ship model as it has been shown that treatment times are faster at the ECC when the patient was first seen at the nECC.[4] In sensitivity analyses when door to needle times are decreased to 30 minutes, door to arterial access times are also adjusted. Among a group of patients who had a median door to needle time of 30 minutes who presented at the ECC in ESCAPE the median door to arterial access time was approximately 75 minutes.[4] Similarly, this was adjusted to be faster in the drip and ship model.
4. First reperfusion after endovascular therapy	30 minutes	N/A	This is representative of the median time from groin puncture to first reperfusion in both ESCAPE and SWIFT PRIME.[4,11]
5. Early reperfusion after alteplase administration a. Time B + Y $\geq$ 70 minutes b. Time B + Y < 70 minutes	a. 70 mins b. Time B+Y	a. N/A b. N/A	a. For the purposes of this model we define early reperfusion as 70 minutes post treatment initiation for two reasons. First, it has been shown in angiography studies that 1.6% of ICA, 23.9% of M1, and 38.9% of M2 occlusions were recanalized at first angiography post alteplase administration (median 70 minutes).[12] Second, this is a relevant time point when considering inter-facility transportation times b. If time B+Y < 70 minutes, then there is not 70 minutes of time available for alteplase to have full effect between the bolus being given at the nECC and the patient arriving at the ECC. In these cases, the early reperfusion time has been adjusted to be equal to B+Y

Model Component	Base Values	Values Used in Sensitivity Analyses	Rationale
6. Time from first medical contact to ambulance arrival and ambulance scene time	30 minutes	N/A	There are representative times from Canadian cities.
7. Decrease in probability of successful reperfusion in relation to time to reperfusion	0.0006	N/A	Endovascular therapy: Estimate from the ESCAPE trial and HERMES data collaboration.[13,14] Alteplase: As the exact time of reperfusion for patients receiving alteplase is not known, we assume the same rate of decay for alteplase-treated patients.
8. P(reperfusion| endovascular therapy)	0.74	0.90	Estimate from the ESCAPE trial.[4]
9. P(early reperfusion| alteplase) a. Time B + Y ≥ 70 minutes b. Time B + Y < 70 minutes	a. 0.18 b. 0.18[(B+Y)/70]	a. 0.40 b. 0.40[(B+Y)/70]	a. Angiography studies have shown that 1.6% of ICA, 23.9% of M1, and 38.9% of M2 occlusions recanalized after alteplase administration (median 70 minutes).[12] The prevalence of large vessel occlusion with a positive LAMS screen (score of 4 or 5) is 62% and occlusion locations are estimated at: 28% ICA, 65% M1, and 5% M2.[15] These data are combined estimate that 18% of patients with a proven large vessel occlusion will achieve early reperfusion with intravenous alteplase. 0.40 was used as a sensitivity analysis to reflect the efficacy of tenecteplase which has shown greater reperfusion rates than alteplase.[16] b. In pre-clinical studies it has been shown that clot dissolving rates with alteplase progress linearly in the initial treatment phase therefore these probabilities were adjusted in a linear fashion (ex. P(early reperfusion|alteplase) within 35 minutes of bolus = 0.09).[1,2]
10. P(good outcome| no reperfusion)	0.30	N/A	The probability of good outcome given no reperfusion was estimated from the cohort of patients in the ESCAPE trial who did not achieve reperfusion after treatment. In this group of patients 30% achieved a good outcome.[4]

nECC: non-endovascular capable centre; ECC: endovascular capable centre; DTN: door to needle time; ICA = internal carotid artery; M1 = M1 segment of the middle cerebral artery; M2 = M2 segment of the middle cerebral artery; STEMI = ST-elevation myocardial infarction; LAMS = Los Angeles Motor Scale; time B: time from alteplase bolus to leaving the nECC; time Y: travel time from nECC to ECC

Table III. Alternate Values for Early Reperfusion Given Alteplase in Models A and D

Time Y	Time of Early Reperfusion	Model A: P(early reperfusion|alteplase)	Model D: P(early reperfusion|thrombolysis)
10	25 minutes	0.06	0.14
20	35 minutes	0.09	0.20
30	45 minutes	0.11	0.26
45	60 minutes	0.15	0.34
≥90	70 minutes	0.18	0.40

Table IV. Mothership and Drip and Ship Models with Baseline and Sensitivity Analysis Values

Model	Mothership	Drip and Ship
A (base model)	*P(good outcome|mothership model)=0.74·[0.75-0.0006(30+Z+90+30)]+0.26·0.30*	*P(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+60+15+70)]+0.82·[0.74·[0.75-0.0006(30+X+60+15+Y+50+30)]+0.26·0.30]*
B	*P(good outcome|mothership model)=0.74·[0.75-0.0006(30+Z+**75**+30)]+0.26·0.30*	*P(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+**30**+15+70)]+0.82·[0.74·[0.75-0.0006(30+X+**30**+15+Y+**45**+30)]+0.26·0.30]*
C	*P(good outcome|mothership model)=**0.90**·[0.75-0.0006(30+Z+90+30)]+**0.10**·0.30*	*P(good outcome|drip and ship model)=0.18·[0.75-0.0006(30+X+60+15+70)]+0.82·[**0.90**·[0.75-0.0006(30+X+60+15+Y+50+30)]+**0.10**·0.30]*
D	Unchanged from Model A	*P(good outcome|drip and ship model)=**0.40**·[0.75-0.0006(30+X+60+15+70)]+**0.60**·[0.74·[0.75-0.0006(30+X+60+15+Y+50+30)]+0.26·0.30]*

Changes from Model A shown in bold face

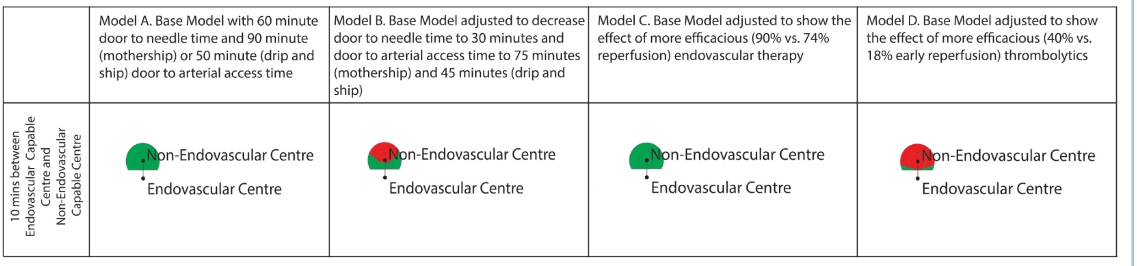

Figure I. Hospitals are 10 minutes apart: The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 10 minutes apart is shown. Red indicates regions where the drip and ship approach is predicted to result in the highest probability of good outcome; green indicates regions where the direct to mothership approach results in the highest probability of good outcome. Model A assumes a door-to-needle time of 60, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, P(reperfusion|endovascular therapy) = 0.74 and P(early reperfusion (within 70 minutes of bolus)|alteplase) = 0.18, this is adjusted linearly for shorter travel times where there is not 70 minutes of time for alteplase to take effect and shows that the mothership option is the most effective strategy. In Model B the door-toneedle time is reduced to 30 minutes and door to arterial access times are reduced to 75 minutes and 45 minutes for mothership and drip and ship, respectively. This model shows the drip and ship model is the most effective strategy if the

patient is very close to the nECC or would have to drive past the nECC. Model C assumes an increased probability of complete reperfusion with endovascular therapy of 90% (compared to 74%) and shows that the mothership approach is the superior option. Model D assumes a novel intravenous thrombolytic agent with 40% recanalization within 70 minutes (compared to the observed 18% for M1-MCA and ICA occlusions), in similar fashion this is adjusted linearly for shorter travel times, and shows that the drip and ship option is the most relevant approach in almost all scenarios.

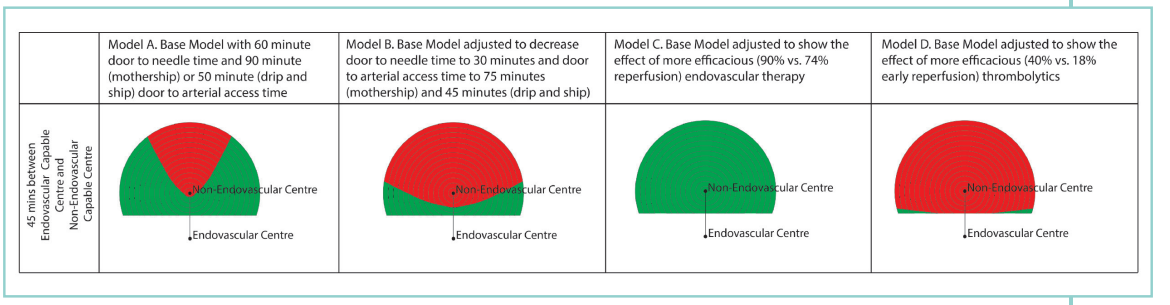

Figure II. Hospitals are 45 minutes apart: The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 45 minutes apart is shown. Red indicates regions where the drip and ship approach is predicted to result in the highest probability of good outcome; green indicates regions where the direct to mothership approach results in the highest probability of good outcome. Model A assumes a door-to-needle time of 60, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, P(reperfusion | endovascular therapy) = 0.74 and P(early reperfusion (within 70 minutes of bolus) | alteplase) = 0.18, this is adjusted linearly for shorter travel times where there is not 70 minutes of time for alteplase to take effect and shows that the drip and ship option is the most effective strategy if the patient is very close to the nECC or would have to travel past the nECC to get to the ECC. In Model B the door-to-needle time is reduced to 30 minutes and door to arterial access times are reduced to 75 minutes and 45 minutes for mothership and drip and ship, respectively. This model shows the area where drip and ship model is the most effective strategy has increased. Model C assumes an increased probability of complete reperfusion with endovascular therapy of 90% (compared to 74%) and shows that the mothership approach is the superior option. Model D assumes a novel intravenous thrombolytic agent with 40% recanalization within 70 minutes (compared to the observed 18% for M1-MCA and ICA occlusions), in similar fashion this is adjusted linearly for shorter travel times, and shows that the drip and ship option is the most relevant approach in almost all scenarios.

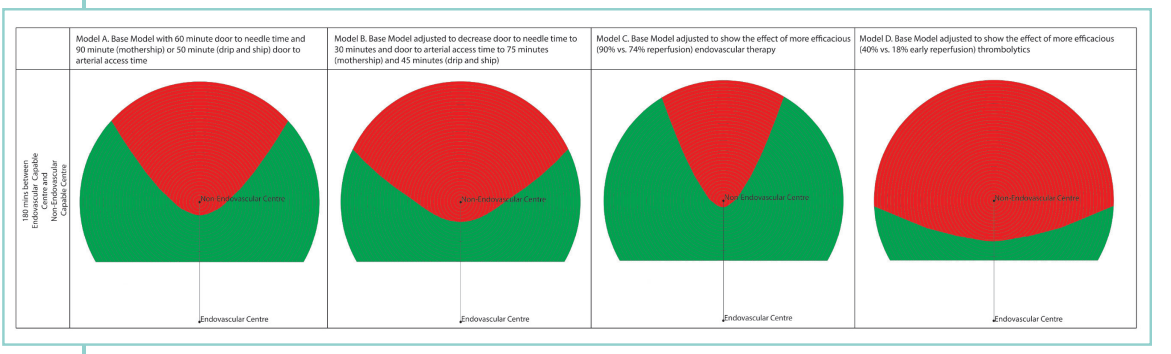

Figure III. Hospitals are 180 minutes apart: The effect of door to needle times and increasing reperfusion rates on the optimization of the use of the drip and ship vs. mothership models of stroke triage and treatment when the endovascular capable centre and non-endovascular capable centre are 180 minutes apart is shown. Red indicates regions where the drip and ship approach is predicted to result in the highest probability of good outcome; green indicates regions where the direct to mothership approach results in the highest probability of good outcome. Model A assumes a door-to-needle time of 60, door to arterial access time of 90 minutes for mothership and 50 minutes for drip and ship, P(reperfusion|endovascular therapy) = 0.74 and P(early reperfusion (within 70 minutes of bolus)|alteplase) = 0.18, this is adjusted linearly for shorter travel times where there is not 70 minutes of time for alteplase to take effect and shows that the drip and ship option is the most effective strategy when the patient is very close to the nECC or would have to travel past the nECC to get to the ECC. In Model B the door-to-needle time is reduced to 30 minutes and door toarterial access times are reduced to 75 minutes and 45 minutes for mothership and drip and ship, respectively. In this model the area where the drip and ship model is the most effective strategy has increased. Model C assumes an increased probability of complete reperfusion with endovascular therapy of 90% (compared to 74%) and shows that the mothership approach is the superior option in more areas than in Model A or B. Model D assumes a novel intravenous thrombolytic agent with 40% recanalization within 70 minutes (compared to the observed 18% for M1 - MCA and ICA occlusions), in similar fashion this is adjusted linearly for shorter travel times, and shows that the drip and ship option is the most relevant approach in almost all scenarios.

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CHAPTER 5.2

Drip ‘N Ship Versus Mothership For Endovascular Treatment Modeling The Best Transportation Options For Optimal Outcomes

Based upon:
Drip ‘n Ship Versus Mothership for Endovascular Treatment
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Stroke. 2017 Mar;48(3):791-794.

ABSTRACT

Background

There is uncertainty regarding the best way for patients outside of endovascular-capable or Comprehensive Stroke Centers (CSC) to access endovascular treatment for acute ischemic stroke. The role of the nonendovascular-capable Primary Stroke Centers (PSC) that can offer thrombolysis with alteplase but not endovascular treatment is unclear. A key question is whether average benefit is greater with early thrombolysis at the closest PSC before transportation to the CSC (Drip 'n Ship) or with PSC bypass and direct transport to the CSC (Mothership). Ideal transportation options were mapped based on the location of their endovascular-capable CSCs and nonendovascular-capable PSCs.

Methods

Probability models for endovascular treatment were developed from the ESCAPE trial's (Endovascular Treatment for Small Core and Anterior *Circulation* Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) decay curves and for alteplase treatment were extracted from the Get With The Guidelines decay curve. The time on-scene, needle-to-door-out time at the PSC, door-to-needle time at the CSC, and door-to-reperfusion time were assumed constant at 25, 20, 30, and 115 minutes, respectively. Emergency medical services transportation times were calculated using Google's Distance Matrix Application Programming Interface interfaced with MATLAB's Mapping Toolbox to create map visualizations.

Results

Maps were generated for multiple onset-to-first medical response times and door-to-needle times at the PSCs of 30, 60, and 90. These figures demonstrate the transportation option that yields the better modeled outcome in specific regions. The probability of good outcome is shown.

Conclusions

Drip 'n Ship demonstrates that a PSC that is in close proximity to a CSC remains significant only when the PSC is able to achieve a door-to-needle time of ≤30 minutes when the CSC is also efficient.

Endovascular treatment (EVT) for acute ischemic stroke substantially improves outcomes compared with usual standard of care for acute ischemic stroke.[1-4] Currently, EVT is only offered at endovascular-capable or Comprehensive Stroke Centers (CSC), which creates uncertainty regarding the best transportation option for patients outside of the catchment area of CSCs to access EVT. As treatment for acute ischemic stroke is changing, the role of the nonendovascular-capable Primary Stroke Centers (PSC) that can offer medical thrombolysis with alteplase but not EVT is unclear. A key question is whether there is a greater benefit in receiving alteplase early at a PSC before being transported to a CSC for EVT (Drip 'n Ship approach).[5] Alternatively, the PSC can be bypassed, and the suspected stroke patient could be transported directly to the CSC (Mothership approach).[6,7] This uncertainly is because of the time dependence of good outcomes with both early intravenous alteplase and EVT[8,9] and the reduced efficacy of alteplase compared with EVT with large vessel occlusive stroke.10,11

One of the key factors in determining the best transportation option is the geographic location of the PSCs and CSCs in relation to the patient origin, as well as regional infrastructure. As part of the DESTINE (Decision Support Tool in Endovascular transport) project, we created mathematical models based on the decay curves for EVT and thrombolysis and generated map visualizations that modeled the best transportation option and the probability of good outcomes.

METHODS

A mathematical model was created using the stroke onset-to-reperfusion and onset-to-treatment decay curves for EVT and thrombolysis, respectively. Data from the ESCAPE trial (Endovascular Treatment for Small Core and Anterior *Circulation* Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) was used to generate a decay curve for patients treated with both EVT and alteplase.[1,8] The decay curve for EVT provided the average probability of good outcomes (PEVT) as defined as modified Rankin Scale score 0 to 2 at 90 days as a function of time from onset to reperfusion. To determine the benefit of alteplase alone, a probability model (PtPA) was developed using the US Get With The Guidelines-Stroke registry.[11] The average probabil-

ity is defined as modified Rankin Scale score 0 to 1 at discharge based on time from onset to alteplase administration.

The total probability of good outcomes was calculated using the formula: P=PtPA+(1-PtPA)×PEVT. This is a sum of the probability of good outcomes from alteplase (PtPA) and the probability of good outcome with EVT (PEVT) for those patients who do not have a good outcome with alteplase (1-PtPA). The time used for PtPA in the Drip 'n Ship scenario is a sum of the following time variables: onset-to-first medical response; on-scene; scene-to-PSC; and door-to-needle time (DNT) at PSC. The time variable for PtPA in the Mothership scenario is the sum of the following variables: onset-to-first medical response; on-scene; scene-to-CSC; and DNT at CSC. The time variable for PEVTin the Drip 'n Ship scenario is the sum of the following variables: onset-to-first medical response; on-scene; scene-to-PSC; DNT at PSC; needle-to-door-out time at PSC; PSC to CSC; and arrival-toreperfusion at CSC. The time variable for the PEVT in the Mothership scenario is the sum of the following variables: onset-to-first medical response; on-scene; scene-to-CSC; and arrival at CSC to reperfusion. This model assumes that all patients receive both alteplase and EVT.

PSC and CSC designations were compiled from the Canadian Stroke Audit and the Joint Commission list of accredited stroke centers in the United States. We incorporated Google's (Mountain View, CA) Distance Matrix Application Programming Interface into MATLAB (Mathworks, Natick, MA). Travel times for emergency medical services were calculated by finding the closest PSC and CSC for each region and calling Google's Distance Matrix Application Programming Interface to determine the drive times using both realistic road speeds and user generated data. Maps were created using MATLAB's Mapping Toolbox, custom color functions, and a generated time database of standard driving times. These maps model the best transportation option for each region that would result in the greatest probability of good outcomes. Maps were generated for all scenarios. All time assumptions are shown in Table.

Table. List of Time Assumptions Made in the Model

	Drip 'n Ship, min	Mothership, min
Onset-to-first medical response	30, 60, 90	30, 60, 90
Time on-scene	25	25
Scene to door	Geographic model	Geographic model
Door-to-needle	30, 60, 90	30*
Needle-to-door-out	20	NA
PSC to CSC	Geographic model	NA
Door-to-reperfusion	115*	115*

CSC indicates Comprehensive Stroke Centers; DNT, door-to-needle time; NA, not available; and PSC, Primary Stroke Centers.

*Sensitivity analysis is performed on these constants. For Mothership, DNT at CSC of 60 min and door-to-reperfusion of 200 min is also included. Additionally, the tipping point of door to reperfusion in the Drip 'n Ship option is also modeled.

RESULTS

Maps were generated for California, United States; Alberta, Canada; and Ontario, Canada (Figure). These maps show the modeled probability of good outcome based on the previously discussed probability model. Green regions represent a greater probability of good outcome via Mothership, whereas red indicates that Drip 'n Ship is best. Orange indicates that either option yields a similar outcome (±2.5%) and neither is necessarily superior. The color tint increases (becomes more white) as the probability of good outcome decreases. Gray indicates areas with sparse infrastructure or little population. Maps are shown for varying DNTs at the PSCs and varying onset-to-first medical response times.

These maps show that the Drip 'n Ship scenario is predicted to result in better or similar outcomes compared with Mothership only when the PSCs are able to administer alteplase within 30 minutes of hospital arrival. When the DNT at the PSC is longer, the Drip 'n Ship scenario is predicted to be beneficial only for those PSCs that are further away from the CSC. When the onset-to-first medical response is longer, the Drip 'n Ship scenario predicts a better probability of good outcomes than the Mothership scenario. The predicted probability of good outcomes declines as the distance to the CSCs increases.

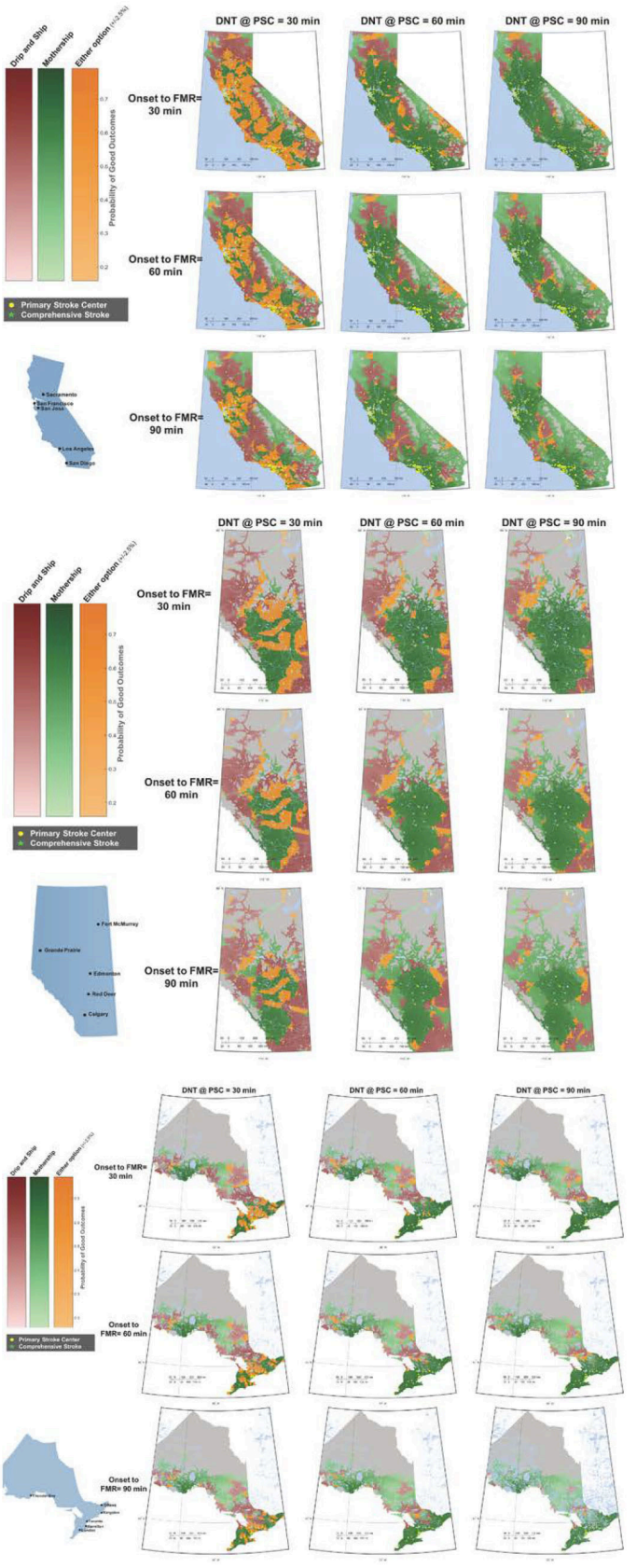

Figure. Modeled endovascular transport option map for California (top), Alberta, Canada (middle), and Ontario, Canada (bottom). DNT indicates door-to-needle time; FMR, first medical response; and PSC, Primary Stroke Center

These results are only valid if the CSC has highly efficient workflow. If the DNT at the CSC is 60 minutes and the door-to-reperfusion time is 200 minutes, Drip 'n Ship is favored with distances of ≥45 minutes between the CSC and PSC (DNT at PSC is 30 minutes). Many CSCs may be able to consistently achieve shorter door-to-reperfusion times in the Drip 'n Ship. Our model favors Drip 'n Ship when the door-to-reperfusion time is ≥70 minutes.

DISCUSSION

These maps demonstrate that any remote PSC retains its significance through the Drip n' Ship scenario, regardless of its DNT, but only if it is a significant distance from any CSC. For those PSCs that are in close proximity to a CSC, their significance is only retained though the Drip 'n Ship approach if they are able to administer alteplase within 30 minutes. The Drip 'n Ship approach becomes more favorable when the onset-to-first medical response time increases. However, the CSC must be efficient in both administering alteplase and also in achieving reperfusion through EVT to retain benefit of the Mothership scenario.

This work provides an initial model incorporating geolocation mapping for the transportation of ischemic stroke patients for EVT; therefore, there are limitations to this work. We used the best available decay curves, but the patient groups for the 2 curves are different. The ESCAPE curves are from an ideal research trial for all patients who received EVT, and the Get With The Guidelines-Stroke curves are from a patient registry for all patients treated with alteplase, including those who would not be eligible for EVT, such as milder strokes with distal occlusions who tend to do better with alteplase. The probability of good outcomes for these 2 groups is different with a more rigid definition with the Get With The Guidelines-Stroke group (modified Rankin Scale score 0-1 at 90 days), which may provide some compensation for the inclusion of milder stroke patients in the alteplase decay curve. These data only show travel times through the fastest ground transport, and transport times may be shorter through both rotary and fixedwing air transport. As more data become available, alteplase decay curves for large vessel occlusion and actual EVT data from registries can be used to improve this model.

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CHAPTER 6

General Discussion

The primary aim of this thesis was to provide proof for the efficacy of endovascular thrombectomy (EVT). Secondary aims include: evaluating various sub-groups through the establishment of a patient-level database from multiple trials; understanding the importance of workflow, further establishing the importance of 'time is brain', and better understanding the bottlenecks to early treatment; innovate on imaging strategies to allow for faster and better decision making and lastly, innovate and improve on strategies on systems of care in light of evidence supporting endovascular thrombectomy.

Effect And Safety Of EVT And Evaluation Of Various Sub-Groups

At the time of the presentation of the MR CLEAN trial (1) results, the ESCAPE trial (2) had enrolled 316 patients. There was a planned interim analysis at 300 patients and the 90-day follow-up was being collected for evaluation by the data safety and monitoring board (DSMB). As such, it was felt that subsequent to the results of the MR CLEAN trial, it was appropriate to put the trial on hold and evaluate the results of the first 300 patients before taking a decision as to whether the trial needed to be continued. The results showed an overwhelming superiority of endovascular treatment over the control arm and at that stage the trial was permanently stopped (Chapter 2.1). Some of the other unique features of the ESCAPE trial were: a. Patients were enrolled up to 12 hours from symptom onset. The treatment effect size was similar in patients treated within 6 hours and those treated beyond 6 hours although the effect of intervention versus control in patients who were included beyond 6 hours did not reach statistical significance (3). b. A significant mortality benefit at 90 days; c. Focus on efficiency of endovascular treatment by improving time to treatment resulting in a median time from study CT scan of the head to the first reperfusion of 84 minutes, which was significantly faster than previous similar trials (4, 5); d. The use of collateral imaging to further reduce the likelihood of enrolling patients that were unlikely to benefit. I carried out an intensive training program on collateral imaging across all the participating sites. In addition, we helped the sites set up multiphase CTA (mCTA) (6) to allow for easier and more robust evaluation of collateral vessels. We also used this opportunity to educate sites and investigators regarding the use of collateral imaging to refine the ASPECTS reading and as such reduce the likelihood of patients with extremely poor ASPECTS to get enrolled into the trial.

Subsequent to the results of MR CLEAN trial and the stopping of the ESCAPE trial, the principal investigators of the SWIFT PRIME trial considered it imperative to hold an urgent executive meeting (7). At that time there were 196 patients enrolled into the trial. A decision was made to halt the trial and perform an interim analysis. This interim analysis once again showed overwhelming benefit of EVT over the control treatment (Chapter 2.2). The unique features of the SWIFT PRIME trial were: a. All patients received IV tPA; b. Every patient in the endovascular arm was treated using the SolitaireTM stent retriever. In the SWIFT PRIME trial as well, there was focus on workflow resulting in a median time from qualifying image to groin puncture of 57 minutes in the endovascular arm. SolitaireTM stent retriever was found to be highly effective with a rate of substantial reperfusion (mTICI 2b-3) at the end of the procedure of 88%.

Collectively, in light of the overwhelming positive results from the ESCAPE and SWIFT PRIME trials over and above the results from the MR CLEAN trial and contemporaneous release of the results of two other trials (REVASCAT, EXTEND IA (8, 9)), EVT became part of usual care for anterior circulation ischemic stroke due to large vessel occlusion. This led to a change in guidelines across the world over the next 3-4 months including the American, European, and Canadian guidelines (10, 11).

Given my involvement across multiple trials (I was one of the principal investigators of the ESCAPE and SWIFT PRIME trials and headed the core-lab for cross-sectional imaging in the REVASCAT trial), I successfully put together a collective group consisting of the principal investigators of all the 5 trials. Taking the first letter from each of those 5 trials (ESCAPE, REVASCAT, MR CLEAN, EXTEND IA and SWIFT PRIME): yielded ERMES. Given its resemblance to the name HERMES in Greek mythology (Hermes was the emissary and messenger of the gods), We added H to the initial acronym and from there on the collaboration was called: HERMES collaboration. Subsequently, the expanded form of the HERMES collaboration was switched to 'Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke *Trials*'. An additional important reason for switching to the new expanded form was to allow greater flexibility for further trials to participate in this collaboration without having to rename the collaboration.

The first publication of the HERMES collaboration was a meta-analysis of 1287 individual patient data.(12) (Chapter 2.3). It further added to the growing evidence supporting

endovascular thrombectomy and allowed for better subgroup analysis. The number needed to treat with endovascular thrombectomy to reduce disability by at least one level on the modified Rankin scale for one patient was 2.6. Additionally, given the large numbers of patients we were able to show clear evidence of benefit a) in patients 80 years or older, b) those randomized more than 300 minutes after symptom onset, and c) those not eligible to receive IV tPA. Another interesting result of the analysis was the observation that age and baseline severity of stroke, as measured by NIHSS, were independent predictors of outcome; although in those with advanced age or severe stroke there continued to be demonstrable benefit of EVT (13).

Importance Of 'Time Is Brain' And Understanding The Bottlenecks In Workflow

Given my involvement in the IMS3 trial,(4) I had the opportunity to analyze the workflow data from this trial (Chapter 3.1). Notable delays occurred in the time intervals from IV tPA initiation to groin puncture (median 84 minutes) and from start of endovascular treatment to reperfusion (median 85 minutes). The time interval from CT scan of the head to groin puncture was significantly shorter during working hours than after. Interestingly, patients with CTA had shorter emergency department to reperfusion and symptom onset to reperfusion times. While the exact reason for this is not clear, multiple factors can be identified such as: CTA being performed at higher volume centres with a well-oiled machinery for stroke care; CTA data acquisition takes a very short time and finally, CTA of the neck allowed the interventionalist to know the anatomy and obviated the need of doing a complete angiogram and it also helped in the choice of appropriate devices and catheters. Transfer of patients from primary stroke centre (PSC) to an endovascular capable centre (generally called a Comprehensive Stroke Centre (CSC)) resulted in a longer symptom onset to reperfusion time compared with those referred and treated in the same centre (14). This detailed information helped not only in the design of ESCAPE and SWIFT PRIME trials but also in the execution of these trials. Based on these data, I was able to focus the efforts of the site investigators towards the bottlenecks: places where maximal gains were possible. Interestingly, it further convinced me on the usefulness of CT angiography (CTA) not only for the documentation of the proximal vessel occlusion but further to increase efficiency in workflow. I traveled to all sites to teach about ways

to plan the entire procedure on the CTA: evaluate the arch and accordingly choose the diagnostic catheter based on the anatomy; not to use an exchange wire but use a long diagnostic catheter within a balloon guide catheter and directly go to the vessel of interest; evaluate the carotid bifurcation and plan for stenosis if present; evaluate tortuosity in the cervical internal carotid artery; understand variations of anatomy such as a fetal posterior communicating artery that could be relevant as one advances the microwire, and have a mental map of the precise site of occlusion. Additionally, CTA obviated the need to do a complete angiogram and evaluate the other vessels prior to retrieving the clot. It also allowed evaluation of potential danger points e.g. presence of an intracranial aneurysm (such as a posterior communicating aneurysm) en route.

The analysis of workflow within the ESCAPE trial (chapter 3.2) validated the efforts towards workflow bottlenecks and we could show data to convince the stroke community that attention to workflow is crucial for improving outcome of EVT. In addition, the push towards increase in efficiency did not increase the complication rate. The data showed that every 30-minute increase in CT to reperfusion time resulted in a reduced probability of achieving a functionally independent outcome of 8.3% (15). Interestingly, in this trial, we were unable to demonstrate the association between symptom onset to imaging time and outcome. This finding has been a great source of discussion and was not replicated in all the other trials. One explanation could be the selection criteria wherein as the symptom onset to randomization increased, only the 'slow-progressors' were included in the trial. The workflow analysis from the REVASCAT trial also showed a relatively flat line for 'onset to imaging' versus outcome (16). In the REVASCAT trial the median time from hospital arrival to groin puncture was 109 minutes; median time from imaging to groin puncture was 67 minutes and the median time from groin puncture to revascularization was 59 minutes (16). In the EXTEND-IA study, the median time from hospital arrival to groin puncture was 113 minutes; the median time from initial imaging to groin puncture was 93 minutes and the median time from groin puncture to mTICI 2b/3 or completion of procedure was 43 minutes (9). In the MR CLEAN trial, of the total 500 patients enrolled, 281 were directly referred to the endovascular capable centre while 219 received IV tPA in another hospital before referral (drip and ship)(17). In the patients who arrived directly to the endovascular capable centre, the median time from admission to vessel imaging was 39 minutes; the median time from vessel imaging to randomization was 53 minutes; the median time from admission to groin puncture was 170 minutes. The

median time from groin puncture to reperfusion was 56 minutes (17). Thus, not only were the workflow times in the ESCAPE trial significantly faster than in the IMS3 trial, these were also much faster than the contemporary trials (EXTEND IA, MR CLEAN, REVASCAT) suggesting the impact of our focus on efficiency and the effect of the quality assurance during the running of the trial.

It was not an unexpected result that symptom onset to endovascular hospital arrival time was 34 minutes longer among patients receiving IV tPA at the referring hospital (drip and ship) versus patients directly transferred to the endovascular capable centre (mothership). However, it is important to note that nearly all patients in the ESCAPE trial were from Canada where systems of care, especially in the large cities, are quite well organized and overall, most patients were directed to "mothership".

The workflow analysis in the ESCAPE trial also demonstrated that CT to groin puncture time was 15% (8 minutes) shorter among patients presenting during work hours versus off hours, 41% (24 minutes), shorter in drip and ship patients versus mothership patients, and 43% (22 minutes) longer when general anesthesia (GA) was administered. However, sites that used GA as a routine were not considered in the site selection process. As such, the data comparing GA to no-GA may not be a true reflection of delays by GA especially if it is used on a routine basis in a well-oiled machine. Finally, the use of a balloon guide catheter during endovascular procedures shortened puncture to reperfusion time by 21% (8 minutes).

I was in-charge of workflow during the conduct of the SWIFT PRIME trial (18). Analysis of the results of this trial provided additional opportunities due to the large number of sites in the trial, a much greater percentage of drip and ship patients and the variable use of CT perfusion (CTP) (Chapter 3.3). Interestingly, in the stent retriever arm of the study, symptom onset to reperfusion time of 150 minutes led to 91% estimated probability of functional independence, which decreased by 10% over the next hour and by 20% with every subsequent hour of delay. This decrease in good outcome rate due to time delays was more prominent compared to the ESCAPE trial especially in the later time windows. This might be explained by the use of CTP that somehow influenced what kind of patients was enrolled. Another possibility is that this difference is random chance: the number of patients in the endovascular arm in both of these trials is not that high.

In the SWIFT PRIME trial, the median time from arrival at the emergency department to groin puncture was 90 minutes (interquartile range, 69-120 minutes), and time to reperfusion was 129 minutes (interquartile range, 108-169 minutes). While these times were slightly slower than the times in the ESCAPE trial, they still represented a substantive improvement on previously reported times. Patients who initially arrived at a referring facility had longer symptom onset to groin puncture times compared with patients who presented directly to the endovascular capable centre (275 vs 179.5 minutes). This is an overall significant result that, as discussed later, had major implications on setting up the appropriate systems of care.

We also analyzed the treatment effect according to imaging strategies with a special focus on CTP. We found no difference in either the outcome of patients undergoing EVT or on the treatment effect size based on whether CTP was performed, or whether CTP was utilized for decision making. This data is important and is in line with the results from the MR CLEAN trial where they were also able to show no benefit of performing CTP (19).

Analysis of workflow and effect of time on EVT was assessed within the HERMES collaboration (Chapter 3.4). Among all 1287 patients enrolled in the 5 trials, time from symptom onset to randomization was 196 minutes. Among the endovascular group, symptom onset to arterial puncture was 238 minutes (IQR, 180 to 302) and symptom onset to reperfusion was 286 minutes (IQR, 215 to 363). The odds of better disability outcomes at 90 days (mRS scale distribution) in the endovascular group declined with longer time from symptom onset to arterial puncture with an absolute risk difference for lower disability scores of 39.2% at 3 hours, 30.2% at 6 hours and 15.7% at 8 hours. Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each one-hour delay to reperfusion was associated with a less favorable degree of disability and less functional independence. Thus, in our individual-patient data meta-analysis of patients with large-vessel ischemic stroke, faster treatment with endovascular thrombectomy plus medical therapy compared with medical therapy alone was associated with lower degrees of disability at 3 months (20). Benefit became non-significant after 7.3 hours. Considering outcome distributions across all mRS health states, for every 9-minute delay in symptom onset to substantial endovascular reperfusion time, 1 of every 100 treated patients had a worse disability outcome (higher score by 1 or more levels on the mRS). The probability of functional independence (mRS 0-2) at 3 months declined from 64.1% with symptom

onset to reperfusion time of 180 minutes to 46.1% with symptom onset to reperfusion time of 480 minutes. The 'time is brain' curve was even steeper if one looked at emergency department to reperfusion time. Rates of functional independence at 3 months declined with the delay in symptom onset to reperfusion time in a parallel manner in 6 of the 7 analyzed subgroups: age, baseline stroke severity, clot location, initial extent of cerebral infarction (ASPECTS), patient arrival directly or by transfer, and time from symptom onset to IV tPA start.

One of the most important findings from the study was further confirmation of the influence of the patient first going to a non-endovascular capable centre (generally called PSC). Even though transfer patients had faster processes of care at the endovascular capable hospital (generally called CSC) than direct arrival patients, the longer symptom onset to arrival times (median 207 minutes versus 65 minutes for direct arrival patients) resulted in overall longer symptom onset to randomization intervals (median 260 minutes for transfer patients vs 165 minutes for direct arrival patients). Similar results were shown in the MR CLEAN trial (17). However, this finding must be kept in perspective of geography. This finding becomes highly relevant in a highly populated urban area where there are multiple competing centres close to each other where the distance between the PSC and CSC is quite small. For patients in rural settings, the decision between whether to bypass the CSC is more complicated and discussed in Part V.

Understanding The Influence Of Imaging Variables On Outcome And Innovation In Imaging Strategies To Allow For Faster And Better Decision Making

I was (along with Dr. Andrew Demchuk) the core-lab for cross-sectional imaging in the IMS3 trial. Baseline neurovascular imaging was impactful not only in terms of its influence on outcome and efficacy of endovascular treatment, but also in its influence on workflow (Chapter 4.1). Only 47% of the patients underwent baseline CTA or magnetic resonance angiography (MRA) and 92% had an arterial occlusion on CTA or MRA (21). Patients with proximal occlusions at baseline CTA demonstrated no difference in functional independence outcome. The subgroups of carotid T- or L-type occlusion (terminal internal carotid artery [ICA] with M1 middle cerebral artery and/or A1 anterior cere-

bral artery involvement) or tandem (extracranial or intracranial) ICA and M1 occlusions showed a trend favoring endovascular treatment over IV tPA alone for primary outcome. Based on these results, I concluded that neurovascular imaging should be mandated in future endovascular trials.

The analysis of the relationship between baseline CT and CTA findings and final outcome in the SWIFT PRIME trial (Chapter 4.2) showed that smaller baseline infarct (ASPECTS 8-10) was associated with better outcomes in patients treated with thrombectomy versus IV tPA alone (66% versus 41%) compared with patients with larger baseline infarcts (ASPECTS 6-7) (42% versus 21%). Interestingly, the benefit of thrombectomy over IV tPA alone did not differ significantly by ASPECTS. The site of occlusion did not matter: all sub-groups showed benefit. Outcomes stratified by collateral status had a benefit with thrombectomy over control across all groups: poor collaterals (33% versus 0%), good collaterals (58% versus 44%), and excellent collaterals (82% versus 28%). Using a 3-level classification and regression tree analysis, we observed optimal outcomes in patients with favorable baseline ASPECTS, complete/near-complete recanalization (TICI 2b/3), and early treatment (mean mRS, 1.35 versus 3.73), while univariable and multivariable logistic regressions showed significantly better results in patients with higher ASPECTS. While benefit was seen with endovascular treatment across multiple subgroups, the greatest response was observed in patients with a small baseline core infarct, excellent collaterals, and early treatment. There were hardly any patients with poor ASPECTS within this dataset to allow any comment on that sub-group. Also given that single-phase CTA was performed, I remained skeptical about the results regarding none to fair collaterals group. With the increasing speed of CT scanners, in a single-phase CTA, some patients may seem to have poor collaterals when it is related to imaging timing as the collaterals haven't had enough time to fill in. Other variables such as early triggering, cardiac output may also influence the visibility of collaterals on a single-phase CTA. Thus, based on these factors it is expected that if on a single-phase CTA, good collateral filling is seen, the collaterals are not poor. However, if the collaterals are not filling well, it is possible that there are other factors at play such as early phase, very fast scanner, relatively poor cardiac output.

This exact issue was the driving force for the invention of multiphase CTA (mCTA) (US patents US9486176B2 and US9423143B2; see appendix) (Chapter 4.3). Another major consideration was the lack of consistency of CTP studies that continue to be highly de-

pendent on many factors such as brand name of CT scanner, how old the scanner is, the protocol used, the length of the acquisition, the radiation dose, the influence of motion, the influence of selection of arterial input function and venous output function, and presence of other pathologies such as significant carotid stenosis in the neck (22). In addition, the same dataset would yield different results based on what software was used. Most importantly, CTP can be time consuming. While the data acquisition is short, it has to be transferred to a dedicated workstation to allow post-processing. There is also the issue of what constitutes dead brain (infarct core) based on the CTP maps. In addition, as our efficiency and quality of reperfusion increased, we were beginning to see ever-increasing number of patients with the so-called 'reversal of core'. Thus, we started using mCTA for decision making. We studied systematic decision making based on mCTA and how it compared to CTP-based decision making (the PROVE IT study). The results showed that Interrater reliability for multiphase CT angiography is excellent. We also recognized some limitations of the technique; many of which were similar to CTP. The quality of the images produced were dependent on scanner parameters, patient cooperation, amount and rate of contrast injected and patient factors like cardiac output. Like CTP, presence of significant carotid stenosis could impact the delay. One other limitation was the subjectivity of the interpretation: what exactly does poor collaterals mean? I did put effort into creating educational material and added it to an educational website (aspectsinstroke.com).

While we continued to work to overcome these limitations, given our experience we felt that there was sufficient validation for the use of mCTA within the ESCAPE trial. Additionally, it overcame some of the problems of CTP and was not dependent on the scanner brand or the age of the scanner. No complex post-processing was needed. There was no additional contrast and very little additional radiation which was much lower than radiation needed for CTP. This at least in part could be responsible for the increased efficiency of workflow within the ESCAPE trial compared to the SWIFT PRIME trial while having nearly the same outcomes. Subsequently, data from the MR CLEAN trial also showed the positive correlation of collaterals with outcomes and treatment effect (of note, this was using single-phase CTA and not exactly comparable) (23).

Subsequent to the trial, one of the issues that came up for mCTA was the ability to test regionally (following the ASPECTS regions). We systematically tested the ability to predict tissue fate based on mCTA in all the cortical ASPECTS regions within the PROVE

IT database (24). Multiphase CTA parameter washout and CTP parameter Tmax were significantly associated with follow-up infarction in all models. The area under the receiver operating characteristic curve for mCTA models ranged from 92% to 94% and was not different compared with all CTP models. Thus, we were able to show that similar to CTP, mCTA can be used to predict tissue fate regionally in acute ischemic stroke patients (Chapter 4.4).

Subsequent to the publication of THRACE (25) and PISTE (26), these two trials also agreed to join the HERMES collaboration. Thus, the HERMES collaboration now comprised of 7 trials. We were able to bring all the imaging together, created a new imaging database and had expert re-reads of all imaging with the imaging experts anonymized to which arm of the trial the patient was in, what trial the imaging belonged to and final outcome (27). We were able to show the benefit of treatment in patients with ASPECTS as low as 3-5 (Chapter 4.5). The TENSION (Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window) trial (Clinical*Trials*.gov: NCT03094715) will specifically be investigating the effect of treatment in these patients.

Organization of stroke care: getting the correct patient to the correct hospital.

When a patient presents with stroke-like symptoms and has the first medical contact usually by a paramedic, broadly speaking there are the following possibilities: a. Ischemic stroke b. Hemorrhagic stroke and c. Stroke mimic. Within the category of ischemic stroke, one can further sub-divide these into a. Patients eligible for endovascular treatment (have a large vessel occlusion (LVO) which can be assessed by CTA or MRA and small ischemic core which can be assessed by ASPECTS scoring, collaterals, perfusion imaging). Based on current guidelines, if eligible, these patients are also administered IV tPA. b. Patients who are eligible for IV tPA but are not eligible for EVT (do not have an LVO, or do not have salvageable brain tissue). Various scoring systems have been created such as LAMS (Los Angeles Motor Score) and RACE (Rapid Arterial oCclusion Evaluation) for assessment in the field by paramedics (28, 29). The aim is to separate those patients that have a high likelihood of LVO so that these patients can be taken directly to the CSC, which is an endovascular capable centre,

bypassing a PSC that is capable of giving IV tPA but not endovascular capable. However, none of these scoring systems is very good at separating patients who are candidates for EVT.

Data from the SWIFT PRIME trial and HERMES have clearly shown the degree of delay introduced in endovascular thrombectomy by taking the patient first to a PSC and then getting transferred to a CSC (12, 30). For patients with a particular cut-off on a scale such as LAMS or RACE, it is important to decide what is in the best interest of the patient: being taken to a PSC or a CSC. This depends on a number of factors including relative distance (or travel time) from where the patient is to the PSC versus CSC, likelihood of finding an LVO (how good the scoring system is), efficiency of the PSC (door in door out time if the patient does have an LVO), time decay curve of IV tPA effect if the patient is taken directly to the CSC, there will be a delay in IV tPA administration, time decay curve of EVT effect if the patient is first taken to the PSC and then transferred, there will be a delay in EVT, effectiveness of EVT treatment (speed and quality of reperfusion at the CSC).

Our mathematical model (Chapter 5.1), takes all these data points using the data from various trials. In the first version, we used the ESCAPE trial data and time-decay curves and used the simplest assumption of a patient who does have an LVO in the field. For such patient, how can one model the travel time to PSC versus CSC, efficiency of workflow within the PSC and then travel time from PSC to CSC to determine the optimal solution for a particular geography. Subsequently, we overlaid these on known geography with known location of PSCs and CSCs and travel times based on google maps (Chapter 5.2). We plan to continue to expand on this work and as a next model, we will try to understand how the utilization of in-field scores such as LAMS or RACE, influences the model. Furthermore, we want to understand how a mobile stroke unit (MSU) benefits the system.

In parallel, there is a randomized trial running in Catalonia called RACECAT (Clinical*Trials*.gov: NCT02795962). Their aim is to determine using actual data whether a direct to mothership approach is better than a drip and ship approach. The trial is enrolling faster than expected and the results would be known in approximately two years. However, it seems unlikely that the results from this trial would be generalizable across the world, given the uniqueness of the Catalonia geography and health care system. In addition, it

seems likely that the efficiency and effectiveness of EVT will continue to improve based on better technology, technique and training. This will likely have a dramatic impact on the results. On the other hand, the effectiveness of IV tPA is not likely to change. In theory, there could be an improvement in the efficiency of door to needle time at the PSC but that also seems unlikely as the treatment has been around for over 15 years. There is a concern that the door to needle time may worsen as the volume of patients drops with more and more patients going directly to the CSC. We know that the positive predictive value (PPV) of the current scoring systems (LAMS, RACE) is not very good. There is likely to be improved technology addressing this problem. Something simple like a multi-way conference call with a specialist at the CSC and the team from the PSC could be a starting solution. Not only could this increase the quality of the clinical assessment (thus increasing the PPV) but it also considers soft measures as immediate availability of team members. For example, a CT technologist may not be in-house in a PSC at 2 am and would need to be called from home. All these data can be collectively taken into account to improve decision making. Another approach is the use of video-conferencing, which could be further enhanced by using wearable technologies such as google glass, to allow a virtual examination of the patient by the CSC specialist.

It is clear that this aspect of stroke organization is in its infancy and will continue to evolve. This is why I believe that our approach of a mathematical model should be the preferred approach as it allows for changing the output of the model on the fly as better data becomes available or there are changes in the input data such as improved PPV of the scoring systems or improved reperfusion rates for EVT. Additionally, the model can be adapted for any geography or changing conditions within the same geography (such as increased travel times due to bad weather).

Unknown unknowns.

There is a general feeling that a certain volume of procedures is needed to have a high functioning team and good clinical outcomes. This makes intuitive sense. There is some data in this regard; however, most of the data is biased and published by large centres that have an inherent interest in moving towards centralization. But what is the optimal level of centralization and how is it determined? Should it be based on population denominator e.g. one CSC per million population? What about rural, thinly populated regions? Should

the rules be different for very densely populated regions such as Manhattan, where a small number of centres of excellence can do a very high volume of cases? If one was to go down a pathway of centralization, would there be such a drop of volume at some of the PSCs that they are no longer motivated to provide a 24/7 service or are unable to sustain a call schedule? While some feel that we should be opening more CSCs and training more people, one of the concerns is that the perceived shortage of EVT in some regions is not due to an overall shortage but a problem of distribution (31). Big cities are generally attractive places to live especially for a working couple (higher likelihood of finding two jobs and other necessary resources) and hence, there may already be too many CSCs in big cities but not enough in rural areas. The situation is somewhat analogous to the work of Nobel Laureate Amartya Sen and his work on famines where he showed that very often it is a problem of food distribution rather than an overall food shortage (31).

Even more importantly, one may create the mathematical models and show data for an ideal set-up and organization of stroke care. However, how will this be implemented? Who is responsible for making policies to make it happen? Will it be a top-down approach where centres will be told based on the overall population distribution and geography whether they can or cannot be a CSC? What are the best ways to measure whether a group of CSCs and PSCs are providing an overall good service to the population? Even if such measurement tools were created, how would the results of the measurement influence who gets to be a CSC.

There are some articles that suggest the over-training of fellows (neurointerventionists in the US and possibly other jurisdictions as well) (32, 33). These fellows are motivated to find jobs after finishing their training and similarly, it is likely that more and more PSCs will try to provide EVT. Thus, rather than moving towards centralization, it is possible that things may in fact go in reverse with more and more centres becoming capable of offering EVT with lower volumes per centre.

The issue of stroke call is another issue. In an ideal world for maximal efficiency and better quality of life, a centre should have a high volume to justify having the entire team be in-house 24/7. This, however, can be expensive and if the team is small can be onerous. Going into the future, there is and will continue to be a greater need of cooperation among various hospitals in a jurisdiction to be able to share call (34).

Where Had We Reached; What Else Needed To Be Done; Challenges And Opportunities

Because of this work and other trials, endovascular treatment became the standard-of-care for acute ischemic stroke due to LVO in the anterior circulation. The fact that 'time is brain' got established beyond doubt. However, it raised many questions that can be broadly divided into:

1. What is the generalizability of the results of the trial? As is expected, there are concerns about the generalizability of the results of the trials. As an example, the median age in the trials was lower than the population we encounter in day to day practice. There were also concerns that the trials were conducted at hand-picked centres with high level of expertise. It is important to note that EVT is supported by 6 positive RCTs performed in different parts of the world in differing health care systems. The medical teams had varying levels of expertise. There were sizeable differences in execution of treatment in terms of patient selection, workflow efficiency and quality of reperfusion. In spite of all these differences, all the trials showed a consistent result strongly favouring EVT. It is expected that there will continue to be improvements in systems of care, workflow, interventionist skills, devices and technology. Additionally, the patient level summation of the data (the HERMES collaboration) has allowed us to look at many of the sub-groups e.g. the older population. The treatment effect of EVT is seen across all the various sub-groups. It is also important to acknowledge the practical issues of trial design that can ultimate affect generalizability. Very often trial sample size has to be decided based on issues such as number of sites, expected enrolment rate, and access to monies and other resources. *Trials* with broader inclusion criteria risk not being successful at demonstrating benefit of treatment if the sample size is not large enough. In the current situation though, even the trials with the most inclusive inclusion criteria such as MR CLEAN showed a positive result. There are two other important considerations: a. the natural history of disease of acute ischemic stroke due to LVO is poor and b. the complication rate of EVT is overall quite low. Thus, overall there does not seem to be much concern regarding generalizability of the results of the trials.

2. What are the limits of endovascular treatment: patient selection?

   a. Should patients beyond M1 be treated? There is limited data from the HERMES collaboration of benefit in M2 occlusion, but this has not been formally tested. The current generation of devices have been designed for M1 and not for more distal vessels like A2 or smaller M2 occlusions.

   b. Should patients beyond 6 hours be treated? I have long believed that this time interval is arbitrary and decision making should be based on imaging. We published on the idea of two epochs: symptom onset to imaging decides the likelihood of favourable imaging; imaging to reperfusion decide the likelihood of favourable outcome (35). Hence, when we designed the ESCAPE trial, we decided to enroll patients up to 12 hours. Unfortunately, almost none of the other trials did that and the number of patients within the ESCAPE trial beyond 6 hours did not reach statistical significance (3). This led to two further trials, DAWN and DEFUSE3. Both trials showed an overwhelming efficacy of EVT (36, 37). One concern is the extremely tight imaging criteria following by each of these trials which are quite restrictive. Further trials with more inclusive inclusion criteria are currently enrolling (MR CLEAN LATE; www.mrclean-late.nl).

   c. Should patients with moderate to large core be treated? Both the ESCAPE trial and the SWIFT PRIME trial had selection criteria designed to avoid enrollment of patients with a large core. While other trials did not, most patients enrolled had a small core. Data from the HERMES collaboration showed benefit in patients with low ASPECTS. This would likely need further formal testing and refining of adjunctive criteria e.g. do these patients benefit only if they are young and present early after stroke symptoms.

   d. Should patients with minimal stroke symptoms (low NIHSS) but with LVO be treated with endovascular thrombectomy? Once again, most trials had inclusion and exclusion criteria to avoid such patients. Overall very few such patients got enrolled. Additionally, such patients are relatively rare and progress slowly, obviating the need for urgent decision making. While such a trial would help the field, it may be a tough trial to conduct.

e. Opening the doors for other research questions. As an example, one of the obvious next question is to test the usefulness of IV tPA in patients undergoing endovascular thrombectomy. Given the costs, the risk of intracranial hemorrhage (ICH) and the relative limited efficacy in patients with LVO, many in our field feel that this may not be a necessary step. Various trials are being started to look at this question. There is a recent study (EXTEND-IA-TNK) (38) showing the superiority of tenecteplase over tPA in patients selected for undergoing EVT. This study showed that at the time of the first angiographic run, 22% of patients administered tenectaplase has achieved recanalization as opposed to only 10% of the tPA patients. This study has the potential to cause a major shift in practice. Also, it may influence the design and impact of trials looking at the question of benefit of tPA in patients undergoing EVT. The WAKE-UP study (39) showed benefit of thrombolysis in carefully selected patients in the late time window. Patients were selected using the Diffusion-FLAIR mismatch paradigm on MR imaging. The EXTEND trial results were presented at the late breaking session at the World Stroke Congress in Montreal in October 2018 and showed benefit of thrombolysis in the late time window (4.5-9 hours). The results are yet to be published. It is likely that other trials will look at the same question using CT imaging that is more widely available. While both these studies increase the opportunity to improve outcomes and further offer therapeutic choices to stroke patients, it seems unlikely that they will have a dramatic impact on the implementation of EVT in patients with LVO. In my opinion, it seems unlikely that (using imaging-based technologies) in the near future, we will be able to predict confidently which patients with LVO will respond so well to IV thrombolytics to obviate the need to plan/organize EVT.

3. What are the limits of endovascular treatment: training, technology and technique?

Results from HERMES showed a 71% mTICI 2b-3 rate of reperfusion (13). In my opinion, this is clearly low with a lot of scope for improvement, both in terms of quality and quantity. I had suggested the need for increased granularity of this classification as many of us were reaching reperfusion close to TICI3 suggesting the term TICI 2c (40). This is now widely in use at many centres. However as yet it has not been routinely used in research.

a. Technique: After the successful trials, there has been a major jumpstart in innovation with many ideas and products for endovascular thrombectomy. New techniques such as combination of local aspiration using a large bore catheter with stent retriever are being increasingly used. Some of these have been or are being formally tested in trials. There is also a move towards combining a balloon guide catheter, distal aspiration catheter with stent retriever to take advantage of each of these technologies.(41, 42) However, the best outcome measure for these trials remains controversial. There is also a move towards use of aspiration only (popularly called ADAPT technique by some).(43) A recent randomized study (ASTER trial) showed similar outcomes for aspiration and stent-retriever based approaches in terms of the degree of TICI reperfusion, which was the primary outcome of the trial, but showed a trend towards better clinical outcomes in the stent-retriever arm.(44)

b. Technology: Many new technologies are being developed. At the current moment, it is unclear which of these would pan out and reach clinical practice. As previously explained, it is also unclear what methodology should be used to test new technology against existent technology. The bar for getting approval for new technology varies significantly across different jurisdictions being much easier in Europe compared to North America. As such, most companies aim for a European approval to conduct initial human studies and subsequently, aim for an American approval. It seems entirely possible that there will soon be multiple similar technologies on the market with no clear data or evidence of superiority of one over the other. In parallel, there will continue to be efforts to better understand patient characteristics (e.g. does the embolus in a patient with atrial fibrillation differ from one in a patient with carotid stenosis? Should a different technique or technology be used?), clot characteristics on imaging (e.g. degree of perviousness on multiphase CTA or degree of hyperdensity on non-contract CT scan), time from symptom onset (e.g. do patients who present in a delayed fashion after symptom onset of stroke have tougher and more fibrin rich clot compared to patients who present early?). While these are interesting questions, in my personal experience, I have not found any of these factors to be significant. Also given the high rates of successful reperfusion with current techniques, it may be difficult to assess for meaningful improvements. It is important to note, howev-

er, that there is still a substantive gap between reperfusion and clinical outcomes. The reduction is this difference and further improvement in clinical outcomes will likely result from improvement in systems of care and pre- and/or peri-interventional medication (e.g trials such as MR CLEAN MED and ESCAPE NA1).

Cost of procedure may become another major driver of technology especially for the developing world. In India, the biggest driver to using aspiration technology is the cost of the stent retriever. In China, there is a major push to use a locally manufactured stent as it is cheaper. It is worth noting that the cost of stroke is astronomical and data from recent trials showed the procedure to be highly cost effective in spite of the current high cost of the procedure (45, 46). Most of such data are based on US figures and these will vary across different jurisdictions.

Development of technology to save time. It is likely that soon there will be new add-ons to the armamentarium available to the interventionist that will overall reduce the time to reperfusion. I developed a local solution called BRISK (Brisk Recanalization Ischemic Stroke Kit) many years ago (47). This is basically an open setup where all the things that are needed for an acute stroke procedure are openly laid on a table ready to go. The inspiration for this came one night around 8 years ago, when I was paged in the middle of the night. I reached the hospital much earlier than my team and started to work on setting up things as the nurse, technologist and other members arrived. I remember counting the number of small and large individually packaged things I had to open: a total of 57. It took me over 10 minutes to just open the packets and then I realized that they were all piled up on the table, so it took time to sort out what is needed at what stage of the procedure. That is when I decided to create BRISK. The way we currently do it is: all the inexpensive products e.g. drapes, syringes, three-way stopcocks are laid open on the sterile table. Each product has a specific position on the table so that when one comes in to do a case, the interventionist and team knows where everything is going to be. In addition, all the expensive products like the stent retriever are kept right beside the table. The table is then covered by a sterile drape and then signed by the nurse regarding the time the tray was made. Arbitrarily, we keep the tray for a maximum of 24 hours and as it gets close to 24 hours, it gets used for the next procedure whether it be an aneurysm coiling or a diagnostic angiogram. Initially there was significant concern regarding increas-

ing the rate of infections; however, we have had this process in place for over 7 years and have not noted any increase in infection rates. During the running of the ESCAPE trial, we were able to implement it across most ESCAPE sites. When the ESCAPE trial was launched, and we started visiting all the sites, I found that most sites initially cannulated the relevant artery using a diagnostic catheter and then exchanged it to a balloon guide catheter. I had, for many years, given up the step of the exchange wire and directly went up with a diagnostic catheter co-axially through the balloon guide catheter. This was a significant saving of time and we could successfully implement it. Now, after all the trial results, there are many commercially available products specifically designed for this purpose and the range of these products will continue to increase.

c. Training. This is an area that is currently somewhat ignored. There are multiple issues that need to be overcome. Some of these are:

   i. The world of stroke is totally different from the world that the majority of interventionists have grown up in where there is no emergency, the patient is totally still under general anesthesia and there is a lot of discussion regarding anatomy and choice of devices, size of coils or the concentration of glue. Some have trouble adapting to working under the 'chaotic' conditions of an acute stroke and the sense of urgency with a very often uncooperative patient.

   ii. There has been a significant drop in the number of diagnostic angiograms over the last 10 years with increasing quality of CTA and MRA. In addition, there are many more centres doing neurointervention and training fellows. Furthermore, many fellows are coming from specialties like neurology where they have very little catheter experience prior to the fellowship. All of these are affecting the expediency and ease with which one can negotiate past a tough, tortuous arch.

   iii. Stroke generally affects an older population that have co-morbidities such as hypertension, diabetes. These are also predisposing factors for atherosclerotic disease in multiple vessel beds and very often these patients have

peripheral vasculopathy as well. Overall, a typical stroke patient is quite different from a typical sub-arachnoid hemorrhage patient making vascular access much tougher. One may be faced with a situation where the femoral arteries are not palpable, or the patient has undergone previous surgery for peripheral vascular disease. Thus, the interventionist may have to resort to alternative access approaches such as radial artery or direct carotid puncture. These may be outside the comfort zone of many.

All these are issues that, in my opinion, are not being adequately discussed. There will likely be development of training modules and use of simulation technology to solve these problems. Simulation technology is widely used in the airplane and space industry. Pilots and astronauts undergo all kinds of possible scenarios that may or may not be common, so that they are fully prepared for actual situations. Similar technologies are being developed for various medical procedures. With increasing computation power, better software design and greater demand, these will likely continue to improve.(48) These will be helpful not only for the purposes of training of the trainees but also help in keeping up performance indices for experienced staff as well especially for emergency situations like acute stroke. There is likely to be growth of personalized medicine, where the interventionist may have an opportunity to practice on that particular patient's anatomy, the one that they are going to treat immediately after. This can help in building muscle memory, reduce mistakes and further increase efficiency.

4. The possibility of re-birth of neuroprotection. Many neuroprotective agents that have shown a lot of promise in animal experiments have failed in human trials. There are of course, many well understood and likely not well understood factors that influence this. One factor that may have played a major role is the continued ischemia of the affected territory. Thus, an agent that may be transiently neuroprotective will ultimately fail unless blood flow is restored. For the first time, we have a dependable and predictable human version of an ischemia-reperfusion model: patients present with an M1 occlusion that can subsequently be opened up by EVT. This may provide a unique opportunity to advance the science of neuroprotection. We have started the ESCAPE NA1 trial (NCT02930018; clinicaltrials.gov) testing a novel compound

NA1. All patients undergo EVT and are randomized to drug versus placebo after the CT angiogram. Other similar studies are being planned.

Thus, as demonstrated in this thesis, there is incontrovertible proof of the efficacy of EVT in patients with acute stroke due to LVO in the anterior circulation. The treatment is very robust and shown to be effective irrespective of age and sex. However, it is highly time dependent and hence, one of the biggest challenges going forward is to create systems of care to get the correct patients (patients with acute stroke symptoms likely to be due to LVO) to the correct hospital (a hospital able to offer EVT) as quickly as possible. This will not only require improvements in technology but will require cooperation, training and change in policy. It will require us to collectively overcome human and political barriers. The organization of stroke can learn from cardiology. The organization of cardiac care underwent a similar transformation three decades ago and were able to effectively organize patient transport to the appropriate hospital. One of the major successes of cardiology was in patient awareness and education. Currently, in nearly any part of the world, there is excellent recognition of signs and symptoms of an acute coronary syndrome. As we collectively work on organizing stroke care, education and transportation, we can learn from our cardiology colleagues rather than needing to reinvent. It is expected that there will continue to be improvements in technology and technique at all levels of stroke care whether it is stroke detection in the field or new catheters to pull the clot out. With dramatic increase in number of centres it is possible that training and performance issues may come up. In my opinion, many of these issues can be overcome by investment in simulation technologies.

The natural history of acute ischemic stroke due to LVO is dismal. For any person presenting to the hospital with an acute M1 occlusion, it is probably the single, worst day in their lives. These recent changes in stroke care, have for the first time provided the opportunity to make a giant difference in the lives of these patients. I feel deeply honoured and privileged to be part of this story. At the same time, I do recognize that the story is far from complete and over the next many years, I hope to engage, teach, inspire and mentor young, bright minds to continue to improve stroke outcomes using the standard tool set: cooperation among talented people, working with a great team, work hard and not give up!

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CHAPTER 7

Summary in English and Dutch

Stroke is a serious and common illness. There is a stroke about every minute and a person dies of stroke about every 3½ minutes in the US. At the moment, there are 3 to 4 million Americans who had a stroke yet are still alive. It is likely that the incidence of stroke is even higher in the developing world. Approximately 80% of strokes in the Western world are ischemic and of these, those due to large vessel occlusion (LVO) have the worst prognosis. The efficacy of IV tPA in these patients is limited.

The aim of this thesis is to describe my research which was to provide new proof for the effectiveness of Endovascular Thrombectomy (EVT). Secondary aims include: evaluating various sub-groups through the establishment of a patient level database from multiple trials. Additionally, the thesis also evaluates importance of workflow and speed in acute stroke management and provides better understanding of the bottlenecks to early treatment; innovate on imaging strategies to allow for faster and better decision making and lastly, innovate and improve on strategies on systems of care in light of evidence supporting EVT. This thesis is divided into four parts: Effect and safety of endovascular treatment (Chapter 2); Importance of workflow (Chapter 3); Imaging variables and outcome (Chapter 4); and Optimizing systems of care (Chapter 5).

Chapter 1 General introduction

Chapter 1 provides a general introduction. It provides an overview of acute stroke treatment and traces the history of reperfusion therapies from various thrombolytic drugs to mechanical thrombectomy. It broadly comments on possible reasons for failure to show benefit of EVT in the first generation of RCTs and goes on to provide possible solutions to overcome obstacles during the design of subsequent trials.

Chapter 2: Effect and safety of endovascular treatment in acute ischemic stroke

Chapter 2.1 presents results of the ESCAPE trial. The results show that in patients with acute ischemic stroke last seen normal within 12 hours and with imaging features showing presence of moderate to good Alberta Stroke Program Early CT Score (ASPECTS), moderate to good collaterals and presence of an LVO, patients undergoing EVT have substantively better outcome at 90 days compared to the control group. The trial was

conducted across centres in Canada, US, South Korea and Ireland. In the design and conduct of the trial there was focus on workflow. There was a strong quality improvement program to improve logistics and diagnostic procedures during the conduct of the trial. The expectation of workflow and efficiency in the trial was: start of CT scan to groin puncture < 60 minutes and start of CT scan to first reperfusion in < 90 minutes. In addition, all patients have CT based imaging with use of ASPECTS and collaterals (preferably on multiphase CTA).

Chapter 2.2 presents the results of the SWIFT PRIME trial. This randomized controlled trial with open label treatment allocation tested the benefit of EVT using the SolitaireTM device (Medtronic). In this trial all patients were eligible for and received IV tPA. The imaging selection criteria were similar to the ESCAPE trial: presence of LVO and a relatively small core (either using perfusion imaging or ASPECTS). The results once again showed substantive benefit in patients undergoing EVT with a number needed to treat (NNT) of 4 to achieve functional independence at 90 day (modified Rankin Score (mRS) of 0-2). At the start of the trial, CT perfusion (CTP) was compulsory but was made optional after the first 71 patients. Irrespective of whether CTP was used or not, there was clear benefit of treatment. The SWIFT PRIME trial also had focus on workflow. The primary metric to measure workflow was imaging to groin puncture time. The trial was conducted across 39 sites in US and Europe. In the EVT group, the median time from imaging to groin puncture was 57 minutes and rate of substantial reperfusion (mTICI 2b-3) was 88%.

Chapter 2.3 presents the results of a patient level meta-analysis (HERMES collaboration) combining the data of randomized controlled trials testing the benefit of EVT over standard of care and in whom EVT was performed using modern thrombectomy devices (stent retrievers) (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, EXTEND IA). Given the much larger number of patients, this study allowed evaluation of various subgroups (e.g. early vs. late patients; moderate or good ASPECTS; both sexes; different age groups; various sites of occlusion). All the evaluated sub-groups showed benefit of EVT. The study was able to show benefit of treatment at all ages including the very elderly with age being a prognostic factor. The number needed to treat with EVT for reduction of disability by one level on the mRS was 2.6. Mortality within 90 days, risk of developing a parenchymal hematoma or symptomatic intracranial hemorrhage did not differ across the two groups.

Chapter 3: Importance of workflow in acute ischemic stroke

Chapter 3.1 presents a historical perspective evaluating workflow in the IMS3 trial. It showed various bottlenecks, advantages of performing a CT angiogram and time lost in various steps of patient care. These results were quite informative in the design and execution of the subsequent trials. We were able to show that routinely including CTA for the imaging work up of the patient resulted in time savings. Also, patients who presented direct to the endovascular centre (mothership) had overall faster workflow and shorter onset to endovascular treatment times compared to the 'drip and ship' patients. This study also showed slightly slower times on weekends and after working hours. Most importantly, however, was an overall realization of the relatively slow workflow in the trial that provided opportunities for improvement at all steps.

Chapter 3.2 presents the results of workflow from the ESCAPE trial. It documents the substantive gains in speed and efficiency compared to previous trials. In addition, it showed that by using imaging-based selection it was possible to think of the time in patients with acute ischemic stroke as two epochs: onset to imaging time influences the likelihood of favorable imaging; imaging to reperfusion time decides the likelihood of favorable outcome. Administration of general anesthesia was associated with prolongation of CT-to-groin puncture time by 43%, on average, in comparison with patients who did not receive general anesthesia. The use of a balloon guide catheter as part of the endovascular technique was associated with shortened time from groin puncture to first reperfusion by 21% (8 minutes), on average. For every 30-minute increase in imaging to reperfusion time, we were able to show an associated decrease in the probability of functionally independent outcome by 8.3%. No statistically significant relationship was noted between stroke symptom onset to qualifying CT time and functionally independent outcome in either arm of the trial.

Chapter 3.3 presents the results of workflow in the SWIFT PRIME trial. Some of the key highlights from this analysis were: the dramatic amount of time lost in the 'drip and ship' paradigm compared to the mothership paradigm; delays introduced by performing perfusion imaging and once again, further corroborating the concept of 'time is brain'. With a tight quality assurance program following during the conduct of the trial, the qualifying image acquisition to groin puncture was achieved with a median time of 52

minutes; in 61% of patients, the optimal time of less than 70 minutes was achieved. The probability of functional independence among patients with stent retrievers was 91% if reperfusion was achieved 150 minutes from symptom onset, which decreased by approximately 10% over the next 60 minutes and then 20% with every subsequent 60-minute delay. In multivariable analysis, initial presentation to a referral facility added 129 minutes to when the patient finally arrived at the endovascular capable centre (these times were directly related to the times noted in the trial and were not corrected for the travel distance and actual patient location, location of the primary stroke centre and location of the endovascular centre).

Chapter 3.4 presents the workflow analysis for the pooled analysis from the five RCTs (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, EXTEND IA). The odds of better disability outcomes at 90 days with the endovascular group declined with longer time from symptom onset to arterial puncture: common odds ratio (cOR) at 3 hours, 2.79; cOR at 6 hours, 1.98; cOR at 8 hours,1.57; retaining statistical significance through 7 hours and 18 minutes, the time point at which the lower bound of the 95%CI for the estimated treatment benefit first crossed 1.0. Among the endovascular group patients in whom substantial reperfusion was achieved, delay in symptom onset to reperfusion times was associated with increased levels of 3-month disability. For every 9-minute delay in symptom onset to substantial endovascular reperfusion time, 1 of every 100 treated patients had a worse disability outcome (higher score by 1 or more levels on the mRS). The probability of functional independence declined from 64.1% with symptom onset to reperfusion time of 180 minutes to 46.1% with symptom onset to reperfusion time of 480 minutes. In addition, the data further added to the growing evidence of the importance of getting the patient to the 'correct' (EVT capable) hospital directly rather than using a drip and ship paradigm.

Chapter 4 Imaging variables and outcome

Chapter 4.1 presents the analysis of non-invasive vascular imaging (CTA) from the IMS3 trial. While non-invasive vascular imaging was performed in less than half the patients in this trial, the data reinforced the importance of vascular imaging and played an important role in the design of subsequent trials. For all patients with CTA-proven intracranial

occlusions before randomization, endovascular treatment plus IV tPA was effective compared to IV tPA alone for primary outcome.

Chapter 4.2 presents imaging analysis from the SWIFT PRIME trial. This study provided corroborative data on prognostic factors in patients with acute ischemic stroke due to LVO: small core, good collaterals and fast and good reperfusion. The study showed that smaller baseline infarct (ASPECTS 8-10) was associated with better outcomes in patients treated with thrombectomy versus IV tPA alone (66% versus 41%) compared with patients with larger baseline infarcts (ASPECTS 6–7) (42% versus 21%). High-quality collaterals (good-to-excellent) were associated with a median baseline ASPECTS of 9. A beneficial effect of endovascular therapy was observed over IV tPA alone across all levels of collateral flow, with the greatest effect in patients with excellent collaterals. Corroborating data from other trials, we were able to show that using a classification and regression tree analysis, optimal outcomes were achieved in patients with favorable baseline ASPECTS, complete/ near-complete recanalization (TICI 2b/3), and early treatment (mean mRS, 1.3 versus 3.7 in patients without these characteristics).

Chapter 4.3 describes the new imaging technique, multiphase CTA (mCTA) and shows that it can be performed with lower radiation, contrast dose and time compared to CT perfusion. In addition, interpretation of mCTA images have very high interobserver reliability and facilitate faster and reliable decision making in acute stroke. This imaging technique was used in the ESCAPE trial and is also being used in the ongoing ESCAPE NA1 trial. Single-phase CT angiography consistently resulted in underestimation of pial arterial filling when compared with multiphase CT angiography; thus, many patients with moderate pial arterial filling at multiphase CT angiography were labeled as having a poor score. Comparison of results of single- phase CT angiography, multiphase CT angiography, and perfusion CT in predicting a 50% decrease in NIHSS at 24 hours showed that the C statistic was highest for multiphase CT angiography. Single-phase and multiphase CTA showed much lower vulnerability to patient motion compared to CT perfusion.

Chapter 4.4 shows the results of a comparative analysis of regional collaterals (using mCTA) and CT perfusion imaging to predict tissue fate, i.e. whether the tissue progresses to infarction on follow up imaging. It showed no difference between mCTA and CTP to predict regional tissue fate in patients with acute ischemic stroke due to LVO. We were

able to demonstrate that washout parameter on mCTA was associated with follow-up infarct size in all prediction models based on mCTA. The Tmax parameter was significantly associated with follow-up infarct volume in all CTP models. The area under the receiver operating characteristic (ROC) curve for mCTA models ranged between 92% and 94%, whereas all CTP models had an area under the receiver operating characteristics between 90% and 92% (difference not statistically significant). The addition of recanalization/reperfusion and clinical parameters did not significantly affect the discriminative value of the models. Thus, between Chapter 4.3 and 4.4, we were able to show the effectiveness of mCTA in decision making as well as prediction of tissue fate. We were also able to show advantages of the technique over CTP.

Chapter 4.5 shows the results of the detailed imaging analysis (CT, CTA, MRI, MRA) performed for the HERMES collaboration. After the initial five trials, by the time of this analysis two additional trials (THRACE, PISTE) also joined the HERMES collaboration. For the first time, we were able to show benefit of EVT in patients with ASPECTS 3-5. While this may need to be further tested in randomized controlled trials, this may significantly extend the indications of imaging criteria eligible for EVT. All the imaging subgroups (ASPECTS, site of occlusion, clot burden score, collaterals, presence or absence of hyperdense MCA sign, greater than 33% of the MCA territory involvement) suggested benefit of EVT with no statistically significant interaction across sub-groups. Similarly, we found no treatment effect modification by baseline imaging features for mortality at 90 days.

Chapter 5: Optimizing systems of care

Chapters 5 presents a framework for organization of acute stroke care. In light of all the data presented in Chapters 2-4, it became clear that one of the greatest challenges going forward is getting the correct patient to the correct hospital as quickly as possible. Broadly speaking, taking the patient to a non-endovascular capable centre has the potential to delay EVT while expediting IV tPA. On the other hand, taking the patient directly to a further away endovascular capable centre, has the potential to delay IV thrombolytic treatment.

Chapter 5.1 presents the results of the mathematical model using data from the ESCAPE trial to create various geographical scenarios of how these varying factors would play out in patients with known LVO. We were able to show that all patients in close proximity (within 30 minutes driving distance) to the endovascular capable centre should be taken directly there and the primary stroke centres (endovascular non-capable centres) should be bypassed. We then extended the model to see the influence of potential future factors such as higher reperfusion rates, faster door to reperfusion times at the endovascular capable centre of potentially the development of a new drug with superior thrombolytic effect and clinical efficacy compared to alteplase and how these factors would influence decision making of whether to by the primary stroke centre or not.

Chapter 5.2 uses Google Maps to superimpose the data from Chapter 5.1 onto real-world maps. We created various scenarios for different time intervals, e.g. door to needle time at the primary stroke centre. In specific we created maps for Alberta, Ontario and California. These maps show that the Drip 'n Ship scenario is predicted to result in better or similar outcomes for these patients compared with Mothership only when the PSCs are able to administer alteplase within 30 minutes of hospital arrival. When the door to needle time at the PSC is longer, the Drip 'n Ship scenario is predicted to be beneficial only for those PSCs that are further away from the CSC. In addition, as shown in Chapter 5.1, the model allowed the study of how potential secular changes in stroke care (e.g. better reperfusion rates for EVT or faster door to reperfusion time at the endovascular capable centre) would influence decision making and organization of stroke care.

Chapter 6 Discussion

Chapter 6 provides an overview of the main findings of this thesis and discusses the methodological considerations, clinical implications and future perspectives.

In conclusion, work done in this thesis conclusively shows the benefit of EVT in patients with acute ischemic stroke due to large vessel occlusion. In addition, work in this thesis further corroborates the 'time is brain' paradigm and presents actual workflow data from various trials. It shows the substantive gains in workflow that were possible by various design and execution strategies. A new imaging technique, mCTA is described including results comparing it to CT perfusion. Multiphase CTA provides significant benefits such

as lower radiation dose, lower contrast requirement, faster and most consistent interpretation and ability to predict tissue fate regionally. Analysis data from various trials and meta-analysis shows the benefit of EVT in nearly all imaging subgroups including patients with ASPECTS 3-5. Lastly, a framework using current data from RCTs and mathematical modeling is presented to help optimize organization of stroke care.

Het herseninfarct is een ernstige en vaak voorkomende aandoening. In de Verenigde Staten krijgt elke minuut iemand een beroerte en iedere 3½ minuut overlijdt er iemand aan deze ziekte. Op dit moment zijn er 3 tot 4 miljoen Amerikanen in leven die een beroerte hebben doorgemaakt. In West-Europa en de VS overlijden ongeveer 30% van alle beroerte patiënten binnen enkele weken. Gedurende de laatste tientallen jaren hebben we een afname van het sterfterisico gezien. Beroertes komen waarschijnlijk nog vaker voor in ontwikkelingslanden.

Ongeveer 80% van alle beroertes in de westerse wereld betreft herseninfarcten. Herseninfarcten veroorzaakt door 'large vessel occlusion'' (LVO) zijn geassocieerd met de meest slechte prognose. Het effect van IV-trombolytica bij deze patiënten is beperkt.

Het primaire doel van dit proefschrift is het beschrijven van mijn onderzoek dat bedoeld was om nieuw bewijs te leveren voor de effectiviteit van endovasculaire behandeling (EVT). Een belangrijk tweede doel was het evalueren subgroepen mogelijk maken door het combineren van individuele patiëntengegevens uit verschillende gerandomiseerde onderzoeken in een groot bestand. Daarnaast onderzoek ik in dit proefschrift ook het belang van workflow en snelheid in de diagnostiek en behandeling van patiënten met een beroerte. Dit proefschrift moet beter inzicht leveren in de belemmerende factoren voor vroege behandeling, verbeteren van strategieën voor het gebruik van afbeeldend onderzoek, om snelle en betere besluitvorming te bevorderen en tot slot, om strategieën om zorgketens te verbeteren in het licht van het bewijs voor de effectiviteit van EVT. Het proefschrift bevat 4 onderdelen, namelijk Effectiviteit en veiligheid van endovasculaire behandeling (Hoofdstuk 2); Het belang van logistiek (Hoofdstuk 3); Beeldvorming en uitkomst (Hoofdstuk 4); en Optimaliseren van zorgpaden (Hoofdstuk 5).

Hoofdstuk 1 Inleiding

Hoofdstuk 1 bestaat uit een algemene inleiding. Het geeft een overzicht van de acute behandeling van herseninfarct en beschrijft de geschiedenis van reperfusie-behandelingen, van de eerste trombolytica tot aan de mechanische trombectomie. Het gaat in op mogelijke oorzaken voor het niet kunnen aantonen van een effect in de eerste generatie van gerandomiseerde onderzoeken en gaat in op mogelijke manieren om problemen en obstakels in de ontwerpfase van nieuwe studies te vermijden.

Hoofdstuk 2: Effectiviteit en veiligheid van endovasculaire behandeling van het acute herseninfarct

Hoofdstuk 2.1 beschrijft de resultaten van de ESCAPE-trial. Dit onderzoek toont aan dat patiënten met een acuut herseninfarct, die niet langer dan 12 uur tevoren nog zonder klachten waren en bij wie afbeeldend onderzoek een matige tot goede Alberta Stroke Program Early CT Score (ASPECTS) en aanwezigheid van een intracraniële proximale occlusie toont, betere functionele uitkomsten hebben na drie maanden als zij zijn behandeld met mechanische trombectomie. Het onderzoek is uitgevoerd in ziekenhuizen in Canada, Verenigde Staten, Zuid-Korea en Ierland. In het ontwerp en in de uitvoering van het onderzoek was er speciale aandacht voor logistiek. Tijdens de uitvoering van de trial liep een belangrijk kwaliteitsbevorderingsprogramma, gericht op verbetering van logistiek en diagnostiek. Van onderzoekers werd verwacht dat zij streefden naar een start CT tot lies tijd van minder dan 60 minuten, en tijd van start CT tot eerste reperfusie van minder dan 90 minuten. Daarnaast moesten alle patiënten beeldvorming ondergaan gebaseerd op CT, met gebruik van ASPECTS en beoordeling van collaterale circulatie, bij voorkeur met behulp van multifase CTA.

Hoofdstuk 2.2 beschrijft de resultaten van de SWIFT PRIME studie. Dit was een gerandomiseerde niet geblindeerde studie waarin het effect van endovasculaire behandeling met de Solitaire stent (Medtronic) werd onderzocht. In deze studie werden patiënten opgenomen met een indicatie voor behandeling met intraveneuze alteplase. De selectiecriteria op basis van beeldvorming waren vergelijkbaar met de ESCAPE-studie: aanwezigheid van een LVO en een relatief kleine infarctkern, bepaald met behulp van perfusie beeldvorming dan wel met ASPECTS. De resultaten lieten weer een substantieel effect

zien ten voordele van de interventie met een "number needed to treat" van 4 om bij 1 patiënt onafhankelijkheid van hulp (mRS 0-2) te bereiken. Bij de start van de studie was CT-perfusie (CTP) verplicht, maar na de eerste 71 patiënten niet meer. Het behandeleffect bleef bestaan, en was niet afhankelijk van het gebruik van CTP. De SWIFT PRIME trial was eveneens gericht op logistiek. De belangrijkste parameter was de tijd van start CT tot liespunctie. De studie was uitgevoerd in 39 verschillende centra in de Verenigde Staten en Europa. In de groep die met EVT was behandeld bedroeg de mediane tijd van afbeeldend onderzoek tot liesprik 57 minuten, en werd bij 88% van de patiënten substantiële reperfusie (mTICI 2b-3) bereikt.

Hoofdstuk 2.3 beschrijft de resultaten van de meta-analyse met individuele patiëntengegevens van de HERMES-groep, waarin de gegevens van de 5 gerandomiseerde trials die het effect van EVT toegevoegd aan de gebruikelijke behandeling onderzochten (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, EXTEND IA) zijn gecombineerd. Alle 5 trials maakten gebruik van moderne hulpmiddelen voor trombectomie (zogenaamde stent retrievers). Door het grotere aantal patiënten konden nu verschillende subgroep-analyses worden uitgevoerd (vroege versus late patiënten; matige versus goede ASPECTS; geslacht; verschillende leeftijdsgroepen en occlusielocaties). In alle subgroepen werd een gunstig effect van EVT gezien. De studie toonde een gunstig effect van de behandeling voor alle leeftijdsgroepen, zelf voor de zeer oude patiënten, hoewel leeftijd wel een ongunstige prognostische factor was. Het "number needed to treat" met EVT om minstens 1 niveau minder gehandicapt te zijn op de mRS was 2.6. De kans om overleden te zijn binnen 90 dagen na randomisatie was niet verschillend voor beide behandelgroepen, evenmin als het risico op een symptomatisch intracerebraal hematoom, of de kans op het ontstaan van een intracerebrale bloeding.

Hoofdstuk 3. Het belang van logistiek

Hoofdstuk 3.1 plaatst de evaluatie van logistiek in de IMS3 trial in een historisch perspectief. Deze evaluatie identificeerde verschillende knelpunten, tijdverlies op verschillende punten in het zorgproces, maar toonde ook het belang van het uitvoeren van een CT-angiografie. Deze resultaten waren van grote waarde voor het ontwerp en de uitvoering van de daaropvolgende trials. We konden aantonen dat het routinematig uitvoeren van CTA bij de evaluatie van de patiënt tijd bespaarde. Bovendien bleek dat patiënten die direct

werden gepresenteerd in het interventiecentrum ("mothership") sneller werden geëvalueerd, en een kortere begin tot interventie tijd hadden dan patiënten die waren overgeplaatst uit een ander centrum ('drip and ship'). In de studie waren deze tijden ook korter tijdens de weekends en na kantoortijd. Belangrijkst was echter de gewaarwording dat trage logistiek in de trial belangrijke aanknopingspunten vormde voor verbetering.

Hoofdstuk 3.2 beschrijft de logistiek in de ESCAPE-trial. De substantiële verbeteringen in snelheid en efficiëntie in vergelijking met vorige studies zijn hier vastgelegd. Daarnaast toont deze analyse dat het mogelijk om de tijd tot behandeling in twee episodes in te delen: begin van de verschijnselen tot eerste beeldvorming, dit beïnvloedt de kans op een prognostisch gunstige beeldvorming, en tijd van CT tot reperfusie, dit bepaalt de waarschijnlijkheid van een gunstige uitkomst. Het gebruik van algehele anesthesie was geassocieerd met een verlenging van de CT tot lies punctie tijd met gemiddeld 43% vergeleken met patiënten die geen algehele anesthesie ondergingen. Het gebruik van een "balloon guide" katheter as onderdeel van de endovasculaire techniek was geassocieerd met een verkorting van de tijd van liespunctie tot eerste reperfusie, van gemiddeld 21% (8 minuten). We toonden aan dat per 30 minuten verlenging van de CT tot reperfusie tijd de kans op een goede functionele uitkomst van de patiënt met 8.3% verminderde. Een statistisch significant verband tussen de tijd van begin van de verschijnselen tot beeldvorming en functionele uitkomst kon in geen van de trialarmen worden aangetoond.

Hoofdstuk 3.3 beschrijft de logistiek in de SWIFT PRIME studie. De belangrijkste resultaten waren: een dramatisch tijdsverlies door het 'drip and ship' paradigma in vergelijking met het "mothership" paradigma, tijdsverlies veroorzaakt door het uitvoeren van CT-perfusie, wat allemaal in tegenspraak was met het uitgangspunt "time is brain". Door middel van een streng kwaliteitsbeleid gedurende de uitvoering van de trial lukte het om de tijd van eerste beeldvorming tot liespunctie terug te brengen tot mediaan 52 minuten. Bij 61% van de patiënten werd de optimale tijdsduur van minder dan 70 minuten behaald. De kans op een goede functionele uitkomst voor patiënten die behandeld waren met trombectomie was 91% als reperfusie werd behaald binnen 150 minuten, maar deze nam af met 10% over het eerstvolgende uur, en daarna met 20% per uur. In een multivariabele analyse werd duidelijk dat eerste presentatie in een primair stroke centrum was geassocieerd met een gemiddeld 129 minuten latere aankomst in het interventie centrum. Deze tijden zijn direct gebaseerd op de tijdswaarnemingen die de trials, en derhalve niet gecorrigeerd voor

reistijd, werkelijke locatie van de patiënt, locatie van primaire stroke centrum en locatie van interventiecentrum.

Hoofdstuk 3.4 beschrijft de analyse van de logistiek in de gecombineerde data van de 5 gerandomiseerde trials (MR CLEAN, ESCAPE, SWIFT PRIME, REVASCAT, EXTEND IA). De odds op een betere functionele uitkomst namen af met langere tijd van begin van de verschijnselen tot lies punctie: common odds ratio (cOR) na 3 uur, 2,79; cOR na 6 uur, 1,98; cOR na 8 uur, 1.57) deze effecten bleven statistisch significant tot 7 uur en 18 minuten na begin van de verschijnselen, het tijdstip waar de ondergrens van het 95% betrouwbaarheidsinterval van de effectschatter kruiste met 1.0. Onder de patiënten bij wie goede reperfusie was bereikt, was een duidelijk verband tussen de tijd van begin van de verschijnselen tot reperfusie en verbetering van de functionele uitkomst na 3 maanden. Voor elke vertraging van 9 minuten tot reperfusie had 1 van elke 100 behandelde patiënten een slechtere functionele uitkomst, uitgedrukt als score op de mRS. De kans op een goede functionele uitkomst nam af van 64.1% bij een tijdsduur van begin van de verschijnselen tot reperfusie van 180 minuten, tot 46.1% bij een tijdsduur van 480 minuten. Ook in deze studie bleek het belang van het direct overbrengen van de patiënt naar het 'juiste' (interventie-)centrum, in plaats van gebruik te maken van het "drip and ship" paradigma.

Hoofdstuk 4. Beeldvorming en uitkomst

Hoofdstuk 4.1 beschrijft de analyse van de niet-invasieve angiografische beeldvorming (CTA) in de IMS III trial. Hoewel deze beeldvorming in minder dan de helft van de patiënten in dit onderzoek was uitgevoerd, bevestigden de resultaten het belang van deze beeldvorming; dit was van belang voor volgende trials. Bij de patiënten met een op CTA aangetoonde intracraniële occlusie was EVT plus IV tPA effectief in vergelijking met IV tPA alleen.

Hoofdstuk 4.2 beschrijft de analyse van de beeldvorming in de SWIFT PRIME trial. De studie leverde consistente gegevens over gunstige prognostische factoren bij patiënten met een acuut herseninfarct ten gevolge van een LVO: een kleine infarctkern (core), goede collateralen en goede reperfusie. De studie toonde aan dat kleinere infarcten op de eerste scan geassocieerd zijn met betere uitkomsten in behandelde patiënten dan in

onbehandelde (66% versus 41%) in vergelijking met patiënten met grotere infarcten (ASPECTS 6-7) bij randomisatie (42% versus 21%). Goede tot excellente collaterale circulatie was geassocieerd met een mediane baseline ASPECTS van 9. Een gunstig effect van EVT ten opzichte van IV tPA alleen werd waargenomen over alle niveaus van collaterale circulatie, met het grootste effect van de behandeling bij patiënten met excellente collateralen. Met behulp van classificatie en regressie analyse lukte het ons om aan te tonen dat optimale uitkomsten worden bereikt bij patiënten met een gunstige baseline ASPECTS, complete of bijna complete rekanalisatie (TICI 2b/3) en vroege behandeling (gemiddelde mRS 1.35 versus 3.73 voor patiënten zonder deze kenmerken).

Hoofdstuk 4.3 beschrijft een nieuwe beeldvormende techniek, multifase CTA (mCTA) en toont aan dit deze kan worden uitgevoerd met minder stralingsbelasting, contrast en tijdinvestering dan CT-perfusie. De interpretatie van mCTA beelden kent een zeer hoge "interobserver reliability" en bevordert daardoor snelle en betrouwbare besluitvorming bij patiënten met een herseninfarct. Deze techniek is gebruikt in de ESCAPE-trial en wordt nu ook gebruikt in de lopende ESCAPE NA1 trial. Enkel-fase CT-angiografie leidt tot onderschatting van de piale arteriële vulling in vergelijking met multifase CT-angiografie; dientengevolge zijn veel patiënten met matige piale vulling op multifase CT-angiografie onterecht op mono-fase CTA afgedaan als slechte collateralen. Van mono-fase CTA, multifase CTA en perfusie CT als voorspeller 50% reductie in NIHSS-score op 24 uur na randomisatie, toonde aan dat de "c-statistic" het hoogste was voor multifase angiografie. Monofase CTA was minder gevoelig voor patiënt bewegingen dan CT-perfusie.

Hoofdstuk 4.4 beschrijft de resultaten van een vergelijkende analyse van regionale collateralen met mCTA en CT-perfusie om uiteindelijke infarct grootte bij herhaalde beeldvorming te voorspellen. Er was geen verschil in de voorspellingen van infarctgrootte met mCTA en CTP in patiënten met een acuut herseninfarct door en LVO. We konden aantonen dat de "washout" parameter op mCTA was geassocieerd met follow-up infarct omvang in verschillende mCTA modellen. De Tmax parameter was op zijn beurt weer geassocieerd met follow-up infarct volume in alle CTP-modellen. Meest belangrijk echter was het dat de "area under the receiver operating (ROC) curve" varieerde tussen 92% en 94%, terwijl deze in alle CTP-modellen lag tussen 90% en 92%. Dit verschil was niet statistisch significant. De toevoeging van rekanalisatie/reperfusie en klinische parameters verbeterde de discriminatie van de modellen niet. Met behulp van de gegevens uit hoofd-

stuk 4.3 en 4.4 konden we het nut van mCTA aantonen als hulpmiddel voor klinische besluitvorming en als voorspeller van de mate van weefselschade. Bovendien konden we de voordelen van mCTA boven CTP demonstreren.

Hoofdstuk 4.5 beschrijft de resultaten van een gedetailleerde analyse van de beeldvorming (CT, CTA, MRI, MRA) die is uitgevoerd in de trials van de HERMES-groep. Toen deze analyse werd uitgevoerd waren nog twee soortgelijke gerandomiseerde onderzoeken toegevoegd aan het HERMES-samenwerkingsverband. Voor de eerste keer konden we daardoor het gunstig effect van EVT in patiënten met ASPECTS3-5 aantonen. Hoewel deze bevinding bevestigd moet worden in nieuwe trials, betekent het dat de indicatie voor EVT op basis van beeldvormingskenmerken verder kan worden uitgebreid. Voor alle subgroepen die kunnen worden gevormd op grond van beeldvormingskenmerken (ASPECTS, occlusie-locatie, "clot burden score", collateralen, hyperdens ACM teken, meer dan 33% betrokkenheid van het MCA stroomgebied) leek er een gunstig effect van de behandeling te bestaan, zonder significante interactie met het behandeleffect. Op dezelfde wijze werd evenmin effect modificatie door beeldvormingskenmerken gevonden ten aanzien van mortaliteit binnen 90 dagen.

Hoofdstuk 5: Optimaliseren van zorgpaden

Hoofdstuk 5 beschrijft een raamwerk voor de organisatie van acute beroerte zorg. De gegevens die zijn gepresenteerd in hoofdstuk 2 tot 4, maakten duidelijk dat de grootste uitdaging wordt om te zorgen dat de juiste patiënt in het juiste ziekenhuis wordt gepresenteerd, en wel zo snel mogelijk. Algemeen gezegd, door een patiënt naar een niet-interventiecentrum te vervoeren vertraagt men de mogelijke endovasculaire behandeling als die geïndiceerd blijkt, maar directe overplaatsing naar een (verder gelegen) interventiecentrum leidt tot vertraging in de behandeling met een intraveneus trombolyticum.

Hoofdstuk 5.1 beschrijft de resultaten van een rekenmodel, gebaseerd op data van de ESCAPE trial, waarmee de consequenties van verschillende geografische scenario's voor patiënten met een vastgestelde LVO worden beschreven. We beschreven dat alle patiënten in de nabijheid (binnen 30 minuten rijden) van een interventiecentrum direct daarheen zouden moeten worden gebracht, waarbij andere ziekenhuizen met alleen mogelijkheid voor intraveneuze trombolyse konden worden overgeslagen. We hebben vervolgens het

model uitgebreid om de invloed van mogelijke nieuwe ontwikkelingen, zoals een betere rekanalisatie, snellere deur tot reperfusie tijden, en de mogelijke ontwikkeling van medicijnen met sterker trombolytisch effect en klinische effectiviteit dan alteplase, op de afweging of overslaan door de ambulance van een primair stroke centrum gerechtvaardigd zou kunnen zijn.

Hoofdstuk 5.2 gebruikt Google Maps om de data uit het model beschreven in hoofdstuk 5.1 weer te geven. We ontwikkelden diverse scenario's met verschillende tijdsintervallen, zoals de "door to needle" tijd in het primaire ziekenhuis. We maakten kaarten voor Alberta, Ontario en Californië. Deze kaarten maken inzichtelijk dat volgens het model, voor deze patiënten het "drip and ship" scenario alleen resulteert in betere uitkomsten als de "door to needle time" korter is dan 30 minuten. Wanneer deze tijd langer is, dan is deze strategie alleen beter voor patiënten en primaire stroke centra die zeer ver weggelegen zijn. Ook op deze kaarten is goed te zien hoe verwachte nieuwe ontwikkelingen, zoals betere rekanalisatie na EVT of kortere "door to reperfusion" tijden in de interventie centra, de besluitvorming en organisatie van de zorg zouden kunnen beïnvloeden.

Hoofdstuk 6 Discussie

Hoofdstuk 6 geeft een overzicht van de belangrijkste bevindingen in dit proefschrift en bespreekt de methodologische aspecten, klinische implicaties en toekomstige ontwikkelingen.

Het werk dat in dit proefschrift is beschreven toont het gunstige effect van EVT voor patiënten met een acuut herseninfarct ten gevolge van een intracraniële proximale occlusie. De analyses en studies bevestigen verder het 'time is brain' paradigma en beschrijven logistieke gegevens van verschillende studies. Het laat de gezondheidswinst zien die kan worden behaald door het diagnostisch proces te verbeteren. Een nieuwe beeldvormende techniek, mCTA wordt beschreven, inclusief een vergelijking met CT-perfusie. De voordelen van mCTA betreffen een lagere stralingsdosis, minder benodigd contrast, snellere en meer consistente interpretatie en de mogelijkheid om de omvang van het infarct te voorspellen. Analyse van de data van verschillende trials en meta-analyse bevestigt het effect van trombectomie in alle subgroepen van patiënten gebaseerd op afbeeldend onderzoek, ook in patiënten met ASPECTS 3-5. Tot slot wordt een mathematisch model gepresen-

teerd dat de gegevens van de gerandomiseerde trials gebruikt en is bedoeld om de organisatie van stroke care te optimaliseren.

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Select Opinion Pieces And Editorials

2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials

Based upon:
2C or not 2C: defining an improved revascularization grading scale and the need for standardization of angiography outcomes in stroke trials
Mayank Goyal, Kyle M Fargen, Aquilla S Turk, J Mocco, David S Liebeskind, Donald Frei, Andrew M Demchuk
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INTRODUCTION

Although improvements in thrombectomy devices, stroke management and patient selection in clinical trials over the last two decades have occurred in concert with increasingly greater angiographic recanalization rates, clinical outcomes have remained largely unchanged.[1] For example, recently completed prospective trials using Stentriever technology have reported successful recanalization or reperfusion in upwards of 90% of enrolled patients, yet the percentage of patients with a good outcome at 90 days remains at only 35-55%.[2-4] The association between adequate recanalization and good functional outcome has been well-documented in a number of studies.[5-12] Furthermore, those making a dramatic recovery, defined as a decrease in the NIH Stroke Scale (NIHSS) score to ≤3 within 24 h, are more likely to have had early or more complete recanalization.[13]

However, the definition of 'successful' or adequate recanalization/reperfusion as an angiographic endpoint for treatment effect in such trials has become increasingly varied and confusing. The different grading scales and non-standardized definitions of successful thrombectomy reported in published stroke trials have made direct comparison of results difficult. In fact, some authors have called for increasing standardization of reporting among the stroke community using angiographic reperfusion to enhance generalizability.[14,15] In this paper we review the current grading systems for recanalization/reperfusion, discuss the current controversies in grading systems and the need for standardization of recanalization and reperfusion in trial reporting. Finally, we offer a revised grading system that accounts for less than perfect but clearly excellent reperfusion within its scale.

CURRENT REVASCULARIZATION SCALES

There are a number of proposed scales for documenting the degree of revascularization after acute stroke intervention. These include the Thrombolysis In Myocardial Infarction scale (TIMI)[16] recanalization, TIMI reperfusion, Thrombolysis In Cerebral Infarction scale (TICI),[17] the modified TICI scale,[18] the Mori reperfusion scale[19] and the Qureshi score,[20] among others. These scales have been reviewed in detail recently by Zaidat and colleagues, with discussion of the advantages and disadvantages of each of them.[14] From a practical standpoint, the utility of such grading systems is related to their ability to: create a common language for communication of results in the absence of illustrative pictures and diagrams; provide a means to compare across centers, studies, devices and operators; correlate the quality of revascularization with patient outcome or infarct size; and, probably most importantly, provide a guideline to the operators regarding when it would be appropriate to terminate the procedure even though perfect revascularization has not been achieved (ie, the old adage 'better is the enemy of good').

Table 1 Comparison of Thrombolysis in Myocardial and Cerebral Infarction (TIMI and TICI) scales

Score	Thrombolysis In Myocardial Infarction (TIMI) scale	Modified Thrombolysis in Cerebral Infarction (TICI) scale
0	No recanalization	No perfusion or anterograde flow beyond site of occlusion
1	Minimal recanalization	Contrast passes the area of occlusion but fails to opacify the entire cerebral bed distal to the obstruction during angiographic run
2	Partial recanalization	Partial perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower than non-involved territories 2A: Partial filling only (<50%) of territory visualized* 2B: Partial filling ≥50% of territory is visualized†
3	Complete recanalization	Complete reperfusion with normal filling

*2A is represented by partial filling, less than two-thirds of the ischemic territory, in the original TICI scale.
†2B is represented by complete filling that is slower than normal in the original TICI scale.

The two most commonly used scales for documenting the results of revascularization strategies in acute stroke treatment are the TIMI and TICI scales. These scales share similar traits and are shown for comparison in table 1. The utility of these two scales over

other reported grading systems lies in their widespread popularity and ease of use, as well as their use in the majority of intra-arterial thrombectomy trials to date (table 2).

The TIMI score is a simple to use scale that focuses only on the site of occlusion and the rapidity of anterograde flow seen at that segment. However, this scale is limited by its inability to account for distal perfusion or the degree of collaterals present. The TICI score, in contrast, is more complicated but evaluates the degree of perfusion of the ischemic territory after recanalization. This system indirectly assesses the collateral flow by addressing the amount of total territory that has been reperfused, but it does not directly assess collateralization. Due to the inherent limitations in the assessment of perfusion of the distal territory, the TICI scale is much more complex and has been further divided into subcategories within partial perfusion. Both scales are limited by their inability to address the site of occlusion or the eloquence of the tissue within the ischemic territory.[14]

Table 2 Revascularization grading in intra-arterial stroke intervention studies

Stroke study	Definition of successful revascularization
PROACT, 1998[21]	TIMI grade 2 or 3
PROACT II, 1999[22]	TIMI grade 2 or 3
IMS I, 2004[6]	TIMI grade 2 or 3
MERCI, 2005[23]	TIMI grade 2 or 3
IMS II, 2007[7]	TICI grade 2 (2A or 2B) and 3
Multi MERCI, 2008[24]	TIMI grade 2 or 3
Penumbra Pivotal, 2009[8]	TIMI grade 2 or 3
RECANALISE, 2009[9]	TIMI grade 2 or 3
SARIS, 2009[25]	TIMI grade 2 or 3
TREVO 2, 2012[4]	TICI grade 2 (2A or 2B) and 3
SWIFT, 2012[2]	TIMI grade 2 or 3
IMS III, unpublished[18]	TICI grade 2 (2A or 2B) and 3

IMS, Interventional Management of Stroke; TICI, Thrombolysis In Cerebral Infarction scale; TIMI, Thrombolysis In Myocardial Infarction scale.

VARIABILITY IN TRIAL REPORTING

A close review of the best prospective intra-arterial thrombolysis or thrombectomy trials to date demonstrates the lack of standardization in reporting (table 2). Of 12 trials, nine used the TIMI grading system while the remaining three studies (including the unpub-

lished Interventional Management of Stroke III study) used the TICI grading scale. Furthermore, only two-thirds used blinded core laboratory adjudication.

Further confusing the picture is the lack of association between recanalization and clinical outcomes in some studies. For instance, in the Penumbra Pivotal Stroke Study, TIMI grade 2 or 3 recanalization was seen in over 80% of patients but good outcome at 90 days occurred in only 25% of patients, in contrast to prior studies showing lower recanalization rates but better clinical outcomes.[8] Others have argued that the original TICI scale itself is confusing, and there are specific situations where the TICI scale fails to adequately characterize angiographic results.[26,27] For instance, should a revascularized middle cerebral artery (MCA) territory, with slow filling of the MCA compared with the anterior cerebral artery territory yet a late arterial opacification of nearly all of the MCA region, be best represented by TICI 2A or 2B? Additionally, with the original TICI scale, how do you correctly categorize revascularization when it is more than two-thirds of the territory but not 'complete' filling?

There has been a lack of consensus on which scale should be used, and even the most recent studies on the subject (TREVO2 and SWIFT) used different scales. In addition, the definition of good or successful recanalization has varied across studies. Some studies have used 0 and 1 as poor recanalization and 2 and 3 as good recanalization, while other studies have used 2B and 3 as successful recanalization. There has been a difference in interpretation of final angiograms across many studies and many datasets, with participating centers generally reporting higher rates and quality of recanalization compared with core laboratory review.[2]

In general there is a lack of standardization with regard to: (1) what scale to use; what constitutes successful or adequate revascularization within that scale; and individual operator interpretation of the angiograms, given the significant inter-observer variability.

The next obvious questions are: (1) why do different studies use different grading parameters and (2) does the lack of uniformity in reporting matter?

There are probably several reasons for the discordant measurement and reporting of revascularization in stroke trials. First, trial designers may choose a scale that makes their data appear to have the greatest effect on revascularization, especially if the purpose of the study is to get USA Food and Drug Administration approval for a new device. For instance, devices that lead to excellent local recanalization but result in frequent distal emboli may appear better when evaluated by the TIMI scale than with the TICI scale. Second, there are probably inherent differences in operator or study designer preferences in measurement. Such preferences may be related to both prior training and experience in stroke trials as well as the fundamental goal of the proceduralist-to remove the clot and recanalize the vessel versus the re-establishment of cerebral perfusion. While this difference may seem merely an issue of semantics, the goal of the proceduralist has important implications on the assessment of adequate treatment and for termination of the procedure once the goal has been obtained. Many interventionists favor recanalization over reperfusion as an endpoint because re-establishment of territorial perfusion is dependent on many other factors beyond the patency of the vessel that was occluded. For instance, factors that are distinct from the site of the thrombus and have little to do with the technical success of the thrombectomy procedure-such as the size of the ischemic territory and quality and robustness of collaterals-may significantly influence perfusion scoring. In an ideal world one would be able to determine whether the region of poor perfusion is salvageable or not and use that information to decide whether to continue with efforts to 'improve' the regional perfusion. However, given that the stroke community has not yet developed methodology to measure the size and location of the infarct during angiography, this remains a challenge.

To address the question whether uniform reporting is necessary, there is little argument that increased uniformity of scales across different studies is more desirable. Furthermore, improvement of our current scales to adequately quantify reperfusion may help to control for a number of important factors such as the presence or absence of collateralization. Standardization of revascularization measurement and reporting has few, if any, negative consequences. Uniform reporting of adequate recanalization/reperfusion will allow for direct comparison of angiographic success between trials and help to control for highly variable patient anatomy and collateralization when assessing technical thrombectomy success. Finally, standardization of reporting such that all trials use blinded core laboratory adjudication is necessary to control for interobserver variability and proceduralist

bias. Currently, given that the two most common revascularization scales feature different criteria and evaluate different phenomena, we support the argument that journals should mandate reporting of both TIMI and TICI scores for stroke trials.

RECANALIZATION, REPERFUSION OR BOTH?

Arteriographic demonstration of flow restoration or revascularization has two distinct components (recanalization and reperfusion) that are not measured simultaneously with any existing scale. All endovascular trials should therefore measure and report both components in a consistent fashion. Recanalization of the primary arterial occlusive lesion is best measured with the TIMI recanalization scale focused on the most proximal arterial occlusive lesion. Reperfusion past the occlusion into the distal arterial bed and terminal branches is best assessed with the TICI scale.[27] Both components should be evaluated in all endovascular studies.

OPTIMIZING REPERFUSION ASSESSMENT WITH A REVISED TICI SCALE INCLUDING 2C

There is a general consensus that the use of modern stroke devices, most notably the Stentrievers, has improved the frequency and quality of recanalization.[2,4] However, due to the presence of the infarct core and the occurrence of distal emboli, particularly as documented with recent expanded Stentriever use,[28,29] achieving TIMI or TICI 3 flow remains relatively infrequent. This is especially true when the post-procedure angiogram is being evaluated by an experienced core laboratory. However, the frequency of near-perfect reperfusion has dramatically increased in recent years. Currently, the modified TICI score does not differentiate between perfusion of 51% of the ischemic territory and complete perfusion except for the presence of a small distal embolus (95% reperfusion). Patients with small distal emboli after complete recanalization and reperfusion are currently labeled as TICI 2B, yet very likely exhibit a clinical outcome closer to those with complete reperfusion (TICI 3). To address this issue in the past, Noser and colleagues generated a revised TICI scale including 2C, which they defined as 'near complete perfusion without clearly visible thrombus but with delay in contrast run-off'.[30]

To account for near-perfect results, we have started using the term TICI 2C for situations when the angiogram is nearly normal but one or two of the M4 branches demonstrate slow flow or a tiny distal embolus. Similar to Noser's TICI scale, the 2C designation categorizes those patients who have abnormal angiographic findings but probably with minimal clinically significant implications. A revised TICI scale is shown in table 3. Why is this new designation of potential importance?

Table 3 Proposed revised Thrombolysis In Cerebral Infarction scale (TICI) scale including a 2C designation

Score	Revised TICI
0	No perfusion or anterograde flow beyond site of occlusion
1	Penetration but not perfusion. Contrast penetration exists past the initial obstruction but with minimal filling of the normal territory
2	Incomplete perfusion wherein the contrast passes the occlusion and opacifies the distal arterial bed but rate of entry or clearance from the bed is slower or incomplete when compared with non-involved territories
2A	Some perfusion with distal branch filling of <50% of territory visualized
2B	Substantial perfusion with distal branch filling of ≥50% of territory visualized
2C	Near-complete perfusion except for slow flow in a few distal cortical vessels or presence of small distal cortical emboli
3	Complete perfusion with normal filling of all distal branches

First and foremost, this designation very likely correlates much better with patient outcome (although this would be highly dependent on other factors including size of core, rate of infarct growth, efficiency of recanalization from the time of imaging and brain eloquence). The idea that a patient with one small distal cortical embolus is equivalent to a patient with 51% reperfusion through recanalization of a large anterior division (and therefore probably remains aphasic and hemiplegic) is a major limitation of the current methodology. It is highly likely that this is a significant (though not the sole) cause of the disassociation between angiographic and clinical outcomes. Furthermore, the scale can sometimes influence the procedure. If physicians feel TICI 2B is generally the definition of success and that TICI 3 is unlikely, they may be more likely to accept a 50-60% reperfusion and not attempt to reperfuse remaining critical ischemic tissue. By capturing those patients with near-perfect treatment results, this scale would also provide a better means of comparing new thrombectomy devices that achieve high recanalization rates. At our centers we are already using this designation locally as a means of communicating

a near-perfect angiographic result. For instance, what we would previously refer to as 'better than a TICI 2B, but not perfect', we now refer to as a TICI 2C.

PRIMARY DEVICE REVASCULARIZATION ASSESSMENT

In the era of thrombectomy devices, some standardization of evaluation is needed to determine the magnitude of revascularization achieved by the primary thrombectomy device in question, especially when the endovascular procedure is often 'contaminated' by other subsequent ancillary treatments (second thrombectomy device, distal clot manipulation or intraclot or regional thrombolytic administration). A primary device TICI and TIMI arterial occlusive lesion recanalization assessment should be performed once the primary thrombectomy device has been abandoned before ancillary therapies are initiated. This standard approach is now very feasible since primary thrombectomy is the first major endovascular procedure in most cases.

POST-PROCEDURE ANGIOGRAPHIC REASSESSMENT

An additional point to consider when discussing the quality of revascularization obtained is the concept of delayed angiographic reassessment. As continued flowing blood is an excellent thrombolytic, it is possible that the quality of the flow may continue to improve after the procedure is over. On the other hand, the use of intraluminal devices introduces the possibility of intimal injury and platelet activation that can potentially lead to reocclusion after the procedure is concluded. As an example, acute thrombotic complications have been shown to occur in the 30 min following cerebral stenting.[31] As the revascularization is subject to change following thrombectomy, it may be worthwhile evaluating the stability of the revascularization in a delayed fashion, such as 5-10 min after completion. Standardization of delayed post-procedure angiography could potentially be another means of improving the accuracy of the revascularization that is reported.

CONCLUSIONS

The measurement and reporting of revascularization remains variable. To improve the generalizability of procedural results following thrombectomy, we advocate uniform reporting standards. Journals on stroke should mandate reporting both TIMI and TICI grading systems in published trials. In addition, we advocate a revised TICI scale that includes a 2C designation to describe those patients with near-complete reperfusion except for slow flow in one or two distal cortical vessels or the presence of minor distal emboli. This designation would assist in defining an endpoint for treatment success as well as improving comparisons between Stentriever technologies. Finally, we suggest delayed angiographic reassessment as a means of controlling for thrombolytic or thrombogenic phenomena that may occur immediately after completion of the procedure and may potentially influence the clinical outcome.

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Dramatically Reducing Imaging-to-Recanalization Time in Acute Ischemic Stroke: Making Choices

Based upon:
Dramatically Reducing Imaging-to-Recanalization Time in Acute Ischemic Stroke: Making Choices
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In the treatment of acute stroke, we are reasonably sure of certain issues. These are the following:

1. Dead brain is dead brain. Infarcted brain tissue cannot be salvaged.[1] So far, no attempts at neuroprotection have been successful.[2] These issues are relevant from the perspective of the detection of irreversibly damaged brain tissue. Various imaging methods have been shown to be reasonably good at detecting dead tissue (DWI,[3] Alberta Stroke Program Early CT Score [ASPECTS] on NCCT,[4] low CBV or very low CBF on CT/MR perfusion,[5] and so forth). Of these, DWI is the most sensitive and specific, though not perfect.[6]

2. Hyperacute stroke is a dynamic process. In the absence of recanalization, it has been well demonstrated that for most strokes, the ischemic core grows to incorporate the penumbra with time.[7] While exuberant collaterals might prolong the penumbral tissue survival, our ability to sustain these with medical intervention has not been successful.[8]

3. Recanalization helps. This has been the basis of not only IV thrombolytic therapy but also mechanical intra-arterial (IA) approaches.[9]

4. No form of intervention, chemical or mechanical, is without risk.[10-12]

5. Imaging is a snapshot in time of a dynamic process.

On the other hand, there are issues that we do not fully understand. The key ones are the following:

1. What is the rate of infarct progression? At what rate does penumbra turn into core? Which factors influence this rate? How much time does one have before recanalization becomes futile?

2. Do collaterals evolve with time and to what extent? Changes in the length and diameter of collaterals have been demonstrated in animal models, but this process is less well-understood in humans.

3. What is the role of spreading depression?[13] This loss of electrical activity and the associated biochemical and structural alterations, classically described in migraine, may have a role in the ischemic core progression.[14]

4. How does selective vulnerability of neuronal tissue influence patient outcome? It is well-known that certain brain regions are more susceptible to ischemia than others, but the mechanisms underlying this vulnerability and their effect on infarct progression and patient outcome are not understood.[15]

5. What is the best measure of penumbra? This question assumes that the tissue measured conforms to the penumbra definition: nonfunctioning tissue that is currently viable but will die unless blood supply is resumed quickly (please note that in this definition, there is no mention of how much time there is before penumbra dies).[16]

Other relevant issues are related to the imaging technique that is the best, most appropriate, most widely available, and easiest to interpret. At one end of the spectrum is NCCT, which is sufficient for triage and decision-making and has been extensively studied.[17] Most large randomized controlled trials, including the National Institute of Neurological Disorders and Stroke rtPA Stroke Study Group,[18] European Cooperative Acute Stroke Study,[19] and International Management of Stroke-III,[20] used NCCT. At the other end of the spectrum are DWI, perfusion, and MRA.[6] MR imaging has been used in a number of trials including the Desmoteplase in Acute Ischemic Stroke Trial,[21,22] the Echoplanar Imaging Thrombolytic Evaluation Trial,[23] the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution Study,[24] and the ongoing Magnetic Resonance and Recanalization of Stroke Clots Using Embolectomy trial.

These modalities have pros and cons, but most notably, NCCT has the big advantage of convenience (fast, available around the clock, no contraindications) and is supported by evidence from acute stroke trials, while MR imaging is sensitive to identifying the site and extent of early ischemic changes but requires screening for potential contraindications and requires patient cooperation (difficult in an acute stroke setting). In our opinion, the biggest limitation of the MR imaging-based approach is the amount of time it takes to perform the studies. Some centers have developed protocols lasting only 5-7 minutes,[25]

but the total time required from when the test is ordered until all data are postprocessed can exceed 30 minutes.[26]

Recently, there have been significant advances in mechanical IA therapy (the Merci retriever, Concentric Medical, Mountain View, California; the Penumbra System, Penumbra, Alameda, California; Solitaire, ev3, Irvine, California; and so forth).[27] Studies using these devices have consistently shown rates of recanalization approaching 90%.[28] These devices are being used in severe strokes and in proximal artery occlusions. However, these high recanalization rates are not reflected in the rate of functional recovery, which still lags behind.

Of all mentioned items, in our opinion, these are clear:

1. Most infarcts grow over time.
2. We are not good at determining their rate of growth.
3. Early recanalization prevents infarct growth and can lead to better patient prognosis.
4. We are reasonably good at determining the initial size of the infarct core.
5. Newer devices achieve high recanalization rates in patients with large-vessel occlusions.

If we accept these statements as true, we can infer that as soon as a patient is suspected of having an acute ischemic stroke with a small core and proximal vessel occlusion, every attempt should be made to minimize imaging-to-recanalization time because this affects infarct growth. Here, we suggest a protocol to achieve an imaging-to-recanalization time of <60 minutes. After a hemorrhage is excluded, the following steps could be taken:

1. CTA (5 minutes)
2. CT perfusion and postprocessing (15 minutes)

3. Brain MR imaging (45 minutes; this includes ruling out contraindications, doing necessary paperwork, taking the patient to MR imaging, achieving patient cooperation, performing the imaging, and postprocessing). Even though there would be some variability from center to center, in most centers, this protocol takes approximately 45 minutes, leaving only 15 minutes to achieve recanalization.

As soon as imaging is assessed, one must perform the following:

1. Start IV tPA if appropriate (10 minutes).
2. Obtain consent for IA therapy in case it will be necessary (10 minutes).
3. Plan for DSA.
4. Assess patient cooperation and involve anesthesia if necessary (20 minutes).
5. Prep the patient (10 minutes).
6. Obtain vascular access and perform DSA (10 minutes).
7. Achieve recanalization (10 minutes).

To achieve recanalization in <60 minutes, one must make choices and compromises. Is MR imaging really needed? It could be argued that without MR imaging, it is impossible to determine core size precisely. While this is correct, what degree of precision is required? The degree of core estimation on NCCT by using the ASPECTS methodology has been well-tested and validated.[29] Web sites are available to aid in becoming proficient at using this system (aspectsinstroke.com). Optimization of the newer CT scanners allows excellent gray-white differentiation without significant increases in radiation doses.[30]

Is CTA really needed? We believe that it is worth the time spent. Overall, little additional time is needed if the patient is already on the CT table. While there are concerns regarding contrast-induced nephropathy, it has been shown that these are not significant.[31] Benefits of CTA include the following: 1) confirming the presence of proximal occlusion, 2) core assessment on CTA source images,[29,32] 3) collateral circulation assessment,[33] and 4) dis-

playing arch anatomy that may facilitate DSA. Other benefits include ruling out possible contraindications to IA therapy, such as unstable aortic thrombus, and documenting the presence of arterial dissections.

Is CT perfusion really needed? While it helps to define core size, estimate penumbra presence and size, and determine the presence of collateral circulation, we suggest that it is not worth the time spent on it.[34] There is a lack of standardization of protocols and post-processing techniques across vendors.[35] The best parameter to define penumbra is not clear,[5] and there is no consensus about it. Perfusion does not answer the question of the rate of infarct progression.[36] Radiation dose may be an issue in younger patients, especially if whole-brain coverage is obtained.[37] Patient cooperation is important for image quality.

Is anesthesia really needed? This easily adds 20-25 minutes, leaving only 40-45 minutes to achieve recanalization. Additionally, a number of recent publications warn against the potential harm of general anesthesia.[38] While some interventionists think that performing these complex procedures without it may increase complication rates, this is not true in our experience in which conscious sedation is adequate.

Is a complete diagnostic DSA really needed? While it has merits (assessment of collaterals and so forth), it takes time, easily 10 minutes and, in our opinion, provides very little additional information. We favor going straight to the vessel of interest.

One could also argue that an IA treatment approach is not necessary. However, multiple studies have shown poor recanalization rates with IV tPA alone in proximal occlusions.9 It is difficult to precisely determine how long it takes to achieve recanalization with IV approaches. Moreover, if the aim is to achieve an imaging-to-recanalization time of <60 minutes, one may need to try multiple approaches simultaneously. Safety is paramount, and one should not gain efficiency at the expense of safety.

The issue of a well-informed consent in emergency situations still remains controversial.[39] While a stroke neurologist discusses the consent, the interventionist should proceed with preparation of materials, assuming that the consent will be obtained. Obtaining consent for inclusion in a trial can slow down the process, especially if the procedure itself is being tested.

Therefore, in our opinion, in patients with clinically large ischemic strokes, focusing on imaging-to-recanalization time makes the most sense. We think that spending time on CTA is worth the information it provides. MR imaging, while excellent at determining core, takes too long. The verdict on CT perfusion is not clear, but we favor avoiding it. General anesthesia may be avoided unless absolutely necessary, and a complete diagnostic angiogram may not be required. Mechanical approaches to recanalization may be preferable to systemic treatments.

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Amartya Sen and the Organization of Endovascular Stroke Treatment

Based upon:

Amartya Sen and the Organization of Endovascular Stroke Treatment

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The term famine refers to an acute period of widespread death resulting from starvation. The traditional thinking is that this occurs because of shortage of food. However, in Poverty and Famines: An Essay on Entitlement and Deprivation, Nobel Laureate Amartya Sen argues that, when examining starvation and famines, individuals' ability to acquire food (what he calls entitlement) is a distinct and equally important contributor to hunger.[1] This claim underpins his criticisms of the Food Availability Decline view of famines, which attempts to explain famines in supply terms only. Sen's original study examined the 1943 famine in Bengal, which resulted in the deaths of >3 million persons. The findings of the contemporaneous Famine Inquiry Commission attributed this famine to a major shortage of rice. After reevaluating the available data, however, Sen concluded that the overall quantity of rice in Bengal was not exceptionally low, even surpassing the supply of previous years. This famine demonstrates that people's ability to acquire food is dominantly related to distribution rather than the absolute total amount of food available in a region.

With recent advances in acute ischemic stroke treatment leading to endovascular treatment becoming the standard of care,[2] there has been much discussion on shortages of availability of this treatment. Similar to Sen, we need to have a better understanding of the underpinnings of this perceived shortage to develop relevant and long-term solutions to the problem. One could naively assume that increasing the number of neurointerventionalists or the number of biplane angiography suites would solve the problem. This may be far from the truth. It is possible, even probable, that the current perceived shortage may be principally a problem of distribution rather than an issue of overall availability of angiography equipment or trained personnel. If this is true, a sudden increase in training more neurointerventionalists or putting in more biplane angiography suites (without properly understanding the underlying causes) has the potential to worsen stroke outcomes. Why?

First, urbanization is occurring at a greater pace globally. There has been a desire to live in big cities, as reflected by an increase in urban/suburban populations and a decrease in rural populations. In a given city, given the intensity of providing stroke on-call services, a critical mass - a team - of trained personnel is needed in each hospital providing stroke services. No one wants to be the first and only one providing a 24/7 service in a given hospital. The expense or business case around a biplane angiography suite (and a commensurate trained technical and nursing staff, requiring creation of a 24/7 schedule) is

easier to justify when there are other institutional needs that are similar (Interventional Radiology; Interventional Cardiology). Finally, there are preexisting artificial geographical/political boundaries that affect flow of patients. These are not always patient centric; they can be based on historical referral patterns, insurance, tradition, funding of the ambulance system, and competition between centers. Thus, a neurointerventional program can only form in a large city with adequate population to sustain it, but its viability will be affected by multiple other factors.

Second, the success of the neurointerventional stroke program is dependent on the overall stroke system of care. Mathematical modeling of field triage and transport systems for patients eligible for interventional treatment suggests that various workflow factors influence the 90-day outcome.[3] A short door-to-needle time (30 minutes median) is a pre-requisite for a drip-and-ship model of care for most transport scenarios. Longer times favor a direct-to-comprehensive center strategy. Raising the success for complete reperfusion (Modified Treatment in Cerebral Ischemia score 2b/3) to 90% tilts the favored strategy toward a direct transport to a comprehensive stroke centre (CSC) with endovascular capabilities, bypassing the primary stroke center (PSC). Currently, the bar for accreditation of stroke centers in thrombolysis, which is set at a target median 60 minutes door-to-needle time, is too low.[4] Current efforts to improve training, technique, and technology for endovascular treatment may evolve faster than the efficiency of alteplase (tissue-type plasminogen activator) treatment at the PSC. This would further favor the evolution to a stroke system of care with direct transfer to a CSC. A key factor in deciding how to route patients will be measuring and reporting interval treatment times and endovascular reperfusion rates at both the primary and comprehensive stroke centers. Hospital report cards are going to be needed to make system-wide triage and transport policy decisions.

If we now consider all possible patients with stroke syndrome presentation (rather than the simpler case described above of only those eligible for intervention), we must critically consider the ability to detect large vessel occlusion (LVO) in the field. Although there are many scoring systems described, they all have only moderate specificity and sensitivity. Furthermore, the definition of a treatable LVO is a moving target as more and more institutions are treating large M2 and A2 occlusions despite limited evidence. Future innovation to detect potential candidates for endovascular treatment at the time of first medical contact may include video conference calls, wearable technology such as

Google Glass, decision support tools, real-time information about transport distances and resources (eg, the immediate availability of a helicopter), and use of mobile computed tomography ambulances. These innovations will generate a need to overcome genuine concerns on privacy and confidentiality issues. If these efforts are implemented successfully, it may be possible that suspected patients with LVO could be treated medically in the field and go directly to the CSC (up to a certain distance which can be pre-determined based on mathematical modeling) while patients with stroke who have a low likelihood of LVO are routed to the PSC. Of course, it is likely that there will be false-positive referrals to the CSC that can lead to new challenges at the CSC (increased load in the emergency department, additional resources for managing minor strokes, etc). Such a process, may have unexpected consequences. With declining volumes, PSCs may lose efficiency and become less expert in treating major acute stroke.

Third, the population distribution in a particular area will and should influence the placement of stroke centers. There would be absolutely no point to have a PSC within 10 minutes' travel distance of a CSC (in theory, a CSC should be better at treating all strokes, including minor strokes or hemorrhagic strokes). What about 20 minutes' travel time? What about 30? What should be the cut-off of travel time after which it becomes justified to have a PSC? Let us say that distance is 60 minutes. However, at 60 minutes from the CSC (circumferentially), the population density is generally exceedingly low and often rural. If this decrease in population density is evenly distributed, there may be a need to have several PSCs to cover the area, which could be impractical. The issues related to a small town of 100 000 to 250 000 population are also unique. These towns have a strong desire to have a medical infrastructure capable of dealing with emergencies. However, with that population base, what is the likely frequency of LVOs per year? Would that allow for a sustainable CSC? Even if there existed the will and resources to design and fund a CSC, would it attract a critical mass of neurointerventionalists and stroke specialists to provide high quality care?

Fourth, a plethora of quality assurance work in medicine from other fields makes it abundantly clear that the quality of endovascular stroke treatment (including efficiency, quality of imaging, decision making, quality and efficiency of intervention, and aftercare) will be directly related to patient volume. A center treating 100 patients a year is likely to have an efficient workflow compared with a center treating only 5 to 10 per year. For lower

volume centers, it is possible that in a desperate attempt to increase volumes (and remain sustainable), an increasing number of inappropriate patients will be treated, thus negating potential benefits and possibly increasing side effects.

Fifth, stroke is a complex disease and is best treated by a multidisciplinary team where the neurointerventionalist is a component part of a large group of medical professionals.[5] In acute stroke care, there are several critical processes that must be learned to enable the team to function in a coordinated manner.[6] There is sufficient heterogeneity of disease pathophysiology, individual patients, and circumstances to which the team must adapt. The process of decision making is also significantly more complex than acute coronary syndromes, and these include variables such as patient age, pre-morbid neurological and functional status, expectations of outcome, time from onset, imaging factors (size of core, site of occlusion, quality of collaterals), and access factors (tortuosity, peripheral vascular disease). Other factors, such as team and room availability and need for anesthesia, play an important role as well. The importance of having a fully developed plan for post-procedure care cannot be understated. Having a well-functioning stroke unit has been shown to be beneficial. Access to good rehabilitation therapy is critical for good/excellent functional outcomes. Finally, the team will measure its performance using process measures (interval times), appropriateness, and outcomes.

In addition to the factors mentioned above, we acknowledge and accept that there are likely additional factors unique to emerging countries, including (but not limited to) availability of trained personnel, reimbursement and payment issues, issues of affordability, and transportation issues. These factors, while beyond the scope of the current discussion, deserve a detailed discussion as well.

In sum, stroke treatment outcomes would likely be diminished in the absence of a diverse, multidisciplinary team of health professionals - neurointerventionalists cannot work effectively in isolation.

Endovascular treatment of stroke is a powerful treatment backed by several multijurisdictional randomized controlled trials.[7–11] The number-needed-to-treat is in the range of 2.5 (which is dramatic and rare in the practice of medicine). As a collective, we have an obligation to provide this treatment to the population in the best possible manner. If there

were suddenly 100 more neurointerventionalists or 50 more angiography suites in the United States without giving thought to their distribution, the situation could actually be made worse than it currently is. If these resources are allocated to so-called rich areas (that already have adequate resources), it may worsen care by diluting the experience and ability to have high volume, well-oiled, sophisticated multidisciplinary teams. Similar to the ideas put forth by Amartya Sen, this seems in some ways obvious and commonsensical….or is it? Will we be smart enough to broadly recognize these problems and their potential solutions or is there a need for legislative policy to guard against these issues of maldistribution? Will we be flexible enough to change our systems when new treatments, such as drugs to protect the penumbra during transport, new medical treatments to promote reperfusion, or new devices to achieve greater levels of reperfusion change the dynamics of stroke care?

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The Need for Better Data on Patients with Acute Stroke Who Are Not Treated Because of Unfavorable Imaging

Based upon:
The Need for Better Data on Patients with Acute Stroke Who Are Not Treated Because of Unfavorable Imaging
M. Goyal, B.K. Menon, M.A. Almekhlafi, A. Demchuk, and M.D. Hill
AJNR Am J Neuroradiol. 2017 Mar;38(3):424-425

There are 2 "epochs" of time in acute ischemic stroke caused by large vessel occlusion: onset to imaging time, which is deterministic of the likelihood of favorable imaging (mild to moderate early ischemic changes [ASPECTS 6-10]), and imaging to reperfusion time, which is deterministic of the likelihood of a favorable outcome.[1] But what factors influence whether a particular patient with an acute stroke caused by large vessel occlusion will have favorable imaging? What is the rate at which the brain dies after stroke onset? What factors influence the velocity of irreversible infarction?

Ten minutes after stroke onset caused by large vessel occlusion, all patients will have a small core and sizeable penumbra. At the other extreme, in nearly all patients at 24 hours after stroke onset, the infarct will have expanded to its maximum volume and there is no penumbra. The decay curve for growth of infarct (expansion of core, reduction of penumbra) for an individual patient begins at 100% salvageable brain (zero core) at onset and follows a variable downward curve to reach 0% salvageable brain at a certain point (Figure).[2,3]

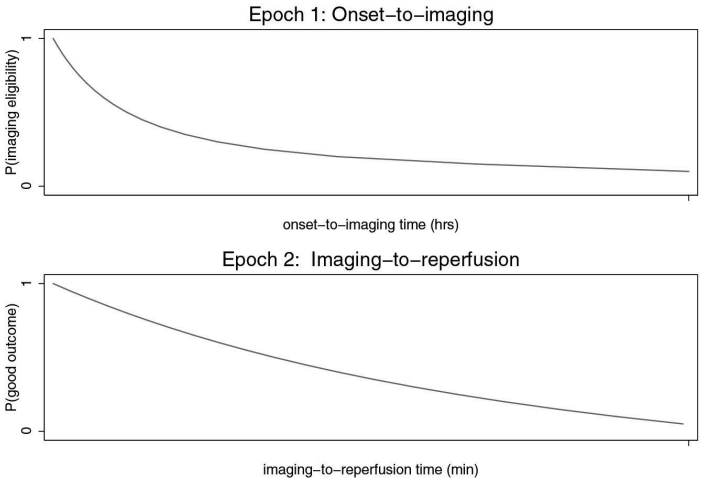

FIGURE. Interval times in acute stroke (modified from Hill et al[17]). With increasing data, we have a good understanding of the second curve (imaging to reperfusion). However, our understanding of the first curve remains limited because of a paucity of appropriate data.

Some patients are likely "fast progressors" (with favorable imaging only very early) and others are "slow progressors" (with favorable imaging even at late time windows). The biologic infarct growth curve could also be linear, parabolic (steep initially and flattening out as time progresses), or even sigmoid shaped (slow infarct growth initially that increases as time progresses, then flattens out at later time points).[3,4] Recent analyses of workflow time relationships for both intravenous tPA and endovascular treatment attest to the variable nature of the infarct growth outcome relationships.[4-8] In particular, in a recent meta-analysis of all the endovascular trials, a nonlinear statistical exploration of the time-versus-outcome relationship showed a shallow slope very early, with a steep fall in good outcome rate from 190-390 minutes after stroke onset and a gradual decline later (see Fig 5 in Saver et al[4]). The nature of this time-versus-outcome relationship may likely be very different if patients with large infarcts at baseline (fast progressors) or those with minimal clinical deficits (very slow progressors) who were likely excluded from the recent intra-arterial therapy trials that were included in this analysis. Although "time is brain" is an established construct, we currently have very limited data on the time-versus-outcome relationship in all comers and how this relationship may be different in different groups of patients.

We also have little quality data on why some patients are fast progressors and some are slow progressors. All the recent trials (overtly or inadvertently) used imaging or clinical parameters that resulted in the inclusion of patients with a small core independent of time from onset.[9] So, by definition, nearly all patients in the later time windows had to be slow progressors. Fast progressors were excluded from these trials. A strong candidate as a pathophysiologic variable to explain the differences between slow and fast progressors is the status of leptomeningeal collaterals. The better the collaterals, the slower the progression of infarct. So what influences the presence of good collaterals, and what do we understand about it? It is likely that collaterals are influenced by genetic factors and coexisting conditions such as diabetes and hypertension. A second candidate variable is tissue susceptibility, which, to date, is impossible to measure in isolation and is poorly defined and understood. Another variable that likely comes into play in patient selection is tissue eloquence (nearly all patients who were enrolled in the recent trials had clinically major stroke symptoms; hence, it is possible that there are patients who have sizeable noneloquent tissue at risk, but were not included in the trials because of clinically mild symptoms).

Animal data suggest that there are significant genetic influences on the robustness of collaterals.[10] Other risk factors associated with poor collaterals include aging, hypertension, diabetes, or the presence of metabolic syndrome and hyperuricemia.[11] The use of statins and angiotensin converting-enzyme inhibitors may be associated with good collaterals.[12] Furthermore, the immediate physiology of collaterals may be acutely influenced by systemic blood pressure, locoregional factors such as carotid artery stenosis, or the degree of vessel occlusion caused by a large bore catheter and other modifiable factors.

Tissue susceptibility may be modifiable. Multiple compounds have been shown to be cytoprotective in ischemia-reperfusion models in rodents and other preclinical models. None have been proved in human stroke. Variables that are explanatory for tissue susceptibility include age and sex, premorbid brain health (perhaps measured crudely by functional status), comorbid conditions (such as diabetes mellitus, congestive heart failure, and cancer). Among these patients, the impact of a moderate stroke may be much worse. Both novel and well-known compounds such as NA-1,[13] minocycline,[14] and uric acid[15] may change tissue susceptibility, perhaps to a varying degree depending upon the patient. So where do we go from here? The shape of the infarct growth curve is unknown. Variable rates of infarct growth likely exist because of variability in robustness of collaterals and tissue susceptibility to ischemia. We have limited understanding of the factors that inflence these variables. Data to understand this issue in humans are limited by sampling biases stemming from current patient selection strategies in available studies. As a first step, we need better databases comprising all patients with acute ischemic stroke caused by large vessel occlusion. Such prospective databases should capture clinical information that includes time of onset, age, comorbidities, and information regarding vital signs (eg, "the patient was not hypotensive"). Imaging data should include modalities that assess the presence of a sizable penumbra indirectly "collateral information" or directly "perfusion imaging." Finally, laboratory investigations should be added for conditions that are known to impact the penumbra/collateral status, such as blood glucose, uric acid, or metabolic syndrome work-up. Clinical follow-up and outcome data irrespective of how patients were treated are essential. Such data bases could be an expansion of existing stroke registries (eg, Austrian Stroke Unit Registry Collaboration[16]) or previous randomized trials that captured data on the patients who were screened for eligibility, but excluded because of unfavorable imaging. These will help advance our understanding of which factors are associated with the fast progressor state and, hopefully, could be modified to improve the stroke outcome of these patients.

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Denominator Fallacy Revisited

Based upon:
Denominator Fallacy Revisited
Mayank Goyal, Ashutosh P Jadhav
J Neurointerv Surg. 2017 Oct;9(10):915-916.

We have previously written about 'denominator fallacy' and its importance in the way that we report and interpret results, especially for endovascular treatment of acute stroke.[1] In most studies, the number of patients going for endovascular thrombectomy (EVT) is taken as the denominator and the number of these patients achieving a modified Rankin Scale (mRS) of 0-2 as the numerator. The number of patients taken for EVT is dependent on the overall set-up, the view of the interventionalists, economic considerations (in some jurisdictions), imaging criteria, and clinical criteria. Of these, imaging criteria probably play a key role: the more stringent the imaging criteria (taking only patients with a very small core, etc), the smaller the number of patients who will go for EVT and the higher the likelihood of good clinical outcome (as a percentage of patients undergoing EVT). However, the more stringent the criteria, the smaller the overall impact of the treatment on the population as a whole. I used examples to illustrate this concept in a previous editorial.

However, let us take this line of reasoning a step further.

We know that time is brain and that infarcts grow during the hyperacute phase. At time zero after onset of symptoms, the size of the infarct core is zero. At 24 hours after onset, most infarcts are fully grown. Therefore it is clear that between 0 and 24 hours infarcts grow. Based on available data, it is quite likely that the overall curve for infarct growth is not linear but logarithmic with infarct growth being greater early on. Thus, it is likely that the earlier the imaging is performed after onset of the stroke, the higher is the likelihood of favorable imaging.[2] If we had the ability to image 100 patients with M1 (middle cerebral artery, 1st segment) occlusion within 30-60 min of stroke onset, probably nearly all the patients would be eligible for EVT based on published and accepted criteria for small to moderate core (ASPECTS>5). Also if we could open most of these vessels quickly, 60% of these might have a good outcome.

How does the situation change if we have 100 patients with M1 occlusion presenting at 2 hours? There is no good dataset to answer this question but some of these patients will probably have poor collaterals (fast progressors) and already have a large core and hence are not eligible for EVT. Let us say 70 of these patients still have favorable imaging and undergo EVT. Of these approximately 60% have a good outcome: 40 patients (out of a total of 100 who presented in this time window). Going further at 4 hours from onset, it

is possible that 50 patients have favorable imaging. Assuming a 60% good outcome after endovascular treatment, 30 of these patients do well (mRS 0-2) (figure 1).

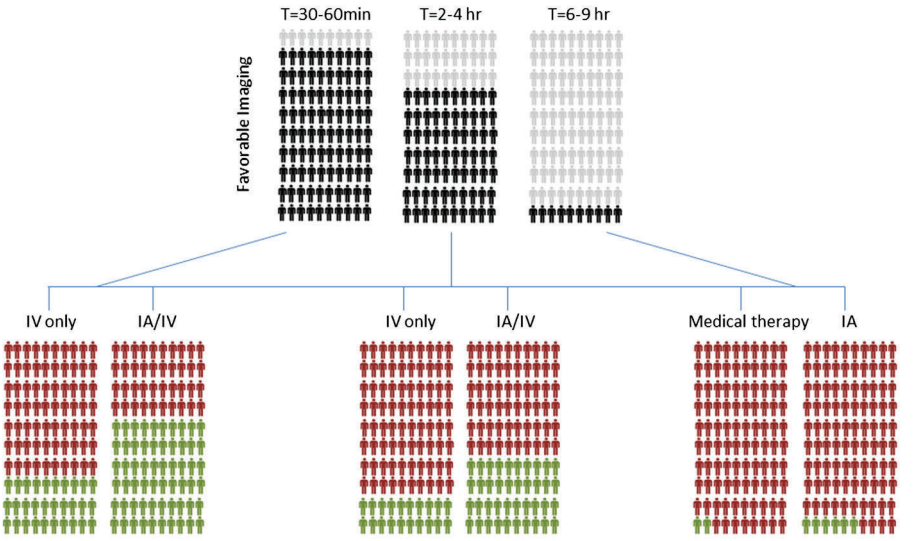

Figure 1 Denominator fallacy: over time after the onset of symptoms, an increasing number of patients have large core infarct and are unlikely to benefit from revascularization therapy. For the purposes of this figure, it has been assumed that these have a bad outcome (modified Rankin Scale 3–6). At an early time point (30–60 min), nearly all patients (90%) have a small core infarct and are probably eligible for IA therapy. At 2–4 hours, 70% are probably eligible for IA therapy, whereas at a late time point (6–9 hours), only 10% of patients are eligible for therapy. Assuming a 30% response with IV therapy and 60% response with IA therapy (and keeping this consistent over time), the total impact at the population level dramatically reduces. Please note that the numbers used in this figure are merely estimates for illustrative purposes and more studies are needed to define the precise number of eligible patients at various time points.

What about at 6-9 hours? It is possible that only 10-20 out of 100 patients are eligible. In all the recent randomized trials,[3] even those that allowed enrollment at later times like the ESCAPE trial, the some indirect data to suggest that in the later time windows, many patients did not have favorable imaging. With successful EVT of 10 of those patients, and assuming a 60% good outcome, six of these patients have a good outcome. Let us say that late window trials show a 40% absolute effect size[4,5] (which is actually quite ambitious): this would mean that two patients who did not undergo treatment would also have a good outcome. However, here is the problem: of 100 patients who presented in the late window with an M1 occlusion, two patients who did not undergo any treatment had a good outcome as opposed to six who did undergo EVT. What is our overall impact on the disease?

Now let us look at the problem in another way: we focus on systems of care, technologies, and education for better identification of large strokes in the field and direct referral to comprehensive stroke centers and let us say that we can create a system enabling all patients to arrive at the appropriate center 2 hours earlier. We know from the SWIFT PRIME data that the 'drip and ship' paradigm was on average 2 hours slower than the 'mother-ship' paradigm.[6]

So those 100 patients who were going to arrive later than 6 hours (with only 10% having favorable imaging) can now reach us at 4 hours and hence 50 of these would have favorable imaging. If the good outcome rate is kept the same, then at the end of treatment, instead of six patients having a good outcome, in this situation 30 would have a good outcome: an effect size of 500%!

In conclusion, using the number of patients undergoing EVT as the denominator can give us a false sense of success. The only denominator that makes sense is the total magnitude of disease in the population. Unfortunately, we do not have good datasets that include all patients with a large vessel occlusion irrespective of whether they are eligible for treatment or not. Given that (1) stroke due to large vessel occlusion is a devastating disease and (2) time is brain, we should focus our energies on systems of care enabling the correct patient to reach the correct hospital faster. Once at the correct hospital, the focus should be on speed, efficiency, and parallel processing to achieve safe and effective reperfusion. This would probably have greater impact than any improvements in imaging-based selection or reperfusion technologies.

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John Nash and the Organization of Stroke Care

Based upon:

John Nash and the Organization of Stroke Care

M. Goyal, A.T. Wilson, D. Mayank, N. Kamal, D.H. Robinson, D. Turkel-Parrella, and J.A. Hirsch

AJNR Am J Neuroradiol. 2018 Feb;39(2):217-218

ABSTRACT

SUMMARY: The concept of Nash equilibrium, developed by John Forbes Nash Jr, states that an equilibrium in noncooperative games is reached when each player takes the best action for himself or herself, taking into account the actions of the other players. We apply this concept to the provision of endovascular thrombectomy in the treatment of acute ischemic stroke and suggest that collaboration among hospitals in a health care jurisdiction could result in practices such as shared call pools for neurointervention teams, leading to better patient care through streamlined systems.

John Forbes Nash Jr was a renowned mathematician whose groundbreaking work in the domain of game theory earned him the Nobel Prize in Economics in 1994. His theories have been key to our understanding of decision-making processes in economics and every other aspect of life involving complex strategic interactions.[1] Nash became a household name due to a critically acclaimed depiction of his life in the film A Beautiful Mind. There is a scene where Nash is struck by an epiphany because of a discussion about an imaginary interaction with some young women. He realizes that Adam Smith's theory of systems fails to take into account that people choose the action that confers the greatest benefit (within the constraints of law and decency). If you have not seen the film or do not remember the scene, check it out at https://www.youtube.com/watch?v=L-JS7Igvk6ZM. The important message is that in game theory as in life, systems work best when every person does what is best for himself or herself, taking into consideration the decisions of the other players. A system in this state is in Nash equilibrium.[2-4]

In acute ischemic stroke due to large-vessel occlusion, we know that the natural history of the disease is generally poor and devastating, endovascular thrombectomy is highly effective, and "time is brain."[5] Our biggest challenge moving forward is to improve the organization of systems of care, getting each patient to the correct hospital the first time around.[6] Additionally, individual cities, jurisdictions, and groups of physicians need to organize themselves so that they can provide endovascular thrombectomy 24/7/365. Neuroinverventionists are often hired mainly on the basis of adequate availability of daytime work and where a hospital is located, the population denominator, and the presence

of other neurointervention centers in the vicinity. Thus, hospitals may be limited in increasing their call pool, making the frequency of calls for each neurointerventionist quite onerous.

In game theory, a game comprises 3 parts: the players, the set of actions available to each player, and a utility function for each player.[4] Here, the players are the health care providers, the actions are the choices they make regarding patient admission and treatment, and the primary utility measure of these actions is the patient's well-being. To achieve optimization (both for patient outcome and use of resources, decent call schedules, and work-life balance) based on Nash's work would require all the players (in this case, all the health care providers in a particular jurisdiction) to evaluate not only their own choices and strategy but also the choices and strategies of the other players.

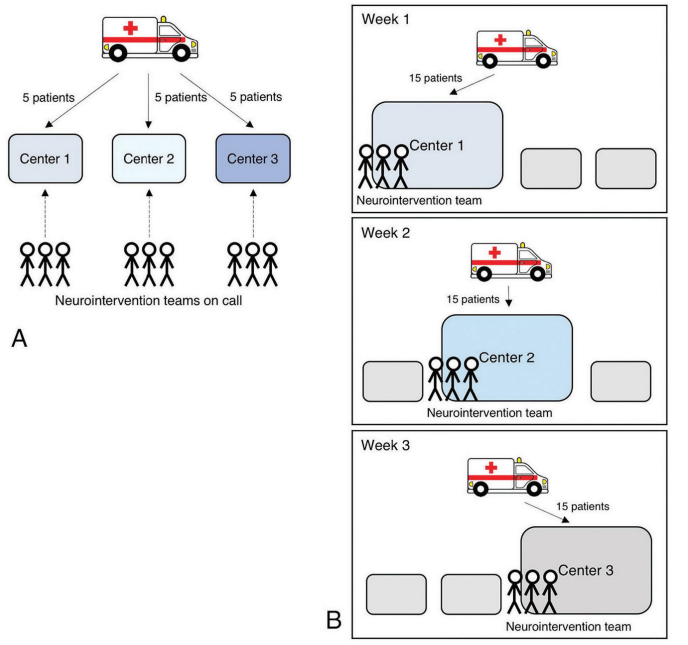

FIGURE. Schematic demonstrating different approaches to the neurointervention service for acute stroke in a community. *A*, In an isolationist setting, each stroke center has its own call schedule and receives patients. The patient volume is divided among the centers. Nearly all components of the neurointervention team are called from home. *B*, In a more cooperative setting, a call schedule is shared among the 3 centers and parts of the neurointervention team are in-house (eg, angiography nurse and technologist, stroke fellow/nurse practitioner) when that center is the active center. The active center receives a higher patient volume, making use of the neurointervention team more effective. The presence of an in-house team allows better workflow and increased efficiency. It is likely that stroke patients who are not eligible for endovascular thrombectomy (intracranial hematoma, no large-vessel occlusion) will also receive better care. Note that the total volume of patients treated by each hospital remains unchanged.

Nash's work suggests that patients with stroke could be better served in their community if hospitals or neurointervention groups engaged in collaborative practices, rather than each insti-tution working exclusively to its best interest in isolation. In this sense, each player would show his or her "hand" and, subsequently, take the best action for himself or herself based on every other player's hand. This would constitute a mutually beneficial cooperative Nash equilibrium in which the system is in a stable state, with each player maximally benefitting.[4,7] In this sense, outcomes of patients with stroke (the shortest possible onset-to-reperfusion time in appropriately chosen patients[8]) will be improved in the community as a whole.

When one starts thinking this way, the obvious conclusion is to have a shared city- or jurisdiction-wide call schedule (Figure). This could be communicated well in advance to the paramedic staff so that they could determine where to bring the patient on the basis of a predetermined call schedule. In jurisdictions where many patients are brought directly to the hospital by family and friends, an alternative approach could be for the neurointerventionist on call to have privileges in all the relevant hospitals and to therefore travel to the patient. There are simple solutions to overcome the variances of catheterization laboratory setup and individual choices of tools: Physicians could carry a Brisk Recanalization Ischemic Stroke Kit (BRISK) in their cars and walk in with all the tools they need.[9] Of course, establishing such a system will require cooperation and trust; however, this is easier to achieve when one is backed by a Nobel-winning mathematician's math and game theory. Is it time to start this discussion?

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Consistently Achieving Computed Tomography to Endovascular Recanalization <90 Minutes Solutions and Innovations

Based upon:
Consistently Achieving Computed Tomography to Endovascular Recanalization <90 Minutes Solutions and Innovations
Mayank Goyal, Bijoy K. Menon, Michael D. Hill, Andrew Demchuk.
Stroke. 2014 Dec;45(12):e252-6

Time is brain. Recent data from the Interventional Management of Stroke Trial 3 (IMS3) and other studies have provided further data to support this.[1-3] Data from IMS3 suggest that a 30-minute delay in recanalization reduces the average absolute rate of a good outcome by 11%.[1] Mazighi et al[3] have demonstrated a relationship between delays and increased mortality. A similar analysis from the Solitaire FR Thrombectomy for Acute Revascularization (STAR) Study data set suggests a 38% relative reduction in good outcome by a 1 hour delay in recanalization.[2] Rate of cell death has been estimated to be ≈2 million neurons/min in M1 occlusion.[4] Currently in the United States, the mean time from symptom onset to groin puncture is 6 hours with an additional hour to achieve revascularization.[5] It is clear that we as a collective need to improve overall workflow in endovascular management of acute large vessel ischemic stroke.

We have demonstrated that computed tomography (CT) head to reperfusion within 60 minutes is achievable.[6] However, the process of achieving this metric requires some key processes to be in place. These include the presence of an organized emergency team to evaluate and stabilize vitals, secure airway, register the patient into the hospital information system, make a complete but quick clinical assessment, understand the patient's premorbid status, expectations of outcome, advance directives, contraindications to treatment (and participation in trials), and need for ventilation/anesthesia support. Imaging needs to be geared up toward efficiency and rapid decision making. The key imaging components are rule out an intracranial bleed (and other intracranial conditions such as a tumor or subdural hemorrhage), identify that the patient has a small core of infarction and a proximal vessel occlusion on CT angiography. Other considerations may include anatomy (does the patient have aberrant anatomy or pathology that may influence endovascular access), presence of penumbra/collaterals. Intravenous tissue-type plasminogen activator (tPA) needs to be administered based on standard of care but without creating any delay in the effort toward achieving reperfusion. Assuming that the patient is suitable for the endovascular procedure (or an acute endovascular trial), the next steps include obtaining consent, getting the cath laboratory team together, organizing anesthesia if necessary, transporting the patient to the angiography suite, getting the angiography suite organized, having the patient prepared using standard antiseptic techniques, access the vascular system and the clot, and finally achieve optimal reperfusion. During this procedure, maintenance of the patient's vitals and use medications as necessary to hold the patient still should help expedite the workflow and not delay it. After the procedure, the patient needs to be trans-

ferred to a monitored unit run by trained personnel (stroke unit, intensive care unit) for postprocedure care with planning toward rehabilitation. Below, we highlight innovations in the conduct and administration of this workflow that has helped us achieve our goal of quick and efficient reperfusion in patients with acute ischemic stroke.

Parallel Processing, Trust, and Teamwork

This, in our opinion is the single most important component of success.[7,8] A single person or a group of individuals from 1 discipline cannot achieve successful endovascular treatment of stroke consistently. We have divided the team into 2 key components: the stroke team and the endovascular team. The anesthesia team is added as needed. The emergency room staff are a key component for the initial evaluation and stabilization. The stroke team on call is prenotified and they meet the patient at the door to the emergency. At this stage they take an expeditious history, a quick examination, quantify the National Institutes of Health Stroke Scale, get medical history, and establish a rapport with the family. In parallel, a member of the team notifies the CT scanner and the neurointerventionists. The teams converge in the CT suite as this is the point of decision making. Imaging acquisition and interpretation are streamlined (more details below). Intravenous tPA is administered in the imaging suite after the plain CT. In the meantime additional imaging is performed. The decision of eligibility for endovascular (or a trial) is taken collectively. At this stage, the stroke team gets consent, whereas the neurointerventionist moves to the angiography suite to plan and prepare for the procedure (they participate in the consent process as necessary). Members of the stroke team monitor and manage the patient during the procedure. The team manages complications, outcomes, and postprocedure care collectively. The diagnosis and treatment are performed in parallel by members of both teams to maximize the use of limited time. Trust and teamwork are essential.

Prenotification

We have helped organize and train local Emergency Medical Services staff to first, recognize major strokes; second, prenotify the stroke team through a centralized paging system; and finally, to bring all such patients directly to the Foothills Hospital irrespective of their location within the city. As such, we uncommonly see any drip and ship patients. Delays introduced by the drip and ship paradigm have been shown within the IMS3 data.[9] Prenotification allows for better preparedness of the emergency room staff.

Fast Minimalist Clinical Examination

From a decision-making perspective, we have found that a quick and focused neurological examination is all that is needed especially in severe strokes because of large vessel occlusion. We continue with our examination as the patient is moving from door to emergency department and to CT. We use the provincial electronic medical record system to gather past information about the patient while the patient is getting imaged. This method of acquiring clinical information while patient is moving along the workflow path saves time. Whether the patient has an National Institutes of Health Stroke Scale score of 17 or 19, in our experience does not influence decision making. Of course, from the perspective of studies and trials it is important that there be precise quantification of National Institutes of Health Stroke Scale. As such we find that these can be completed in parallel before or after the CT scan as other things are going on. We do recognize that there is a cost to fast minimalist clinical exams; we may occasionally miss important diagnosis. Nonetheless, such alternative diagnoses are epidemiologically rare. In addition, our imaging paradigm (detailed below) makes this a unlikely scenario especially in the presence of a proximal vessel occlusion on a CT angiogram. In addition, we have instituted a active quality assurance process where the entire team meets once a week to discuss all cases including a detailed discussion on workflow, imaging, errors, and potential improvements, and also use this as an opportunity to teach and learn.

Fast, Minimalist Imaging Based on a Decision-Based Paradigm; No Complex Post Processing of Imaging

Our imaging protocol includes a noncontrast CT head and a multiphase CT angiography (patent pending). It is important to optimize CT head quality to be able to appreciate early ischemic changes. It is imperative to view the images on a high-quality screen with narrow window width and appropriate window level (usually a window width of 50; window level of 35 is a good starting point). The head CT allows for exclusion of hemorrhage and extensive early ischemic changes (large core). These are viewed on the CT console and a decision to treat with intravenous tPA is taken. Although intravenous tPA is being administered (if appropriate), we proceed with a multiphase CT angiogram. The multiphase CT angiography allows for detection of proximal vessel occlusion, allows for discriminating carotid occlusion from a 99% stenosis (identify a slow trickle of contrast in the second phase), determine the precise length of thrombus (proximal end in first phase; distal end in later phases), and finally evaluate collateral circulation. Collateral evaluation is useful in

quick determination of degree of flow to the ischemic brain.[10-13] In addition, the presence of good collaterals correlates well with the Alberta Stroke Program Early CT Score (ASPECTS) score. Patients with good ASPECTS score (small core) have good collaterals (this makes intuitive sense as well).[14,15] Nonetheless, ASPECTS interpretation becomes less reliable in the early presenters or when the CT image is marred by movement or other artifact.[16] Collateral interpretation therefore serves as a check on ASPECTS interpretation. The 2 modalities together help us make the decision. We have derived an easy intuitive collateral scoring system (http://www.aspectsinstroke. com/collateral-scoring/introduction/). An additional advantage of this approach is that there is no need for transfer of images to another workstation or need for complex postprocessing. In our experience, CT angiogram is not significantly affected by patient motion and it does not suffer from the variability of CT perfusion based on vendor, arterial input function, imaging protocol, and postprocessing software.[11] Evidence suggests that the CT angiogram can be done quickly (consistently within 5 minutes in our opinion), allowing significant time saving and expediency.[9,17] We use the following paradigm: small core based on head CT (good ASPECTS score), proximal vessel occlusion, and good collaterals and use a Bayesian approach to decision making.[18] The probability of salvageable brain tissue among patients with a blocked proximal artery, favorable noncontrast CT scan, and good collaterals on multiphase CT angiogram is high. Therefore, because the post-test probability after an additional diagnostic test such as computed tomography perfusion or MRP is unlikely to change, these tests may not be needed for decision making. This Bayesian approach emphasizes that in this clinical situation of major ischemic stroke, only semiquantitative/qualitative information is needed to make a treatment or trial-enrollment decision. We acknowledge that other imaging paradigms including those based on perfusion imaging (CT and MRI) are useful in selecting the right patients for therapy; it is important that such imaging paradigms align well with the principle of fast imaging, post processing, and decision making.

Use the CT Angiography to Plan the Procedure

We use the CT angiography for planning of the endovascular procedure. An analysis of the arch allows a precise determination of what kind of catheter would be needed to access the carotid. An evaluation of the carotid bifurcation can be used to determine where the balloon guide catheter should be placed. An assessment of the circle of Willis and tortuosity can be used to determine the need for a distal access catheter and length

and size of the stentriever, and the possibility of using direct thrombus aspiration as the primary intervention.[19] A combination of the early ischemic changes, distribution of collaterals, and size of the relevant M2 branches can help determine which M2 would be the preferred one to access.

Consent for Procedure and Trials

A standardized approach of going through the natural history and summarizing known knowledge and results of recent trials helps the process. We practice the consent process with our trainees so that they are well versed with it. We have additionally created a training module for our trainees that also covers answers to the commonest questions from the patient's family. The key components in this training are (1) a brief summary of the results of recent randomized controlled trials. For expediency, we limit these results to IMS3. (2) A brief summary of evidence-based standard of care based on current guidelines.

If needed, a brief description of why randomized controlled trials are necessary. We often encourage the use of examples. The most commonly used example is to quote the randomized controlled trial that led to the approval of intravenous tPA and how 20 years ago, patients agree to participate in the trial which is what led to its approval. (4) The answer to commonly asked questions. In our experience the 2 commonest questions are: what if I (the patient) was your (physician) grandmother? What would happen if I (the patient or their relative) refuse to participate in the trial. In future, positive endovascular trials would make endovascular treatment the standard of care and obviate the need for detailed consent to simplify the process of informing families of the risks of the procedure.[20,21]

Anesthesia

We rarely use general anesthesia for multiple reasons. First, it saves time.[2] Second, there are data to suggest that general anesthesia may be potentially harmful.[22] Third, we find that with the current generation of stroke devices and with pre-existent knowledge of the vascular anatomy from the CT angiogram, we are able to successfully and safely open vessels in spite of some degree of patient motion. Finally, performing these procedures awake allows patient evaluation and examination during the procedure. This is especially useful if the thrombus breaks and after the M1 is open, one finds that a distal MCA branch is still occluded. Doing a physical examination halfway through the procedure can

help in determining whether it is worthwhile to go after it. Because the stroke team stays with the patient throughout the procedure there is always a neurological expert available to evaluate the examination.

Setting Up the Angiography Room

We have a standardized stroke kit that is ready to go. As such we have a stroke table laid out with all the necessary materials such as cleaning solution, drapes, and puncture set. In addition, we have standardized, as much as possible, the catheters and devices that are used. We find that in nearly all anterior circulation strokes, we use an 8F sheath, a balloon guide catheter, an inner catheter in a coaxial fashion to access the arch, a 021 microcather and a stentriever. Using this standardized approach saves time not only for the operator but also for the technologists who do not have to search for materials (catheter, wires, etc) for the procedure.

Cross Training of Angiography Staff

We do most of our procedures with the help of a technologist and a nurse. We found that cross training of the staff as much as possible helps especially after hours. As an example, we have trained our nurses about various catheters so that they can pull them off the shelf and trained our technologists how to set up the pressure bags.

Take Safe Short Cuts When You Can

At the time of endovascular procedure, we keep restoration of blood flow in the brain as the highest priority. We have taken many short cuts. For example, we no longer shave the groin. We often do not put in a Foley's catheter (especially in older male patients) till after the stentriever has been deployed. In our typical aneurysm coiling patients we add heparin to our flush lines. However, we forego this step in acute stroke intervention.

In summary, we present the steps (Figure) that we have taken to consistently achieve ultrafast recanalization in large vessel strokes. We have found that parallel processing, our minimalist, and qualitative imaging approach, better organization of the angiography laboratory and setting up the stroke kit has resulted in the greatest time savings. We have been using this paradigm successfully at our and other centers to improve workflow within ongoing acute stroke trials.

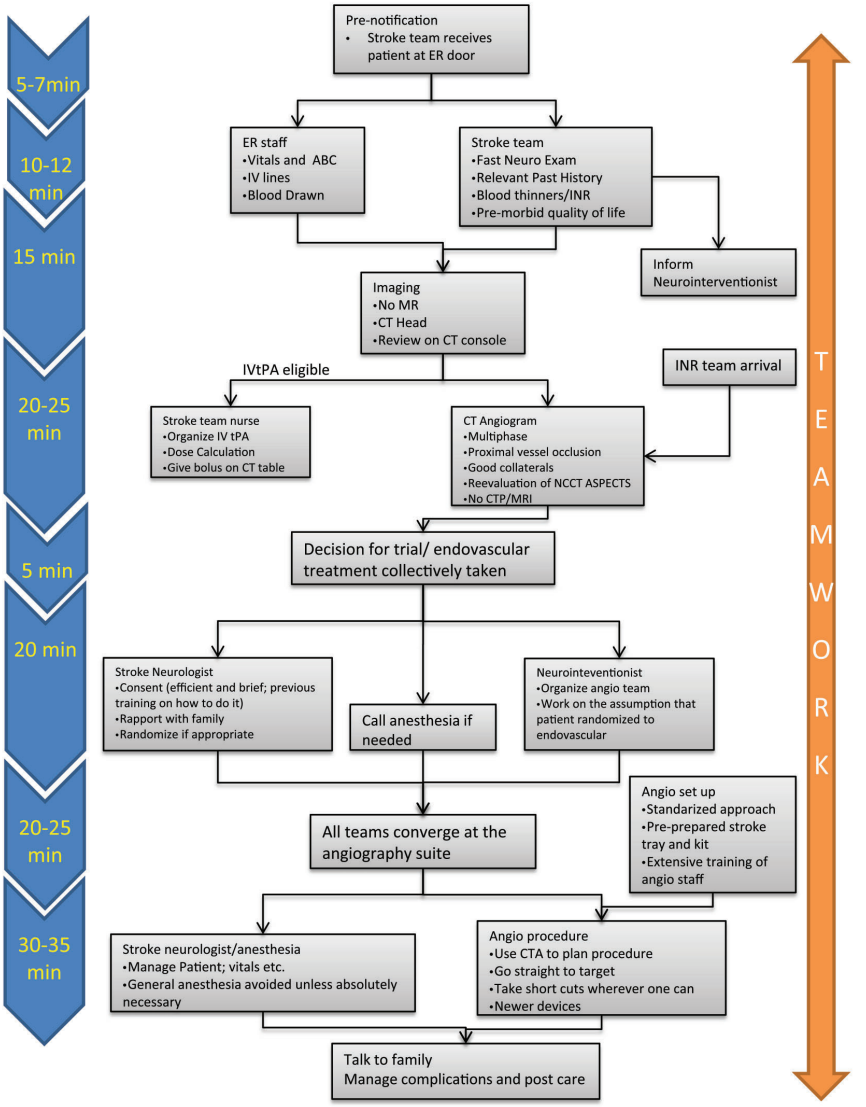

Figure. Flow chart showing workflow and various steps at each stage. Arrows show approximate time savings at each stage compared with IMS3 (all values are approximate). Of note, the median time from computed tomography to recanalization in IMS3 was ≈200 minutes.[1] At our institution, we have been able to bring this down to ≈70 minutes. ABC indicates airway, breathing, circulation; CT, computed tomography; CTA, computed tomography angiography; ER, emergency room; IMS3, Interventional Management of Stroke Trial 3; INR, international normalized ratio; IV, intravenous; NCCT ASPECTS, noncontrast CT Alberta Stroke Program Early CT Score; and tPA, tissue-type plasminogen activator.

In the future, we think that centralization of acute stroke care will be essential. We will need to create Emergency Medical Services redirect of severe strokes to a comprehensive stroke center. Currently, major delays of ≤2 hours to endovascular treatment are occurring by first transporting patients to primary stroke centers.[23] Use of the Los Angeles Motor Scale (LAMSS) score or an even simpler all hemiplegias to comprehensive stroke center philosophy could dramatically reduce delays.[24] This, however, is a significant challenge especially when there is a possibility that such a change could potentially delay the administration of intravenous tPA. Current data from IMS3 do suggest that there are significant time savings from an endovascular standpoint in a mothership paradigm compared with a drip and ship paradigm without delaying intravenous tPA.[9] Whether this could be widely instituted across all geographical jurisdictions will depend on the outcome of current endovascular treatment trials and the subsequent political willingness to centralize stroke care along a trauma model.

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Ongoing Acute Endovascular Stroke Trials Is Execution More Important Than Design?

Based upon:
Ongoing Acute Endovascular Stroke Trials
Is Execution More Important Than Design?
Mayank Goyal
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With the failure of multiple recent acute stroke trials to show the benefit of endovascular treatment, there has been a lot written and spoken about next steps.[1-3] In the wake of these results, many new trials have started with slightly varying principles, selection criteria, and depending on their sponsor, different devices. All these trials have tried to overcome the design limitations of the previously failed trials. However, there are certain general principles that we think we know well and essentially all ongoing trials are using these in the best way they think they can. What are these factors?

Dead Brain Is Dead Brain

It is clear that to be able to successfully demonstrate benefit of endovascular treatment, one has to choose patients with small core. Although there may be differences across trials, investigators, or the physician community at large about what is the best way of doing this, overall everyone agrees. It is also clear that there is a significant time interval between imaging and recanalization. As such, what may be more relevant to outcome is the amount of dead brain at the time of recanalization. In other words, if there was a way not only to measure dead brain on imaging but also to quantify the rate of progression of core to predict what the core would look like over the next 100 minutes or so when recanalization is achieved. This is currently unachievable.

Proximal vessel occlusions do not respond well to intravenous tissue-type plasminogen activator[4,5] and are more suitable to endovascular thrombectomy (compared with distal occlusions). As such, all trials are aiming to choose only those patients with proximal vessel occlusion. Again there are slight variations in methodology. Most trials are using some form of noninvasive vascular imaging such as computed tomography angiography or magnetic resonance angiography; some trials are using the dense middle cerebral artery sign on the noncontrast computed tomographic scan. It is also well known that some patients with proximal vessel occlusion do respond to intravenous tissue-type plasminogen activator. However, we currently lack sufficient understanding of clot characteristics, clot size, flow parameters, etc, to reliably predict these patients.

Presence of Salvageable Tissue

Although there is general agreement in the concept of presence of penumbral or salvageable tissue for the patient to be part of the trial, there is lack of agreement regarding the

definition of penumbra and the best way to quantify it. In a simplistic approach, some think that most patients early in their stroke will have some degree of penumbra; others are using clinical information such as a high National Institutes of Health Stroke Scale score (along with a small core) as an indicator for presence of penumbra. Other trials are using more imaging-based markers such as cerebral blood flow maps, Tmax maps (from perfusion imaging) or collateral assessment from single or multiphase computed tomography angiography. Irrespective, it is clear that patients who have no salvageable tissue are not suitable candidates for participation in a trial.

Time Is Brain

Based on multiple recent publications (from Interventional Management of Stroke III [IMS3] and other nonrandomized data sets such as the Solitaire FR Thrombectomy for Acute Revascularization [STAR] study), we have now further confirmation of what we already knew: time is brain.[6,7] This also means that to be able to show benefit of endovascular treatment, the recanalization in the endovascular arm has to be achieved within a short period from imaging (or even better from onset). Various trials are trying to accomplish in different ways. Some trials are attempting to accomplish an imaging (from computed tomographic head scan when one knows for sure that it is not a hemorrhagic stroke) to recanalization within 90 minutes. Others are aiming more toward an imaging to groin puncture time.[8] The trials are using intensive training and quality control measures to achieve this and hopefully succeeding in this regard.

Adequate Sample Size

This is a more tricky one as here we are stuck with multiple constraints including budget (each patient enrolled costs significant monies; the budget for IMS3 for ≈35 million), availability of good centers that can demonstrate a good team, adequate imaging and workflow, and the infrastructure to conduct high-quality trials. There is also the issue of the total duration of trial, investigator tiredness, changing technology, and sustained funding.

Need for Good Quality Recanalization

The thrombolysis in cerebral infarction (TICI) scoring system is a well-established way to compare the quality of recanalization across trials. Data from IMS3 and other studies

have shown a clear correlation between the quality of recanalization and outcome. In IMS3, ≈40% of patients had a TICI 2B-3 flow.[1] This has shown a dramatic increase with newer devices approaching 90% in some studies.[9] In addition, we and others have noticed several patients in whom the final angiogram is better than a TICI 2B but not a TICI 3. We came up with the term TICI 2C.[10] We have shown that there is a direct correlation with outcome as the quality of recanalization improves even from a TICI 2B to a TICI 2C.[11] With the use of newer devices and better procedural training, we should aim to have a dramatic jump in high-quality recanalization compared with the older trials.

All this is now common knowledge. In fact, based on various data sets (including IMS3, STAR, and Calgary stroke program data sets), I have come up with an approximate value on the effect size between the 2 arms based on these factors (Table).

Table. Approximate Effect Size Based on Modeling of Data From IMS3, STAR Study, and Calgary Data

Problem	Older Trials (Data Based on IMS3)	Newer Trials (Primarily Based on ESCAPE and SWIFT PRIME)	Effect Size % (Approximately)
Workflow	50% of patients had >200 min: from intravenous to recanalization	Aiming for imaging to recanalization time <90 min	12–15
Quality of recanalization	≈40% of patients had a TICI 2b/3 flow	Better devices. STAR data and other studies suggests 80%–90% TICI 2b/3 is achievable	10–15
Some patients with large core enrolled	≈15% had bad ASPECTS score	Improvement in CT technology; better training. Some centers using MRI. Corroboration with other data: collaterals, automated CT perfusion software. Shift analysis (can potentially show benefit even with somewhat larger core)	3–4
Not all patients had a proximal vessel occlusion	≈100 patients in endovascular arm: no treatable lesion	CTA/MRA restriction to proximal vessel occlusion (ICA+M1, M1)	3–4
Dichotomous analysis	Fails to capture subtleties of stroke outcomes. Potential loss of information if subsets of patients go from mRS of 2 to 0 or 5 to 3.	Shift analysis	3–5

Approximate effect size based on modeling of data from IMS3, STAR study, and Calgary data in newer trials (using ESCAPE and SWIFT PRIME as examples) compared with the older trials (using IMS3 as an example).[1,6,7,9,11] Of note, it is also likely that the control arm in the newer trials may do worse than the previous trials because of (1) intravenous tissue-type plasminogen activator being given ≤4.5 hours and (2) all patients have known proximal vessel occlusion. ASPECTS indicates Alberta Stroke Program Early CT score; CT, computed tomography; CTA, computed tomography angiography; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; ICA, internal carotid artery; IMS3, Interventional Management of Stroke III; MRA, magnetic resonance angiography; mRS, modified Rankin scale; STAR, Solitaire FR Thrombectomy for Acute Revascularization; SWIFT PRIME, Solitaire FR as Primary Treatment for Acute Ischemic Stroke; and TICI, thrombolysis in cerebral infarction.

Why then can we fail? Or based on this and the design of the new trials, should we feel that these trials are just a formality? No. Because in my opinion, it is no longer about trial design, it is about trial execution. What are the key components of trial execution?

Choosing Good Centers

There are a limited number of good centers that have a well-established referral pattern, ability to perform sophisticated imaging fast, and then have a quick and accurate interpretation, having the necessary infrastructure and workflow to achieve efficient endovascular recanalization and finally the will to randomize patients. In the process of conducting these trials (I am one of the principal investigators of the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke [ESCAPE] trial and the Solitaire FR as Primary Treatment for Acute Ischemic Stroke [SWIFT PRIME] trial), I have had the opportunity to travel to >30 stroke centers. We are fortunate to be living in times that we have a large of centers that meet all these criteria; however, when one looks at the number of trials being done (or being planned) and all of them want to go to the same centers, suddenly the number starts to look small. In addition, some of the best centers have lack of willingness to randomize. I remember spending 3 hours with one of the best stroke centers (in my opinion) trying to convince the neurologists and interventionists of this center to randomize without success. Their logic was that their endovascular results are so good that they cannot ethically randomize patients.

Education and Quality Assurance

This is key especially in the domains of imaging-based selection and achieving excellent workflow and fast recanalization. Not only does this require tremendous effort from the trial leaders, but also requires willingness on the part of centers for change. Overall, no one likes change especially when the change involves moving dramatically faster, introducing the possibility of driving to the hospital at 2:00 AM on a snowy night and finding out the patient got randomized to the control arm. It is important to recognize that not one solution fits all hospitals. As such, I strongly think that the process of education has to be a 2-way street: understanding the strengths and weaknesses of each site and helping them achieve their best. Also, it is more than likely that there are going to be other centers that are also facing similar issues. One way is to have increased interaction across sites and rather than having the education and quality assurance as a top-down initiative, think of it more like cross-pollination of ideas and practices. In addition, it would be important

to predefine indices of performance and a clear mandate to the consequences of poor performance. As an example, I was recently faced with an issue of a center that enrolled 2 consecutive patients in whom there was no demonstrable occlusion on the computed tomography angiography done before randomization. Although this of course is an obvious trigger for further education on imaging, trial criteria, it also requires a better understanding of the workforce within that center and if it is determined that the problem is nonsolvable, then to recognize it early and excuse the center from the trial.

Consecutive Enrollment

I have previously written on this topic.[12] This, in my opinion, is the single biggest challenge that we currently face. It is not easy to randomize a 50-year-old otherwise healthy patient, 2 hours from onset, National Institutes of Health Stroke Scale core of 17, M1 occlusion, and a small core to a trial especially, when one practices in a good stroke center with extensive experience and success with endovascular thrombectomy. However, as I have previously written, it is important to recognize the following: (1) Trial results are a summation of all the data in the trial. It is possible and likely that the effect size of endovascular treatment is not evenly distributed across the entire data set. Selectively enrolling patients means potential reduction in effect size (meaning an exponential increase in sample size to demonstrate the effect) and of course, slower enrollment. (2) Endovascular treatment of stroke is not the standard of care. In fact, in view of the recent negative trials, one cannot apply the parachute analogy and claim that it should be exempt from randomized controlled trials in view of bad natural history of disease and dramatic effect size. The only way to continue to offer endovascular therapy for acute stroke is by showing positive randomized controlled trials.

Overcoming Delays in Getting Centers Up and Going

There is wide variability in the amount of time it takes to get a center up and going ready to randomize. The key components are Institutional Review Board approval of the protocol, a contract with the hospital, and training of the participants. In addition, some trials may have additional requirements such as installation of additional software. Managing these local variables is best done by the site principal investigator and, of course, by planning for all these events. However, in my experience, the single biggest factor to overcome delays is presence of a local champion who is in the best position to understand the processes and move things along.

Hold the Line

Trialists may have a tendency to panic if a few unexpected bad events happen especially in the treatment arm. As such, there may be a tendency toward multiple protocol amendments. This has the potential to introduce confusion among the investigators and, of course, deployment of scarce resources toward the amendment and all the necessary work that goes along with it such as training, resubmission to Institutional Review Boards. If one concurs with the central theme of this editorial, it is not about trial design; it is more about trial execution, then one would agree that it is important to hold the line. The commonest cause for a few unexpected bad events is randomness. Of course, it should trigger investigation and education.

Managing Changing Expectations, Technology, and Referral Patterns

Technology in acute stroke endovascular therapy has been changing at a rapid pace. There is no reason to think that is going to stop. When a major change in technology happens during a trial, it raises a few different problems. (1) The new technology may be attractive, but ultimately its efficacy and safety may be unknown. How this should be accounted for in the trial. (2) There may be a mass movement toward the new technology, and if it cannot be used within the trial (because of lack of safety data or just because it is going through the necessary paperwork through various amendments), it may lead to decreased enrollment because investigators may not want to enroll patients in the absence of the option of using the new technology. (3) Many of the newer trials are industry sponsored. If the new technology belongs to a competitor, it could potentially affect the funding for the trial. What are the solutions to these issues? The most obvious one of course is to have fast enrollment and complete the trial in a short period of time before there are major changes in technology. The other one is having greater cooperation among industry and discussion and negotiation with organizations such as Food and Drug Administration to consider a class approval for endovascular devices rather than individual devices.

In addition, there is the issue of referral patterns. A drip and ship paradigm clearly induces delays that selectively affect the endovascular arm of the trial.[6,13] In addition, there are other potential problems associated with patients not coming directly to the hospital participating in the trial. I recently visited an excellent stroke center where most of their patients are referred in from smaller hospitals. There are 2 hospitals not too far from

each other. One hospital (the one I visited) believes in trials and evidence-based medicine, whereas the other does not. As soon as the trial starts, the hospital that is not part of the trial actives markets its absence of trial and randomization to the referring hospitals to capture the market. This is not easily solvable in the short term. Hopefully, it is a relatively rare occurrence. In the long term though, the solution lies in creating a culture of evidence-based medicine that starts at the medical school level.

In conclusion, I do think that we have learnt from all the years of hard work and failed trials. I do think we know the key design components to demonstrate the superiority of endovascular treatment in a select population of acute ischemic stroke. I agree that there is significant controversy and variability across ongoing trials regarding how these key design components are implemented. However, a well-designed, poorly executed trial can still fail. Successful trials are going to require hard work, leadership and cooperation of all stakeholders including hospitals, referring doctors, professional organizations (Society of Neurointerventional Surgery, American Heart Association, etc), and a commitment to trials and evidence-based medicine.

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Patents


US009324143B2

(12) **United States Patent**
Goyal

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(45) **Date of Patent: Apr. 26, 2016**

(54) **SYSTEMS AND METHODS FOR DIAGNOSING STROKES**

(71) Applicant: **Mayank Goyal**, Calgary (CA)

(72) Inventor: **Mayank Goyal**, Calgary (CA)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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(58) **Field of Classification Search**
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See application file for complete search history.

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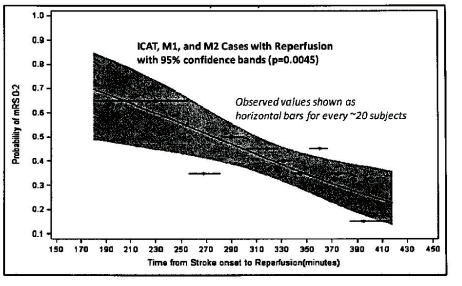
Primary Examiner — Seyed Azarian
(74) *Attorney, Agent, or Firm* — McGlew and Tuttle, P.C.

(57) **ABSTRACT**

The invention relates to systems and methods for diagnosing strokes. In particular, systems and methods for acquiring timely patient status information are described that enable a physician to make diagnostic and treatment decisions relating to ischemic and hemorrhagic strokes. The systems and methods enable the efficient and quantitative assessment of arterial collaterals within the brain for aiding these decisions in the case of ischemic strokes. In the case of hemorrhagic strokes, the systems and methods are effective in determining if there is a leak and what is the rate of leaking.

24 Claims, 11 Drawing Sheets

Time to Reperfusion and Good Clinical Outcome



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US009486176B2

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Goyal

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(54) **SYSTEMS AND METHODS FOR DIAGNOSING STROKES**

(71) Applicant: **Mayank Goyal**, Calgary (CA)

(72) Inventor: **Mayank Goyal**, Calgary (CA)

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(60) Provisional application No. 61/697,282, filed on Sep. 5, 2012.

(51) **Int. Cl.**

G06K 9/00	(2006.01)
A61B 6/00	(2006.01)
A61B 6/03	(2006.01)
G06T 7/00	(2006.01)
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(58) **Field of Classification Search**

USPC 382/100, 103, 107, 128–134, 162, 168, 382/173, 181, 209, 219, 232, 254, 274, 382/286–291, 294, 305, 312; 424/9.45; 600/437, 407, 454; 703/11; 358/3.26; 378/4, 21

See application file for complete search history.

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Primary Examiner — Seyed Azarian

(74) *Attorney, Agent, or Firm* — McGlew and Tuttle, P.C.

(57) **ABSTRACT**

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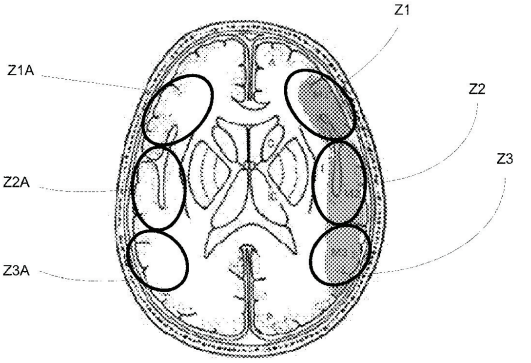
10 Claims, 13 Drawing Sheets



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Menon et al., Multiphase CT Angiography: A New Tool for the Imaging Triage of Patients with Acute Ischemic Stroke, Radiology: vol. 000: No. 0, 2015.

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LIST OF ABBREVIATIONS

AIS	Acute Ischemic Stroke
LVO	Large Vessel Occlusion
MRI	Magnetic Resonance Imaging
ICH	Intracranial Hemorrhage
sICH	Symptomatic Intracranial Hemorrhage
MAST	Multicenter Acute Stroke Trial
MAST-E	MAST- Europe
MAST-I	MAST- Italy
IVT	Intravenous Thrombolysis
tPA	Tissue Plasminogen Activator
ECASS	European Cooperative Acute Stroke Study
EPITHET	Echoplanar Imaging Thrombolytic Evolution Trial
IV	Intravenous
PROACT	Prolyse in Acute Cerebral Thromboembolism
MCA	Middle Cerebral Artery
IA	Intra-arterial
r-proUK	Recombinant Prourokinase
EVT	Endovascular Thrombectomy
MERCI	Mechanical Embolus Removal for Cerebral Ischemia
RCT	Randomized Controlled *Trials*
FDA	Food and Drug Administration
TIMI	Thrombolysis in Myocardial Infarction
mRS	Modified Rankin Scale
AB	Aneurysm Bridging

SWIFT	SOLITAIRE™ FR With the Intention For Thrombectomy
TREVO2	Thrombectomy REvascularization of Large Vessel Occlusions in Acute Ischemic Stroke
IMS	Interventional Management of Stroke
SYNTHESIS EXPANSION	A Randomized Controlled Trial on Intra-Arterial Versus Intravenous Thrombolysis in Acute Ischemic Stroke
MR RESCUE	Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy
GA	General Anesthesia
ESCAPE	Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke
SWIFT PRIME	Solitaire with the intention of Thrombectomy as the Primary Endovascular Treatment
MR CLEAN	Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands
MR CLEAN LATE	Multicenter Randomized Clinical Trial of Endovascular Treatment of Acute Ischemic Stroke in The Netherlands for Late arrivals
MR CLEAN MED	Multicenter Randomized CLinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands - The effect of periprocedural MEDication: heparin, antiplatelet agents, both or neither
ESCAPE NA1	Safety and Efficacy of **NA-1** in Subjects Undergoing Endovascular Thrombectomy for Stroke
DSBM	Data Safety and Monitoring Board
CT	Computed Tomography
CTA	CT Angiography
mCTA	Multiphase CTA
CTP	CT Perfusion
TICI	Thrombolysis in Cerebral Infarction
mTICI	Modified TICI
REVASCAT	Endovascular Revascularization With Solitaire Device Versus Best Medical Therapy in Anterior *Circulation* Stroke Within 8 Hours
EXTEND	Extending the time for thrombolysis in Emergency Neurological Deficit
EXTEND IA	Extending the time for thrombolysis in Emergency Neurological Deficit - Intra-arterial

EXTEND-IA-TNK	Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial Using Intravenous Tenecteplase
ERMES	ESCAPE REVASCAT MR CLEAN EXTEND IA SWIFT PRIME
HERMES	Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke *Trials*
NIHSS	National Institutes of Health Stroke Scale
PSC	Primary Stroke Centre
CSC	Comprehensive Stroke Centre
IQR	Interquartile Range
ICA	Internal Carotid Artery
PROVE IT	Measuring Collaterals With Multi-phase CT Angiography in Patients With Ischemic Stroke
THRACE	The Contribution of Intra-arterial Thrombectomy in Acute Ischemic Stroke in Patients Treated With Intravenous Thrombolysis
PISTE	A Randomised Controlled Clinical Trial of Adjunctive Mechanical Thrombectomy Compared With Intravenous Thrombolysis in Patients With Acute Ischaemic Stroke Due to an Occluded Major Intracranial Vessel
TENSION	Efficacy and Safety of Thrombectomy in Stroke With Extended Lesion and Extended Time Window
MR	Magnetic Resonance
MRA	MR Angiogram
LAMS	Los Angeles Motor Score
RACE	Rapid Arterial Occlusion Evaluation
MSU	Mobile Stroke Unit
RACECAT	A Trial Comparing Transfer to the Closest Local Stroke Center vs. Direct Transfer to Endovascular Stroke Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory
PPV	Positive Predictive Value
US	United States
DAWN	Diffusion Weighted Imaging (DWI) or Computerized Tomography Perfusion (CTP) Assessment With Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention

DEFUSE3	Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3
WAKE-UP	Efficacy and Safety of MRI-based Thrombolysis in Wake-up Stroke: a Randomised, Double-blind, Placebo-controlled Trial
Diffusion-FLAIR	Diffusion-Fluid Attenuated Inversion Recovery
ADAPT	A Direct Aspiration First Pass Technique
ASTER	Interest of Direct Aspiration First Pass Technique (ADAPT) for Thrombectomy Revascularisation of Large Vessel Occlusion in Acute Ischaemic Stroke
BRISK	Brisk Recanalization Ischemic Stroke Kit
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
NNT	Number Needed to Treat
cOR	Common Odds Ratio
CI	Confidence Interval

EPILOQUE (DANKWOORD)

I am pleased to have this opportunity to convey my gratitude to all those whose invaluable help, support and guidance helped me through this journey. I look at this thesis as a culmination of years of work that ended by establishing the effectiveness of endovascular thrombectomy. My two supervisors, Diederik and Aad, make it additionally special; the trial that they led (MR CLEAN) was the first to show benefit and the ripples from their results presented in October 2014 resulted in early termination of all the other trials. In addition to supervisors, I see them as collaborators and dear friends, and hope to continue to work with them far beyond the realm of this work. I have learnt a lot from both of them in slightly different ways. Diederik has inspired me to follow the path of science to the best of my abilities with absolutely no compromises. Aad through his gentle and humble management style has shown me the power of cooperation and teamwork. Through my interaction with Diederik and Aad, I had the opportunity to interact with some brilliant PhD students in Netherlands. I am really grateful to two of them, Olvert and Maxim who have kindly agreed to be my paranimfs and helped me through the practical aspects of the PhD defense.

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energy, enthusiasm, wit and presence of mind is something one can only aspire toward but never actually attain. Bob, my program director, was not only a great teacher, but also personally extremely helpful as I settled into a new continent. Watching Walter quietly go about his day taught me the value of being an 'old fashioned' plain and simple doctor that always puts the patient first.

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A. Barber P Goyal M; Hill MD; Magnetic Resonance Imaging Evaluation of NA1 Neuroprotection on Infarct Growth Following Endovascular Treatment for Acute Ischemic Stroke. (REPERFUSE-NA1)

B. Coutts S. Hill MD, Goyal M. TEMPO-2 - A randomized controlled trial of TNK-tPA versus standard of care for minor ischemic stroke with proven occlusion.

C. Saver J, Goyal M. SWIFT PRIME. Covidien. 2012-2015.

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E. Coutts, SB (PI), Hill MD (co-PI), Goyal M (co-PI), Demchuk AM, Greisenegger S, Kelly P, Menon BK, Muir K, Parsons M. TEMPO-2 - A randomized controlled trial of TNK-tPA versus standard of care for minor ischemic stroke with proven occlusion.

F. Coutts, SB (PI), Hill MD, Goyal M. TEMPO-2 - A randomized controlled trial of TNK-tPA versus standard of care for minor ischemic stroke with proven occlusion.

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H. Menon, BK (PI), Demchuk AM, Goyal M, Hill MD. Imaging tools for quick and

appropriate triage of stroke patients. CIHR project scheme grant

I. Menon B (PI), Goyal M, Forkert ND, Sajobi TT, Ahn S, D'Esterre C, Demchuk AM, Frayne R, Lee T, Hill MD An Automated Imaging Tool for Quick and Appropriate Triage of Stroke Patients. University of Calgary Medical Group (UCMG) Bridge Funding 2015-2016

J. Menon B (PI), Goyal, M (Co PI). Precise and Rapid assessment of collaterals using multi-phase CTA in the triage of patients with acute ischemic stroke for IV or IA Therapy (PRoVe-IT).

K. Hill MD, Goyal M, Demchuk AM. ESCAPE trial (Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times) 2014-2015. Hotchkiss Brain Institute.

L. Hill MD, Goyal M, Demchuk AM. ESCAPE trial (Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times).

M. Demchuk AM (PI), Dowlatshahi D, Goyal M, Hill MD, Menon B, Dowlatshahi D. Identifying New approaches to optimize Thrombus characterization for predicting Early Recanalization and Reperfusion with iv tPA using Serial CT angiography (INTERRSeCT).

N. Goyal M. HERMES collaboration. Medtronic Inc. 2015-2018.

O. Goyal M. UNMASK EVT study. Stryker. 2017-2019.

Invited lectures

1. Acute stroke: where are we at and where are we going. Keynote speaker. European Society of Neuroradiology. Rotterdam, Netherlands. October 2018.

2. Acute stroke: past, present and future. Grand rounds. Munich, Germany, November 2018.

3. Imaging in acute stroke. Neuroweek. Berlin, Germany. October 2018.

4. What we don't know. American Society of Neuroradiology. Vancouver, Canada. June 2018.

5. Drip and ship vs. Mothership. World Stroke Congress. Montreal, Canada. October 2018.

6. Summary of Stroke *Trials*. Neuroweek. Berlin, Germany. October 2018.

7. Strategies for effective EVT. World Stroke Congress. Montreal, Canada. October 2018.

8. Systems of care. Medtronic symposium. World Stroke Congress. Montreal, Canada. October 2018.

9. Imaging selection for endovascular stroke treatment: meta-analysis of the HERMES collaboration. Anatomy-Biology-Clinical correlations - Working group in Interventional Neuroradiology. Val d'lsere, France. January 2018.

10. Drip 'n ship vs. mothership: modelling stroke patient transport for all suspected large vessel occlusion patients. Anatomy-Biology-Clinical correlations - Working group in Interventional Neuroradiology. Val d'lsere, France. January 2018.

11. How much is too much? Should we exclude patients with ASPECTS < 5 from EVT? Lisbon Stroke Summit. Lisbon, Portugal. April 2018.

12. How do I do EVT!. 5T Stroke Conference. Banff, Canada. May 2018.

13. HERMES highlights. 5T Stroke Conference. Banff, Canada. May 2018.

14. Treat fast but abandon time from ischemic stroke onset as a criterion for treatment. Live Interventional Neuroradiology, *Neurology* and Neurosurgery Course (LINNC). Paris, France. June 2018.

15. Endovascular clot retrieval: the state of the. Stroke 2018 Bridging the Continuum. Sydney, Australia. August 2018.

16. Optimizing work flow for endovascular thrombectomy in acute ischemic stroke. First Erasmus MC Conference on acute Stroke Treatment. Rotterdam, the Netherlands. March 2017.

17. Indication for stroke treatment; gut feeling or evidence base [ESMINT debate presentation]. 9th Congress of the European Society of Minimally Invasive Neurological Therapy. Nice, France. September 2017.

18. Hermes, what's up? 9th Congress of the European Society of Minimally Invasive Neurological Therapy. Nice, France. September 2017.

19. Current imaging approach in acute stroke - the Calgary model. 18th Annual Interventional Neuroradiology Symposium. Toronto, Canada. September 2017.

20. Workflow in acute stroke: how to optimize it in light of time is brain. 76th An-

nual Meeting of the Japan Neurosurgical Society. Nagoya, Aichi, Japan. October 2017.

21. Pre-thrombectomy imaging. 14th Congress of the World Federation of Interventional and Therapeutic Neuroradiology. Budapest, Hungary. October 2017.

22. My approach to preparing for the case as efficiently as possible. 5T Stroke Conference. Banff, Canada. March 2017.

23. HERMES perfusion. 5T Stroke Conference. Banff, Canada. March 2017.

24. NCCT/multiphase CTA is the perfect balance for a PSC. 5T Stroke Conference. Banff, Canada. March 2017.

25. Diagnostic imaging and hyperacute stroke. 11th Annual Cerebrovascular Symposium - Interdisciplinary Care of the Stroke Patient. Seattle, USA. May 2017.

26. Initial hospital (achieving the 30-60 metrics). Society of NeuroInterventional Surgery 13th Annual Meeting. Boston, USA. July 2016.

27. Endovascular stroke intervention trials - importance of patient and imaging selection. American Heart Association Scientific Sessions. Anaheim, USA. November 2017.

28. Hyperacute ischemic stroke therapy (endovascular recanalization therapy): past, current, and future. International Conference Stroke Update and Internal Conference on Intracranial Atherosclerosis Joint Conference 2016. Jeju, Korea. September 2016.

29. Changing stroke therapy: a journey. The 12th New York Symposium on Neurological Emergencies and Neurocritical Care. New York, USA. June 2016.

30. Multimodality CT imaging: the crucial role of collateral. The 12th New York Symposium on Neurological Emergencies and Neurocritical Care. New York, USA. June 2016.

31. Advances in treatment of acute ischemic stroke through image guided interventional revascularization therapy. 4th Annual Stroke and Cerebrovascular Conference. Kansas City, USA. June 2018.

32. HERMES update. ABC-WIN. Val d'Isere, France. January 2018.

33. Organization of stroke care. ABC-WIN. Val d'Isere, France. January 2018.

34. Planning future stroke trials: what to watch out for. ABC-WIN. Val d'Isere, France. January 2018.

35. Acute stroke: past, present and future. University Hospital. Essen, Germany. February 2018.

36. Acute stroke: past, present and future. University Hospital. Goettingen, Germany. February 2018.

37. Acute stroke: past, present and future. University Hospital. Freiburg, Germany. February 2018.

38. Collaterals: whad did we learn from the recent trials. International Stroke Conference. Los Angeles, USA. January 2018.

39. Acute stroke: past, present and future. University Hospital. Hamburg, Germany. February 2018.

40. Workflow in acute stroke: how to optimize it in light of time is brain. Japanese

Neurosurgical Society. Nagoya, Japan. November 2017.

41. Imaging in acute stroke. WFITN. Budapest, Hungary. October 2017.

42. Organization of stroke care. Invited speaker. 19th Nordic Congress of Cerebrovascular Diseases. Aarhus, Denmark. August 2017.

43. Approach, protocols with interactive case discussions; Imaging in acute stroke in the light of current evidence; Penumbral status is the future of acute stroke imaging selection for revascularization; Speed in acute stroke: what does the data show? Monsoon Summit 2017 -- International Update in *Neurology*. Kochi, India. July 2017.

44. Changing acute stroke: a journey. University of Massachusetts Medical School. Worcester, USA. May 2017.

45. Guest faculty speaker. 8th Annual Baylor Stroke Conference. Dallas, USA. May 2017.

46. Stroke prevention and management guidelines forum. Munich, Germany. April 2017.

47. Best imaging strategy for selecting ELVO patients for endovascular therapy-ASPECTS/CTA collateral score. American Society of Neuroradiology. Long Beach, USA. April 2017.

48. Acute stroke: past, present and future. Dinner symposium. Melbourne, Australia, February 2017.

49. Changing acute stroke: a journey. American Academy of *Neurology* 68th Annual Meeting. Vancouver, Canada. April 2016.

50. Results of recent endovascular intervention trials. The Fourth Annual Neuro ICU Symposium. Houston, USA. March 2016.

51. Crossfire Debate: blood pressure must be less than SBP of 120-130mmHg in order to avoid hemorrhagic complications after TICI 2b/3 recanalization after an acute ischemic stroke due to M1 or carotid-T occlusion (yes). The Fourth Annual Neuro ICU Symposium. Houston, USA. March 2016.

52. Changing acute stroke: a journey. The Fourth Annual Neuro ICU Symposium. Houston, USA. March 2016.

53. Imaging in acute stroke. Stroke rounds. Melbourne, Australia, February 2017.

54. Changing acute stroke: A journey. Canadian Association of Radiologists 80th Annual Scientific Meeting. Montreal, Canada. April 2017.

55. Rethinking stroke imaging in light of recent evidence. Canadian Association of Radiologists 80th Annual Scientific Meeting. Montreal, Canada. April 2017.

56. Acute stroke: past, present and future. Dinner symposium. Brisbane, Australia, February 2017.

57. Acute stroke: past, present and future. Neuroscience rounds. Sydney, Australia, February 2017.

58. Acute stroke: past, present and future. Neuroscience rounds, Gold Coast, Australia, February 2017.

59. Collaterals in Asia. Los Angeles, USA. November 2016.

60. Imaging and workflow in acute stroke, Denis Melancon Neuroradiology Conference Montreal, Canada. October 2016.

61. Hyperacute ischemic stroke therapy (endovascular recanalization therapy): past, current and future. Jeju, South Korea. September 2016.

62. Initial hospital (achieving the 30-60 metrics.) Boston, USA. July 2016.

63. Changing acute stroke: an ongoing journey. Toronto, Canada. March 2016.

64. Imaging in acute stroke. Indian Society of Neuroradiology. Indore, India. October 2015.

65. Changing acute stroke: a journey. Indore, India. October 2015.

66. Patient Selection: Clinical, Multimodal Imaging or Just a CT and CTA? SVIN meeting. Bonita Springs, USA. October 2015.

67. Changing acute stroke: a journey. Dinner symposium. New Orleans, USA. October 2015.

68. Patient Selection post IV tPA: Who and When? Do You Wait or Take Everyone to the Lab? SVIN meeting. Bonita Springs, USA. October 2015.

69. Embolectomy: How to Speed Things up: The Canadian Approach. SVIN meeting. Bonita Springs, USA. October 2015.

70. Summary of recent trials. Stroke symposium. Kualalumpur, Malaysia. October 2015.

71. Mothership vs. drip and ship: what does the data show? Stroke symposium. Kualalumpur, Malaysia. October 2015.

72. Decision making and organization in acute stroke. APSO congress. Kualalumpur, Malaysia. October 2015.

73. Imaging and decision making in acute stroke. Stroke symposium. Kualalumpur, Malaysia. October 2015.

74. Parallel processing and workflow in acute stroke. Stroke symposium. Kualalumpur, Malaysia. October 2015.

75. Planning the procedure on a CT angiogram. Stroke symposium. Kualalumpur, Malaysia. October 2015.

76. Table and patient preparation. Stroke symposium. Kualalumpur, Malaysia. October 2015.

77. Ecnonomic analysis: SWIFT PRIME. Stroke symposium. Kualalumpur, Malaysia. October 2015.

78. Future of stroke research. Stroke symposium. Kualalumpur, Malaysia. October 2015.

79. Stroke management and the results of recent trials. Mumbai, India. July 2015

80. Stroke management and the results of recent trials. Dinner symposium, Bangalore, India. July 2015.

81. Changing acute stroke: a journey NIMHANS special guest lecture. Bangalore, India. July 2015.

82. Results of recent stroke trials and its impact on stroke care. Teleradiology Solutions. Bangalore, India. July 2015.

83. Stroke management and the results of recent trials. Dinner symposium, New Delhi, India. July 2015

84. Stroke management and the results of recent trials. Chennai, India. July 2015.

85. Imaging, workflow and intervention in acute stroke. Bologna, Italy. July 2015.

86. Imaging, workflow and intervention in acute stroke. Las Palmas Gran Canarias. July 2015.

87. Imaging, workflow and intervention in acute stroke. Lyon, France. July 2015.

88. Practical imaging nd decision making in acute stroke. Dinner symposium. Lyon, France. July 2015.

89. ESCAPE trial: design, imaging and workflow. STROKE LIVE LIVE STROKE COURSE, Nice, France, September 2015.

90. Workflow in acute stroke. SLIVE LIVE STROKE COURSE, Nice, France, September 2015.

91. Practical Imaging in acute stroke. STROKE LIVE LIVE STROKE COURSE, Nice, France, September 2015.

92. Changing acute stroke: a journey: Miami, USA. May 2015.

93. Stroke Workflow. Irish Society of Neuroradiology. Dublin, Ireland. May 2015.

94. Changing acute stroke: a journey: Irish Society of Neuroradiology. Dublin, Ireland. May 2015.

95. ESCAPE trial: design, imaging and workflow. International Stroke Conference. Nashville, USA. February 2015.

96. Implications of recent trials on future of acute stroke. Covidien Satellite symposi-

um. International Stroke Conference. Nashville, USA. February 2015.

97. Streamlining protocols for endovascular stroke care. National Neuroscience Institute, Tan Tock Seng, Singapore. October 2015.

98. Acute stroke imaging and intervention. West Palm Beach, USA. April 2014

99. Acute stroke imaging and Intervention. Neurointervention meeting. Temple University. Philadelphia, USA. April 2014

100. Acute stroke imaging. Yonsei University. Seoul, South Korea. April 2014

101. Acute stroke intervention. Daegu University, Daegu, South Korea, April 2014

102. From evidence to practice: advancing systems of care in acute ischemic stroke. Taipei, Taiwan. September 2014

103. Critical success factors in establishing ideal systems of care in ischemic stroke. Asia Pacific Stroke Conference, Taipei, Taiwan, September 2014

104. Imaging and intervention in acute stroke. National Neuroscience Insitute. Singapore. September 2014

105. New paradigms in stroke care. Understanding EVT for ischemic stroke. Clinical Neuroscience Society of Singapore, Singapore. September 2014.

106. Imaging in acute stroke. Singapore General Hospital. Singapore. September 2014.

107. Intervention in acute stroke: future directions. National University of Singapore, Singapore, September 2014.

108. Imaging and intervention in acute stroke. Prince of Wales Hospital, HongKong,

China. September 2014

109. AIS management. HongKong Society of Interventional *Radiology*, HongKong, China. September 2014.

110. Efficient imaging in acute stroke. International Conference on Intracranial Atherosclerosis. Chengdu, Sichuan, China, September 2014.

111. Optimizing stroke workflow. International Conference on Intracranial Atherosclerosis. Chengdu, Sichuan, China, September 2014.

112. Update of stroke imaging and intervention since MR-RESCUE: focusing on imaging strategy (CT and/or MR). Korean Congress of *Radiology*, Seoul, South Korea. October 2014.

113. Changing acute stroke: a journey. Korean Society of Neurointervention. Seoul, South Korea. October 2014.

114. IV vs IA is not the argument: Revascularization needs to be fast. AIM VEITH symposium. New York, USA. November 2014.

115. CT and CTA Best imaging triage: The Calgary way. AIM VEITH symposium. New York, USA. November 2014.

116. Ultrafast door to groin puncture times. AIM VEITH symposium. New York, USA. November 2014.

117. Acute stroke workflow and organization. SWIFT PRIME Investigators meeting. San Diego, USA. February 2014.

118. Acute stroke imaging and intervention. West Palm Beach, USA. April 2014.

119. Acute stroke imaging and Intervention. Neurointervention meeting. Temple University. Philadelphia. April 2014.

120. Acute stroke imaging. Yonsei University. Seoul, South Korea. April 2014.

121. Optimizing acute stroke workflow. Covidien Satellite symposium. San Diego, USA. February 2014.

122. Workflow in Acute stroke. Society of NeuroInterventional Surgery meeting. San Diego, USA. February 2014.

123. Getting to angio fast: lessons learnt from ESCAPE trial. International Stroke Conference. San Diego, USA. February 2014.

Awards (Recent)

- Canadian Association of Radiologists Distinguished Career Achievement Award Recipient 2018
- Researcher of the year: Clinical faculty. Cumming School of Medicine. 2015
- Contributions to Innovation in the field of Neurointervention. Society of Vascular and Intervention *Neurology*, 2015.
- President's Excellence Award: Research 2016. Alberta Health Services
- Fellowship to the Canadian Academy of Health Sciences 2018
- Fellowship to the Canadian Association of *Radiology* 2018

Knowledge Translation

- Multiphase CTA. This is a technique of imaging of acute stroke patients developed by me. Subsequently it was used in the ESCAPE trial and has shown usefulness in acute stroke decision making in multiple ways: a. Saves approximately 20 mintues as compared to an imaging algorithm based on CT perfusion (Time is brain in acute stroke) b. is less vulnerable to patient motion c. can be performed on any CT scanner d. does not require complex post-processing and e. potentially leads to better decision making. This technique is now being used at many stroke centres across Canada and is slowly spreading across the world with implementation in South Korea, Spain, India etc.

- Stroke Kit: BRISK (Brisk Recanalization Ischemic Stroke Kit). This was a methodology I developed to pre-organize the angiography suite that leads to more efficient workflow during treatment of an acute stroke patient. Once we were comfortable with it in Calgary, in the process of running the ESCAPE trial I implemented this across the ESCAPE sites in Canada. Consequently, of all the acute stroke trials, ESCAPE was by far the fastest. This has now been implemented in South Korea as well.

- Aspectsinstroke.com. I developed this educational website to train other sites and stroke centres on how to effectively and accurately interpret acute stroke imaging using the ASPECTS score (that was also developed in Calgary) and collateral imaging.

- 5tstroke.ca. I am the chair of this Calgary Stroke Program stroke course. The first one is in Banff in Feb 2016. We are expecting a worldwide audience. One of the main purposes is knowledge translation: teach other centres all that we have collectively learnt during the running of the ESCAPE trial and effectively manage acute stroke patients.

- Letsgetproof.com. I am in the process of setting up this not-for-profit company. The mandate of the company is to increase the efficiency of stroke research. It is divided into two distinct components: crowd-review and crowdfunding. It is likely to be developed in conjunction with the European Stroke Organization.

LIST OF PUBLICATIONS

1. Fisher M, **Goyal M**. Variance of imaging protocols for patients with suspected acute ischemic stroke because of large-vessel occlusion. *Stroke*, 2018.

2. Ganesh A, **Goyal M**. Thrombectomy for acute ischemic stroke: recent insights and future directions. *Curr Neurol Neurosci Rep*, 2018; 18(9):59.

3. Kunz WG, Almekhlafi MA, **Goyal M**. Distal vessel occlusions: when to consider endovascular thrombectomy. *Stroke*, 2018; 49(7):1581-3.

4. Reid M, Famuyide AO, Forkert ND, Sahand TA, Evans JW, Sitaram A, Hafeez M, Najm M, Menon BK, Demchuk A, **Goyal M**, Gupta SR, d'Esterre CD, Barber P. Accuracy and reliability of multiphase CTA perfusion for identifying ischemic core. *Clin Neuroradiol*, 2018.

5. Bernhardt J, Zorowitz RD, Becker KJ, Keller E, Saposnik G, Strbian D, Dichgans M, Woo D, Reeves M, Thrift A, Kidwell CS, Olivot JM, **Goyal M**, Pierot L, Bennett DA, Howard G, Ford GA, Goldstein LB, Planas AM, Yenari MA, Greenberg SM, Pantoni L, Amin-Hanjani S, Tymianski M. Advances in stroke 2017. *Stroke*, 2018; 49(5):e174-e199.

6. Boers AMM, Jansen IGH, Beenen LFM, Devlin TG, San Roman L, Heo JH, Ribo M, Brown S, Almekhlafi MA, Liebeskind DS, Teitelbaum J, Lingsma HF, van Zwam WH, Cuadras P, du Mesnil dR, Beaumont M, Brown MM, Yoo AJ, van Oostenbrugge RJ, Menon BK, Donnan GA, Mas JL, Roos YBWE, Oppenheim C, van der LA, Dowling RJ, Hill MD, Davalos A, Moulin T, Agrinier N, Demchuk AM, Lopes DK, Aja RL, Dippel DWJ, Campbell BCV, Mitchell PJ, Al Ajlan FS, Jovin TG, Madigan J, Albers GW, Soize S, Guillemin F, Reddy VK, Bracard S, Blasco J, Muir KW, Nogueira RG, White PM, **Goyal M**, Davis SM, Marquering HA, Majoie CBLM. Association of follow-up infarct volume with

functional outcome in acute ischemic stroke: a pooled analysis of seven randomized trials. *J Neurointerv Surg*, 2018.

7. Dekker L, Geraedts VJ, Hund H, Cannegieter SC, Nogueira RG, **Goyal M**, van dW, I. Importance of reperfusion status after intra-arterial thrombectomy for prediction of outcome in anterior circulation large vessel stroke. *Interv Neurol*, 2018; 7(3-4):137-47.

8. **Goyal M**, Ganesh A, Brown S, Menon BK, Hill MD. Suggested modification of presentation of stroke trial results. *Int J Stroke*, 2018.

9. **Goyal M**, Menon BK, Wilson AT, Almekhlafi MA, McTaggart R, Jayaraman M, Demchuk AM, Hill MD. Primary to comprehensive stroke center transfers: appropriateness, not futility. *Int J Stroke*, 2018.

10. Graham BR, Menon BK, Coutts SB, **Goyal M**, Demchuk AM. Computed tomographic angiography in stroke and high-risk transient ischemic attack: do not leave the emergency department without it! *Int J Stroke*, 2018.

11. Hill MD, **Goyal M**. Treat fast but abandon time from ischemic stroke onset as a criterion for treatment: the DAWN and DEFUSE-3 trials. *Int J Stroke*, 2018; 13(4):344-7.

12. Kaesmacher J, Mordasini P, Arnold M, Lopez-Cancio E, Cerda N, Boeckh-Behrens T, Kleine JF, **Goyal M**, Hill MD, Pereira VM, Saver JL, Gralla J, Fischer U. Direct mechanical thrombectomy in tPA-ineligible and -eligible patients versus the bridging approach: a meta-analysis. *J Neurointerv Surg*, 2018.

13. Kallmes DF, Kallmes K, **Goyal M**, Hirsch JA, Rabinstein AA, Brinjikji W, Derdeyn C. Equipoise dumbbell. *J Neurointerv Surg*, 2018.

14. Najm M, Al Ajlan FS, Boesen ME, Hur L, Kim CK, Fainardi E, Hill MD, Demchuk AM, **Goyal M**, Lee TY, Menon BK. Defining CT perfusion thresholds for

infarction in the golden hour and with ultra-early reperfusion. *Can J Neurol Sci*, 2018; 45(3):339-42.

15. Wannamaker R, Guinand T, Menon BK, Demchuk A, **Goyal M**, Frei D, Bharatha A, Jovin TG, Shankar J, Krings T, Baxter B, Holmstedt C, Swartz R, Dowlatshahi D, Chan R, Tampieri D, Choe H, Burns P, Gentile N, Rempel J, Shuaib A, Buck B, Bivard A, Hill M, Butcher K. Computed tomographic perfusion predicts poor outcomes in a randomized trial of endovascular therapy. *Stroke*, 2018; 49(6):1426-33.

16. Campbell BCV, van Zwam WH, **Goyal M**, Menon BK, Dippel DWJ, Demchuk AM, Bracard S, White P, Davalos A, Majoie CBLM, van der LA, Ford GA, de la Ossa NP, Kelly M, Bourcier R, Donnan GA, Roos YBWE, Bang OY, Nogueira RG, Devlin TG, van den Berg LA, Clarencon F, Burns P, Carpenter J, Berkhemer OA, Yavagal DR, Pereira VM, Ducrocq X, Dixit A, Quesada H, Epstein J, Davis SM, Jansen O, Rubiera M, Urra X, Micard E, Lingsma HF, Naggara O, Brown S, Guillemin F, Muir KW, van Oostenbrugge RJ, Saver JL, Jovin TG, Hill MD, Mitchell PJ. Effect of general anaesthesia on functional outcome in patients with anterior circulation ischaemic stroke having endovascular thrombectomy versus standard care: a meta-analysis of individual patient data. *Lancet Neurol*, 2018; 17(1):47-53.

17. **Goyal M**, Simonsen CZ, Fisher M. Future trials on endovascular stroke treatment: the not-so-easy-to-pluck fruits. *Neuroradiology*, 2018; 60(2):123-6.

18. Tokunboh I, Vales MM, Zopelaro Almeida MF, Sharma L, Starkman S, Szeder V, Jahan R, Liebeskind D, Gonzalez N, Demchuk A, Froehler MT, **Goyal M**, Lansberg MG, Lutsep H, Schwamm L, Saver JL. Visual aids for patient, family, and physician decision making about endovascular thrombectomy for acute ischemic stroke. *Stroke*, 2018; 49(1):90-7.

19. Arenillas JF, Cortijo E, Garcia-Bermejo P, Levy EI, Jahan R, **Goyal M**, Saver JL, Albers GW. Relative cerebral blood volume is associated with collateral status

and infarct growth in stroke patients in SWIFT PRIME. *J Cereb Blood Flow Metab*, 2017.

20. Assis Z, Menon BK, **Goyal M**, Demchuk AM, Shankar J, Rempel JL, Roy D, Poppe AY, Yang V, Lum C, Dowlatshahi D, Thornton J, Choe H, Burns PA, Frei DF, Baxter BW, Hill MD. Acute ischemic stroke with tandem lesions: technical endovascular management and clinical outcomes from the ESCAPE trial. *J Neurointerv Surg*, 2017.

21. Brinjikji W, Starke RM, Murad MH, Fiorella D, Pereira VM, **Goyal M**, Kallmes DF. Impact of balloon guide catheter on technical and clinical outcomes: a systematic review and meta-analysis. *J Neurointerv Surg*, 2017.

22. Casault C, Al Sultan AS, Trivedi A, Sohn SI, Qazi E, Bokyo M, Almekhlafi M, d'Esterre C, **Goyal M**, Demchuk AM, Menon BK. Collateral scoring on CT angiogram must evaluate phase and regional pattern. *Can J Neurol Sci*, 2017; 44(5):503-7.

23. Jayaraman MV, McTaggart RA, **Goyal M**. Unresolved issues in thrombectomy. *Curr Neurol Neurosci Rep*, 2017; 17(9):69.

24. Assis ZA, Menon BK, **Goyal M**. Imaging department organization in a stroke center and workflow processes in acute stroke. *Eur J Radiol*, 2017.

25. Batchelor C, Pordeli P, d'Esterre CD, Najm M, Al Ajlan FS, Boesen ME, McDougall C, Hur L, Fainardi E, Shankar JJS, Rubiera M, Khaw AV, Hill MD, Demchuk AM, Sajobi TT, **Goyal M**, Lee TY, Aviv RI, Menon BK. Use of noncontrast computed tomography and computed tomographic perfusion in predicting intracerebral hemorrhage after intravenous alteplase therapy. *Stroke*, 2017; 48(6):1548-53.

26. **Goyal M**, Wilson AT, Kamal N, McTaggart RA, Jayaraman MV, Fisher M, Hill MD. Amartya sen and the organization of endovascular stroke treatment. *Stroke*, 2017.

27. Menjot dC, Saver JL, **Goyal M**, Jahan R, Diener HC, Bonafe A, Levy EI, Pereira VM, Cognard C, Yavagal DR, Albers GW. Efficacy of stent-retriever thrombectomy in magnetic resonance imaging versus computed tomographic perfusion-selected patients in SWIFT PRIME trial (solitaire FR with the intention for thrombectomy as primary endovascular treatment for acute ischemic stroke). *Stroke*, 2017; 48(6):1560-6.

28. Rodriguez-Luna D, Coscojuela P, Rodriguez-Villatoro N, Juega JM, Boned S, Muchada M, Pagola J, Rubiera M, Ribo M, Tomasello A, Demchuk AM, **Goyal M**, Molina CA. Multiphase CT angiography improves prediction of intracerebral hemorrhage expansion. *Radiology*, 2017;162839.

29. Raychev R, Jahan R, Saver JL, Nogueira RG, **Goyal M**, Pereira VM, Levy E, Yavagal DR, Cognard C, Liebeskind D. Microcatheter contrast injection in stent retriever neurothrombectomy is safe and useful: insights from SWIFT PRIME. *J Neurointerv Surg*, 2017.

30. Rhodes JM, Faunce DM, Potvin JH, Umbenhauer J, Pedro N, Devine J, **Goyal M**, Jayaraman MV, McTaggart RA. Efficient stroke care at the hospital. *EMS World Magazine*, 2017; 46(10):1-4.

31. Sah RG, d'Esterre CD, Hill MD, Hafeez M, Tariq S, Forkert ND, Demchuk AM, **Goyal M**, Barber PA. Diffusion-weighted MRI stroke volume following recanalization treatment is threshold-dependent. *Clin Neuroradiol.* 2019 Mar;29(1):135-141

32. Sajobi TT, Singh G, Lowerison MW, Engbers J, Menon BK, Demchuk AM, **Goyal M**, Hill MD. Minimal sufficient balance randomization for sequential randomized controlled trial designs: results from the ESCAPE trial. *Trials*, 2017; 18(1):516.

33. Simpson KN, Simpson AN, Mauldin PD, Palesch YY, Yeatts SD, Kleindorfer D, Tomsick TA, Foster LD, Demchuk AM, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, von Kummer R, Molina CA, **Goyal M**, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Broderick JP. Observed cost and variations in short term cost-effectiveness of therapy for ischemic stroke in interventional management of stroke (IMS) III. *J Am Heart Assoc*, 2017; 6(5).

34. Zerna C, **Goyal M**. *Stroke*: Long-term outcome of endovascular therapy for ischaemic stroke. *Nat Rev Neurol*, 2017; 13(7):387-8.

35. Boesen ME, Eswaradass PV, Singh D, Mitha AP, **Goyal M**, Frayne R, Menon BK. MR imaging of carotid webs. *Neuroradiology*, 2017; 59(4):361-5.

36. d'Esterre CD, Trivedi A, Pordeli P, Boesen M, Patil S, Hwan AS, Najm M, Fainardi E, Shankar JJ, Rubiera M, Almekhlafi MA, Mandzia J, Khaw AV, Barber P, Coutts S, Hill MD, Demchuk AM, Sajobi T, Forkert ND, **Goyal M**, Lee TY, Menon BK. Regional comparison of multiphase computed tomographic angiography and computed tomographic perfusion for prediction of tissue fate in ischemic stroke. *Stroke*, 2017; 48(4):939-45.

37. Mokin M, Levy EI, Saver JL, Siddiqui AH, **Goyal M**, Bonafe A, Cognard C, Jahan R, Albers GW. Predictive value of RAPID assessed perfusion thresholds on final infarct volume in SWIFT PRIME (solitaire with the intention for thrombectomy as primary endovascular treatment). *Stroke*, 2017; 48(4):932-8.

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ABOUT THE AUTHOR

Mayank was born in Delhi, India in 1966. He did school at Modern School in Delhi. During school life, Mayank had a passion for math and physics. In 1984, Mayank started his medical education at the All India Institute of Medical Sciences (AIIMS). He subsequently did his residency in Radiology from the same Institution. In 1996, Mayank joined as an Assistant Professor, Neuroradiology at AIIMS.

Mayank moved to Canada in 1998 and initially did a fellowship in Neuroradiology at the University of Toronto. Subsequently, he moved to University of Ottawa and started an academic practice in Neuroradiology. His main research interest even at that time was in acute ischemic stroke and he was instrumental in getting endovascular thrombectomy going there. In 2006, he moved to Calgary to be part of University of Calgary and EFW Radiology. He soon became an integral part of the Calgary Stroke Program. He is currently a Clinical Professor at the Department of Radiology and Clinical Neurosciences at the University of Calgary. He is also the Director of Acute Stroke Imaging and Intervention at the Calgary Stroke Program. He is a Fellow of the Royal College of Physicians of Canada (FRCPC). He is also a Fellow of the American Heart Association (FAHA). He was recently honoured as a Fellow of the Canadian Association of Radiology (FCAR) and Fellow of Canadian Academy of Health Sciences (FCAHS). He was awarded the CAR Distinguished Career Achievement Award in 2018.

Supriya (his wife) and Mayank were batchmates in their medical school class and have known each other since 1984. The got married in 1990. They have two sons. Dhruv was born in 1994 and Arnuv in 2000. Mayank loves sports (football, volleyball in younger days and now more restricted to squash and table tennis). More recently he has tried to dabble in golf without much success. The Goyal family love to travel and explore new places and cultures and have traveled to all continents except Antarctica. Mayank is an avid reader on a wide variety of subjects including science fiction, politics, philosophy, technology and AI etc.