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Imaging in Endovascular Stroke Trials

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Abstract

Ischemic stroke remains a leading cause of death and disability worldwide. Various endovascular trials have addressed clinical outcomes without elucidating the impact of imaging studies in patient selection. The success of recent endovascular trials was bolstered by the use of advanced imaging techniques for optimal selection of reperfusion candidates. This seminal juncture in the history of stroke trials warrants further consideration on the use of imaging to guide future refinements in the treatment of acute stroke. In this article, we systematically review the imaging methodology and key facets used in all published endovascular stroke trials to date, discuss the success of recent trials using latest advanced imaging techniques and focus on the importance of imaging studies for future patient selection.

Keywords

Neuroimaging; stroke; endovascular therapy; clinical trials

Acute ischemic stroke remains a leading cause of disability in adults and the fifth leading cause of mortality worldwide.[1] Intravenous tissue plasminogen activator (IV tPA) can be used within 3 or 4.5-hours of stroke symptom onset, thus limiting its use to only 1%–7% of the patient population.[2–4] Imaging plays a pivotal role in evaluating acute ischemic stroke patients especially before treatment plans are formalized. Major developments have recently occurred in stroke imaging and treatment, with the recently proven safety and efficacy of endovascular thrombectomy techniques for acute ischemic stroke. The primary goal of imaging with initial noncontrast CT (NCCT) or MRI is to differentiate hemorrhage from ischemia for consideration of IV tPA thrombolysis.[3, 5] Recent studies have incorporated secondary goals of imaging before initiating endovascular therapies. This process predominantly focuses on identification of a proximal arterial or large vessel occlusion (LVO) and to assess the extent of ischemic core or areas at-risk of evolving infarction.[6–8]

Multimodal CT or MRI including noninvasive angiography and perfusion techniques has been used only sparingly in decisions regarding thrombolysis with IV tPA. Until quite recently, only limited data supported the role of endovascular therapy. These earlier studies focused on the use of readily available clinical variables, arguing against the use of multimodal imaging as a potential cause of unnecessary treatment delays. Numerous recent

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trials have now demonstrated positive outcomes, possibly driven to a large degree by the use of imaging selection criteria.[9–11] Most of these studies were terminated earlier than planned subject enrollment, also likely fueled by rigorous imaging selection.

Cogent rationale now exists for vascular neurologists to consider the detailed imaging aspects of endovascular trials with a focus on potential generalizability and translation into routine clinical practice. We compiled a systematic, comprehensive review of the imaging used in all endovascular trials to date for acute ischemic stroke. Our primary focus was on the utility of different imaging approaches embedded in these trials. We also consider new imaging techniques that will continue to evolve and that will likely be a key focus in future investigations.

Endovascular Trials up to 2014

Prior to 2014, endovascular therapy techniques including intra-arterial (IA) thrombolysis, thrombus aspiration, angioplasty/stenting and mechanical thrombectomy had been used in select cases, single-arm studies and randomized studies comparing endovascular techniques. In this section, we discuss trials of endovascular therapy in acute ischemic stroke patients during this period and the incorporated imaging of subjects with special focus on patient selection, reperfusion rates and the potential impact on trial results.

PROACT I

The Prolyse in Acute Cerebral Thromboembolism (PROACT) was the first randomized, double-blinded, multicenter trial conducted in 37 centers of United States that compared safety, recanalization rates, and clinical efficacy of IA infusion of recombinant pro-urokinase (rpro-UK). [12] The trial included two rpro-UK doses with 6mg tier to be completed before initiating 12mg tier. Patients with neurological deficits in the middle cerebral artery (MCA) distribution presenting within 6 hours were randomized in 2:1 ratio to receive either rpro-UK or placebo by IA infusion. The investigators used NCCT to exclude patients with intracerebral hemorrhage (ICH), midline shift or tumor, while profiles with early ischemic change were included. NCCT was repeated in 24 hours to evaluate hemorrhagic transformation causing neurological deterioration. Patients had digital subtraction angiography (DSA) to assess Thrombolysis in Myocardial Infarction (TIMI) grades in the first (M1) and second (M2) divisions of the MCA. Central Randomization Center to receive either 6 mg rpro-UK or saline placebo. Serial DSA was performed at 60 minutes and 120 minutes to assess TIMI grade with partial (TIMI 2) or complete (TIMI 3) recanalized patients categorized as “responders.” TIMI 2/3 grades at 120 minutes from treatment onset was observed in 57.7% treated with rpro-UK as compared to 14.3% of placebo group (2p=0.017). Five of rpro-UK–treated patients displayed complete recanalization (TIMI 3) while none of placebo patients achieved such response. One of the limitations of the study was inclusion of patients with early ischemic changes on initial NCCT. IA rpro-UK infusion was associated with superior recanalization in acute ischemic stroke compared with placebo and enhanced recanalization with rpro-UK and heparin.

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PROACT II

PROACT II study was the first randomized, controlled, multicenter, open-label clinical trial with blinded follow-up conducted in 54 centers of United States and Canada that compared the safety, recanalization rates and clinical efficacy of IA infusion of rpro-UK.[13] Patients with neurological deficits in the MCA distribution presenting within 6 hours were randomized in a 2:1 ratio to receive IA r-proUK plus heparin or heparin only (control group). The investigators used NCCT at baseline to evaluate ICH, hypodensity or sulcal effacement in >1/3 MCA territory and at 24 hours to evaluate hemorrhagic transformation or any decline in neurological status. Patients had DSA to assess TIMI grades in the M1 and M2 divisions of the MCA. Serial DSA was performed at 60 minutes and 120 minutes to assess TIMI grade with partial (TIMI 2) or complete (TIMI 3) recanalized patients categorized as "responders." TIMI 2/3 grades at 120 minutes from treatment onset was observed in 66% treated with rpro-UK as compared to 18% of control group placebo ($p<0.001$). 19% of rpro-UK–treated patients displayed TIMI 3, while only 2% of control group achieved such response ($p<0.003$). A few limitations involved the small sample size and higher rpro-UK dose as compared to PROACT I that led to increased sICH (10.2%). IA rpro-UK treatment within 6 hours was associated with superior recanalization and significant clinical improvement at 90 days in acute MCA stroke patients.

MERCI

Mechanical Embolus Removal in Cerebral Ischemia (MERCI) was a prospective, non-randomized, multicenter study that involved 25 centers in United States.[14] The study tested the safety and efficacy of Merci retriever device to restore vessel patency within 8 hours of stroke symptom onset. The investigators used either routinely acquired NCCT or MRI in select cases, with a repeat study at 24 hours to evaluate hemorrhagic transformation or any decline in patient's neurological status. Patients were included if they had occlusion of the intracranial vertebral artery, basilar artery, intracranial carotid artery (ICA), ICA terminus bifurcation or M1/M2 divisions of the MCA. Successful revascularization (defined as TIMI 2/3 flow in all treated vessels) was achieved in 68 /141 patients (48%, $p<0.001$). A few limitations involved in the imaging selection were the single arm study design with no angiographic control group and that spontaneous ICA recanalization was likely overestimated using 18% recanalization rate of proximal MCA occlusions in the control arm of PROACT II as a benchmark. The study established that the Merci retriever device could be safely used to restore vessel patency in IV tPA-ineligible stroke patients within 8 hours of symptom onset.

MELT Japan

Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan was a multicenter, randomized trial conducted at 57 centers in Japan that studied the safety and efficacy of IA-urokinase (UK).[15] Ischemic stroke patients presenting within 6 hours of onset and displaying occlusions of the M1 or M2 segments of MCA on angiography were randomized to the IA-UK or control groups. NCCT was used to rule out hemorrhage, intracranial tumor, aneurysm, arteriovenous malformation, or venous thrombus, while follow-up NCCT was scheduled at 24 hours, 7 days, and 90 days of symptom onset. They

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used DSA to select patients with occlusion of the M1 or M2 segments. Partial or complete recanalization was achieved in 42 of 57 patients (73.7%) treated with IA UK. The study did not reach statistical significance, possibly due to small sample size, inclusion of low NIHSS patients without use of <1/3 early ischemic sign on NCCT and sICH found to be 5 times more common in treatment group. This study suggested excellent functional outcome with IA-UK for patients with acute MCA occlusions within 6 hours of symptom onset.

Multi-MERCI

Multi MERCI was an international, multicenter, single-arm set of studies using multiple thrombectomy devices (Merci Retriever X5, X6 and L5 Retriever).[16] The main objectives of this trial were to gain more experience with Merci Retriever first-generation devices (X5 and X6) in patients ineligible for IV tPA and to supplement the data from MERCI trial exploring the safety and efficacy of using Merci Retriever in IV tPA treated patients who failed to recanalize and to obtain safety and efficacy data on a second-generation thrombectomy device (L5 Retriever). The investigators used NCCT initially to assess hemorrhage followed by 24 hour NCCT or MRI to evaluate hemorrhagic conversion or decline in patient's neurological status. They utilized DSA to evaluate any occlusion in intracranial vertebral artery, basilar artery, ICA, ICA terminus bifurcation, and M1/M2 divisions of MCA. Reperfusion was studied with successful revascularization defined as TIMI grade 2 or 3 flow in all treated vessels. Successful recanalization was achieved in 75 of 131 (57.3%) patients in whom L5 retriever was deployed, while 15 of 33 (45.5%) of cases in which older generation X5/X6 devices were deployed had recanalization (p=0.25). Some limitations included the absence of upper limits for age and NIHSS and that 14% patients had pre-stroke mRS scores greater than 0. Positive trends were noted with lower mortality, good clinical outcome and better recanalization. Higher recanalization rates were noted with the newer generation devices.

PENUMBRA PIVOTAL

The Penumbra Pivotal study was a prospective, multi-center, single-arm trial that assessed the safety and efficacy of the Penumbra aspiration system for revascularization of ischemic stroke patients with large vessel occlusion (LVO).[17] A standard imaging protocol included NCCT to exclude patients with extensive infarction >1/3 of MCA territory, severe edema, and ICH with follow-up 24 hour NCCT to evaluate hemorrhage conversion. DSA was utilized to assess suspected vascular occlusion. Successful revascularization (TIMI 2 or 3 at the site of primary occlusion) was achieved in 81.6% (95% CI: 73.7–88.0) of total patients while 54.4% patients achieved TIMI 2 and 27.2% patients achieved TIMI 3. It was a single arm study with no concurrent control group for comparison. The study concluded that penumbra aspiration system provides safe and effective revascularization in ischemic stroke patients with LVO presenting within 8 hours from symptom onset.

DEFUSE 2

Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) 2 was a multicenter, prospective, cohort study that involved 8 centers in United States and one center in Europe.[18] Consecutive acute ischemic stroke patients (n=104) scheduled to undergo endovascular therapy within 12 hours of symptom onset were enrolled. Patients had

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serial MRI scans including baseline imaging within 90 minutes prior to procedure, follow-up within 12 hours after procedure and later follow-up MRI on day 5 or at the time of discharge. Baseline MRI was used to assess target mismatch profiles with substantial penumbra or areas at-risk and small diffusion weighted imaging (DWI) abnormalities relative to perfusion weighted imaging (PWI) lesions. Reperfusion was defined as >50% reduction in PWI lesion volume (Tmax>6sec) between baseline and follow-up MRI scans. Reperfusion was associated with overall increased rate of favorable clinical response (OR 2.8, 1.2 – 6.2) with target mismatch group (n=78) (OR 5.0; 95% CI 1.9 – 13, p=0.001), while patients without target mismatch group (n=21) reflected less favorable response with reperfusion (OR=0.2; 95% CI 0.0 – 1.4). Study limitations included: a) single arm study with no control group receiving endovascular therapy b) small cohort of non-target mismatch patients that underwent endovascular therapy c) limited application of trial results to patients imaged within the time-window of 4 hours from symptom onset to MRI. The study concluded that patients with target mismatch profile with early reperfusion following endovascular therapy achieved more favorable outcomes and less infarct growth.

SWIFT

Solitaire flow restoration device versus the Merci Retriever in patients with acute ischemic stroke (SWIFT) was a multicenter, randomized, prospective, parallel-group trial with blinded primary endpoint conducted at 18 sites.[19] Acute ischemic stroke patients with angiographically confirmed LVO were randomly divided into Solitaire Flow Restoration (FR) stent retriever and Merci retriever groups. Routine imaging protocol included NCCT or MRI brain to check for ICH or acute ischemic change in ≥ 1/3 MCA territory or > 100 mL of tissue in other territories. Follow-up imaging within 24 hours monitored for hemorrhagic transformation. The central core imaging laboratory evaluated the reperfusion with successful revascularization as TIMI grade 2 or 3 flow in all treatable vessels. TIMI ≥ 2 per core laboratory was achieved in 69% of Solitaire group and 30% of Merci (OR 5.03; 95% CI 2.22–13.66, p<0.001). Total duration involved from placement of guide catheter to recanalization or end of procedure was shorter in the Solitaire group (36 min, IQR 18–65; n=47) as compared to Merci group (52 min, IQR 31–73; n=46; superiority p=0.038). A few limitations were noted including the absence of a no comparison made between Solitaire FR stent retriever and emerging stent retrievers or Penumbra aspiration system and the early halt of trial led to small sample size limiting the precision of treatment effect estimate. The Solitaire FR stent retriever achieved significantly better angiographic, safety, and clinical outcomes compared to Merci Retrieval System.

TREVO EU

Thrombectomy REVascularization of large Vessel Occlusions in acute ischemic stroke (TREVO) EU was a multicenter, prospective, single arm study conducted at 7 sites in Germany, Spain, Austria, and Sweden.[20] Acute ischemic stroke patients with angiographically confirmed LVO were studied using the Trevo stent retriever. The investigators looked for hemorrhage or ischemic areas in >1/3 MCA territory or equivalent in the posterior circulation using NCCT or MRI. They performed follow-up imaging at 24 hours to check for hemorrhagic transformation. Angiographic confirmation of LVO in anterior or posterior circulation was required for enrollment of patients in this trial.

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Revascularization was studied using Thrombolysis in Cerebral Infarction (TICI) score with 92% reperfused to ≥ TICI 2a and 78% patients having ≥ TICI 2b. This single arm study without randomization was a key drawback of this trial. The authors emphasized the efficacy of the novel Trevo stent retriever and potential promising results in future randomized studies.

TREVO 2

Trevo versus Merci retrievers for thrombectomy revascularization of large vessel occlusions in acute ischemic stroke (TREVO 2) was a randomized, prospective, controlled, multicenter, open-label, adaptive, non-inferiority trial conducted at 26 centers in United States and one center in Spain.[21] Acute ischemic stroke patients with angiographically confirmed LVO were randomly divided into Trevo stent retriever and Merci device groups. Investigators assessed any ICH or acute ischemic change in ≥ 1/3 MCA or >100 mL of tissue in other territories using NCCT or MRI. Eligible patients were randomly allocated into two groups after the first angiographic run confirmed the occlusive lesion. Follow-up scans were performed 24 hours after the procedure to review hemorrhagic complications. An independent angiographic core laboratory evaluated the reperfusion and defined successful revascularization as TICI score 2 or greater in the territory of occlusion. TICI ≥ 2 per core laboratory was achieved in 86% of Trevo group and 60% of Merci group (OR 4.22, 95% CI 1.92–9.69; $p < 0.001$). Time to revascularization with TICI ≥ 2 was found to be similar in both groups. Randomization was not balanced for diastolic blood pressures and body mass index associated with recanalization rates and vascular access. Trevo stent retrievers achieved substantially better angiographic and clinical outcomes than the Merci Retrieval System.

IMS III

The Interventional Management of Stroke III Trial was one of the largest multicenter endovascular trials for acute ischemic stroke (n=656) that involved 58 centers across the United States, Canada, Australia and Europe.[22] It was a phase 3, randomized, open-label clinical trial with blinded outcome that tested compared IV tPA followed by endovascular therapy with standard approach of IV tPA only. IV tPA group received standard alteplase dose of 0.9 mg per kilogram while intervention group used Merci retriever, Penumbra system, or Solitaire FR stent retriever. The trialist used NCCT to assess Alberta Stroke Program Early Computed Tomography Score (ASPECTS) with a repeat scan within 24 hours or when any neurologic decline was noted. During the initial phase of the trial, the investigators used NIHSS ≥ 10 as eligibility criteria due to infrequent use of CTA, while CTA was used more frequently in the latter half to identify LVO in patients with NIHSS score of 8 or 9. Recanalization of the primary occlusive lesion was assessed using the modified TICI (mTICI) score, ranging from 0 (no reperfusion) to 3 (full reperfusion in occluded vessel) with mTICI 2b/3 score 41% in endovascular group. A few limitations included that only 47% of patients received CTA during enrollment and about 20% of patients in the endovascular group had catheter-inaccessible thrombus or no LVO. Similar clinical outcomes were found amongst endovascular therapy after IV tPA arm and the IV tPA arm.

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MR RESCUE

The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE) was a phase 2b, randomized, controlled, open-label clinical trial with a blinded outcome conducted across 22 centers in North America.[23] Acute ischemic stroke patients were randomized into following groups based on perfusion results (penumbral v/s non-penumbral) and type of treatment (medical v/s endovascular). IV tPA group received standard alteplase dose while endovascular group used Merci retriever, Penumbra system, or IA tPA. Investigators used a novel approach to study favorable penumbral pattern (substantial salvageable tissue and small infarct core) or a non-penumbral pattern (large core or absent penumbra) on multimodal CT or MRI with perfusion imaging. A favorable penumbral pattern was defined as predicted infarct core of ≤ 90 ml and predicted infarct tissue within penumbral region of ≤ 70%. The limitations of this study included a relative lack of power, only 25% patients achieved TICI 2b or 3 reperfusion, the imaging prediction maps were developed from a single time point that led to varied neuroimaging patterns from the time of initial snapshot and large infarct volumes were observed in patients who received NCCT as compared to those who underwent MRI. Favorable penumbral pattern was correlated with smaller infarct volumes and attenuated infarct growth with substantial reperfusion (>90% reduction in tissue volume with >6-second delay in the time until the peak of the residue function), as compared to non-penumbral pattern, regardless of treatment groups. This finding was corroborated especially in later time windows, due to possible presence of robust collateral supply leading to greater tolerance of occlusion and increased chances of spontaneous recanalization.

SYNTHESIS EXPANSION

SYNTHESIS was a multicenter, open-treatment clinical trial with a blinded end point that included 362 patients across various centers in Italy.[24] Acute ischemic stroke patients were randomized within 4.5 hours of symptom onset into endovascular (IA tPA or mechanic thrombectomy or both) and IV tPA groups. IV tPA group used standard alteplase dose while mechanical thrombectomy was performed with Solitaire (18 patients), Penumbra (9 patients), Trevo (5 patients) and Merci (5 patients). The imaging protocol included initial NCCT to rule out ICH followed by randomization of patients within 4.5 hours of symptom onset. The study was noted to have a few limitations, including: a) no pre-procedural imaging was performed to confirm LVO, b) around 10% of patients randomly assigned to intervention did not harbor LVO at angiography and c) revascularization based on TICI scores were not reported. It was concluded that endovascular therapy was not superior to standard treatment in terms of clinical outcome, safety, or mortality.

Imaging Aspects of the Most Recent Randomized Endovascular Trials

Recently, several successive randomized controlled trials have established the efficacy of endovascular therapy in IV tPA treated ischemic stroke patients. These large, imaging-focused trials have revolutionized the role of endovascular therapy as a routine therapeutic strategy for stroke patients and concomitantly promoted the use of advanced imaging strategies for patient selection. Majority of these studies included patients with LVO for endovascular procedures, small ischemic cores, and more rapid angiographic reperfusion

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compared to predecessor trials. In this section, we discuss their key principles of success and advanced imaging studies involved to select patients with special focus on revascularization rates.

MR CLEAN

Multicenter Randomized Clinical trial of Endovascular treatment for Acute ischemic stroke in the Netherlands (MR CLEAN) was a phase 3, multicenter clinical trial with randomized treatment groups, open-label treatment, and blinded end-point evaluation. The trial enrolled 500 patients at 16 centers in the Netherlands.[9] Endovascular treatment involved IA thrombolysis (0.4%), mechanical treatment (83.7%) with majority of stent retrievers (81.5%), or both (10.3%) plus usual care (IV tPA, if eligible) was compared with usual care alone (control group) in patients with acute ischemic stroke and a proximal LVO in anterior circulation. An imaging committee used NCCT to determine ASPECTS, baseline vessel imaging (CTA, MRA, or DSA) for location of occlusion, and 24-hour follow-up CTA or MRA to evaluate reperfusion. Interestingly, CTP was acquired in 65% subjects although it remains unclear how such information was utilized in prospective fashion. Final infarct volume on follow-up NCCT was assessed using automated, validated algorithm while angiographic outcomes were assessed by a core laboratory using mTICI grading. Recanalization at 24 hours was evaluated using CTA or MRA and final infarct volume was assessed on NCCT at 5 to 7 days. No intracranial occlusion on follow-up CTA was observed in 75.4% of intervention group and 32.9% of control group (adjusted OR 6.88; 95%CI, 4.34 – 10.94). Final median infarct volume on NCCT was 49 ml in intervention group and 79 ml in control group with inter-group difference in volume (19 ml; 95% CI, 3 to 34) in favor of intervention group. Good reperfusion with modified TICI (mTICI) score 2b/3 was achieved in 115/196 patients (58.7%) in the intervention group. Limitations observed in this trial were: a) unbalanced randomization with more patients in control group; b) unavailability of lateral DSA images might have led to underestimation of actual reperfusion rates; c) broad inclusion criteria led to fewer control subjects with mRS 0 to 2 at 90 days; d) patients were aware of treatment groups that might have led to opinion bias. IA treatment in acute ischemic stroke patients with LVO in anterior circulation was found to be effective and safe when administered within 6 hours of symptom onset.

EXTEND-IA

Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial (EXTEND-IA) was a multicenter, prospective, randomized, open label, blinded-end-point trial that included 70 patients at 14 centers in Australia and New Zealand.[10] The trial was stopped early because of efficacy when 70 of the intended 100 patients had been randomized (35 in each arm) after the dissemination of the MR CLEAN results. Acute ischemic stroke patients receiving IV tPA within 4.5 hours of symptom onset were randomly enrolled into either the endovascular group using Solitaire FR stent retriever or medical therapy arm. Investigators used CTA to identify LVO and utilized automated CT perfusion analysis software (RAPID software),[25] to identify salvageable brain tissue. Reperfusion was defined as percentage reduction in the perfusion-lesion volume from the time of initial imaging compared to imaging performed within 24 hours. Final revascularization with mTICI 2b/3 was reported as 86% on DSA, while endovascular therapy subjects showed increased

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reperfusion on follow-up CTA at 24 hours as compared to IV tPA only group (94% vs. 43%, p<0.001). One drawback of the study may be that patients who were excluded due to large ischemic core or absence of penumbral tissue may have benefited from endovascular therapy. Ischemic stroke patients with LVO and salvageable tissue on CT perfusion were found to have early neurologic recovery, improved reperfusion and functional outcomes using Solitaire FR stent retriever after initiation of IV tPA.

ESCAPE

Endovascular treatment for Small Core and Anterior circulation Proximal occlusion with Emphasis on minimizing CT to recanalization times (ESCAPE) was a randomized, open label, blinded outcome, parallel group trial conducted across 22 centers in the U.S., U.K., Ireland and South Korea.[26] The study enrolled 316 patients before being stopped early for efficacy. Ischemic stroke patients who were receiving IV tPA within 4.5 hours of symptom onset were randomly enrolled into the endovascular arm using mechanical thrombectomy or medical arm. Investigators evaluated ICH and utilized ASPECTS to determine core-infarct volume on NCCT. For the first time, any endovascular trial utilized multiphase CTA to assess collateral vascular supply, LVO and select patients with small core volume (based on ASPECTS or CT Perfusion). Successful reperfusion with TICI 2b/3 score was observed in 72.4% of intervention group. On repeat CTA at 2–8 hour interval, 31.2% of patients in control group were found to have arterial occlusive lesion. Potential limitations were the questionable generalizability of results due to implementation of an efficient workflow and imaging processes and no provision of data on ineligible patients based on imaging criteria. Endovascular thrombectomy was found to be highly efficacious associated with reduced disability and improved clinical outcome. Patient selection was cited in the success of trial selecting patients with LVO while excluding large core or marginal collateral profiles.

SWIFT PRIME

Solitaire as Primary Treatment for Acute Ischemic Stroke (SWIFT PRIME) was a multicenter, two-arm, prospective, randomized, open, blinded endpoint trial that enrolled 196 of 833 planned patients in 39 centers in United States and Europe.[26] Acute ischemic stroke patients receiving IV tPA within 4.5 hours of symptom onset were randomly assigned to endovascular therapy using Solitaire FR stent retriever or no further treatment. A core lab used NCCT to determine ASPECTS while CTA or MRA were performed for location of occlusion as baseline vessel imaging. Investigators initially assessed penumbral imaging by RAPID software as utilized previously in EXTEND-IA trial. During a later phase of the study, they switched to a small-to-moderate infarct size strategy using ASPECTS as was used in ESCAPE to expand the inclusion criteria, while RAPID technique was still largely used and encouraged. Reperfusion was calculated as the reperfusion ratio assessed by the core lab i.e reperfusion volume at 27 hours ÷ hypoperfusion lesion volume (Tmax >6 sec) at baseline. Substantial reperfusion referred as mTICI 2b/3 on DSA was found in 88% of endovascular group. Potential limitations included the relatively homogenous cohort of IV tPA given patients and question of generalizability as this study was conducted under continuous quality-improvement programs at participating sites. Endovascular treatment with Solitaire FR stent retriever was found to have excellent reperfusion rates amongst IV tPA treated patients.

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REVASCAT

Revascularization with Solitaire FR device versus best medical therapy in the treatment of acute stroke due to anterior circulation large vessel occlusion presenting within eight hours of symptom onset (REVASCAT) was a multicenter, prospective, randomized, open-label phase 3 trial with blinded evaluation.[27] The study enrolled 206 patients at 4 centers in Spain and evaluated the benefit of intervention with Solitaire out to 8 hours for IV tPA failure patients only. Clinicians were required to wait an additional 30mins at least to determine if IV tPA had been successful. Investigators excluded patients with large ischemic core using ASPECTS <7 on NCCT or a score of <6 on DWI sequence of MRI. CTA or MRA was used on admission and 24-hours later to assess patency of intracranial ICA and M1 segment of MCA. Successful reperfusion with mTICI 2b/3 score (reperfusion of >50% of affected territory) was achieved in 66% of intervention group according to core laboratory. Thrombectomy was found to favor functional independence with mRS of 0 to 2 (43.7% vs. 28.2%; adjusted OR, 2.1; 95% CI, 1.1 to 4.0). Few discrepancies were noted in the study between central and investigator-adjudicated ASPECTS scoring and site of occlusion on CTA. Solitaire FR stent retriever reduced the severity of post stroke disability in patients with anterior circulation stroke who could be treated within 8 hours after symptom onset.

Discussion

Imaging has increasingly been used on a systematic basis for selection of candidates, evaluation of reperfusion and serial evaluation of infarction or hemorrhagic transformation in endovascular trials (Tables 1 and 2). In recent years, more comprehensive imaging techniques including various components of multimodal CT or MRI have been implemented. Three landmark trials in 2013 raised concerns for the effectiveness and role of endovascular procedures.[22–24] Imaging modalities play a pivotal role in selecting acute ischemic stroke patients across most endovascular trials. Quite disparate algorithms for imaging have been utilized in these trials ranging from baseline NCCT to multimodal CT or MRI. NCCT may have relatively substantial sensitivity for detection of initial ischemic changes under expert eyes, yet considerable variability in the yield of this approach persists in routine clinical practice.[28, 29] Detection of early signs of ischemia on NCCT also varies amongst experienced observers as even when scored with ASPECTS.[30–35] ASPECTS ≤ 7 has been associated with poor clinical outcome with 78% sensitivity and 96% specificity while sICH (symptomatic intracerebral hemorrhage) with 90% sensitivity and 62% specificity.[36] DWI has a sensitivity of 99% in detecting ischemic changes as compared to NCCT and a high specificity of 92%.[37–41]

Initial NCCT or MRI to evaluate hemorrhage, ASPECTS to assess early ischemic changes and repeat 24-hour CT for potential hemorrhagic transformation have been used in most endovascular trials to date. Noninvasive imaging techniques used in recent endovascular trials, including multimodal computed tomography, CTA showing LVO and revascularization with mTICI ≥ 2b/3, provide a detailed snapshot of the collaterome in ischemic stroke patients. Recent trials like ESCAPE have included new multiphase CTA to more definitively investigate collateral status, although the narrow selection criteria based on collateral status may preclude broader implications of collateral grade.

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Several studies in the past have shown poor response rates of IV tPA for proximal LVO,[42, 43] while an endovascular approach has better recanalization rates for proximal rather than distal vessel thrombus. [15, 44–47] This justifies more selective vascular imaging to triage acute stroke patients being considered for endovascular therapy. CTA has a high sensitivity (>97%) and specificity (>98%) to detect intracranial stenosis and occlusions,[48–55] with superior detection rates for distal vascular lesions when compared to MRA.[49, 50] While IMS III and the SYNTHESIS Expansion trials had limited use of CTA, all recent trials including MR CLEAN, ESCAPE, EXTEND-IA and SWIFT PRIME used CTA or MRA proven LVO as inclusion criteria.[9–11, 26]

Perfusion and diffusion related mismatch has been used to select patients for endovascular therapy. Presence of a perfusion defect larger than diffusion lesion referred to as “mismatch” has been associated with ischemic core expansion.[56–58] Desmoteplase in Acute Ischemic Stroke–phase II (DIAS-II) was one of the earlier studies that failed to show the superiority of treatment utilizing perfusion mismatch for penumbral imaging.[2] Trials such as DEFUSE, DEFUSE-2, and Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) used a “target mismatch profile” to describe sufficient penumbral tissue using endovascular technique. They selected candidates for revascularization beyond 3 hours by using DWI and PWI and showed these patients experienced better clinical outcome.[18, 59–61] MR RESCUE also used penumbral imaging criteria to select patients but failed to show better clinical outcomes when compared to patients with no selection at all.

Collaterals play an important role in ischemic stroke patients. Several studies have shown that the presence of collateral blood supply to ischemic region increases reperfusion rates, decreases infarct core size and hemorrhagic conversion; hence improving clinical outcome with revascularization therapies.[62–64] Various criteria are available to ascertain intracranial collateral supply.[65–69] Though investigators use divergent methods to assess collaterals, one study showed the reliability of the approach utilized by Miteff in predicting desirable clinical outcome in IV tPA treated patients at 3 months.[70]

Several different neurovascular imaging techniques are now widely available, providing many options for clinicians in the evaluation of acute stroke patients. However, accuracy and time impacts are significant factors to be considered. There has been a shift in trend towards core-infarct volume rather than mismatch as neuroimaging criteria. Patients were excluded based on core-infarct volume with >70 ml in EXTEND-IA and >50ml in SWIFT PRIME respectively.[71] EXTEND-IA used RAPID software to determine accurate core-infarct volume and excluded patients with lack of penumbral tissue that carries high risk of sICH and worse outcomes.[18, 72] The ESCAPE trial excluded patients with ASPECTS<6 while REVASCAT used ASPECTS<7 as a cutoff point to exclude patients. The ESCAPE trial selectively used multiphase CTA, an innovative method to assess potential collateral supply that captures snapshots during standard arterial, venous and delayed venous phases. The ESCAPE investigators defined ≥ 50% collateral supply in affected hemisphere as moderate-to-good collateral supply in ischemic stroke patients. With CTA techniques now widely available, less artifact susceptibility and total scan time ~5 minutes, the future use of multiphase CTA may further enhance patient selection in endovascular therapy. ESCAPE, EXTEND-IA, SWIFT PRIME and REVASCAT corroborate the positive results of MR

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CLEAN to confirm that mechanical thrombectomy is more effective than IV tPA alone, in the setting of appropriate patient selection including imaging techniques.

In conclusion, recent endovascular trials have established mechanical thrombectomy as a safe and superior treatment of ischemic stroke patients compared to standard medical approaches including thrombolysis. Rapid evaluation of acute ischemic stroke patients with NIHSS ≥ 7, ASPECTS ≥ 6 or 7, and LVO with moderate-to-good collaterals using multiphase CTA may be incorporated as a rational clinical and imaging algorithm to select patients for endovascular thrombectomy with stent retriever technology. Future studies, including ongoing registries, may further refine the impact of imaging selection and surveillance of reperfusion, lesion evolution and hemorrhagic transformation in endovascular stroke therapies.

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Table 1

Endovascular studies prior to the stent retriever era

Study	Comparator arms	Imaging	Revascularization	Potential limitations
PROACT I	**a.** IA-rpro-UK **b.** Placebo group	**a.** NCCT **b.** DSA for M1/M2 TIMI grades **c.** 24 hour NCCT	TIMI 2/3 on DSA (at 120 minutes): **a.** IA-rpro-UK: 57.7% **b.** Placebo: 14.3%	Inclusion of patients with early ischemic changes on initial NCCT
PROACT II	**a.** IA-rpro-UK + IV heparin **b.** Control group (heparin only)	**a.** NCCT **b.** DSA for M1/M2 TIMI grades **c.** 24 hour NCCT	TIMI 2/3 on DSA (at 120 minutes): **a.** IA-rpro-UK: 66% **b.** Control group: 18%	**a.** small sample size **b.** higher rpro-UK dose led to increased sICH (10.2%)
MERCI	Merci device	**a.** NCCT **b.** DSA for LVO **c.** 24 hour NCCT	TIMI 2/3 flow: 48%	**a.** Single arm trial with no comparison **b.** Overestimation of spontaneous ICA recanalization
MELT Japan	**a.** IA UK group **b.** Control group	**a.** NCCT **b.** DSA for M1/M2 TIMI grades **c.** 24 hour NCCT	Partial or complete recanalization: IA UK: 73.7%	**a.** small sample size **b.** inclusion of low NIHSS patients without use of <1/3 early ischemic sign on NCCT **c.** sICH found more commonly in treatment group (type II error)
Multi-MERCI	Merci devices: **a.** Retriever X5 **b.** Retriever X6 **c.** Retriever L5	**a.** NCCT **b.** DSA for M1/M2 TIMI grades **c.** 24 hour NCCT	TIMI 2/3 flow: **a.** Retriever L5: 57.3% **b.** Retriever X5/X6: 45.5%	**a.** Single arm trial with no comparison **b.** DSA interpreted by site investigator
PENUMBRA PIVOTAL	Penumbra device	**a.** NCCT **b.** DSA for M1/M2 TIMI grades **c.** 24 hour NCCT	TIMI 2/3: 81.6%	Single arm trial with no comparison
DEFUSE 2	Endovascular therapy for	**a.** Baseline MRI (GRE/ MRA/DWI/	Reperfusion response:	**a.** With no control group, definitive

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Study	Comparator arms	Imaging	Revascularization	Potential limitations
	a. Target Mismatch profile **b.** Non-Target Mismatch profile	PWI) within 90 minutes prior to endovascular procedure **b.** 12 hour follow-up MRI after procedure **c.** Late follow-up MRI (GRE, DWI and FLAIR) on day 5 or discharge	**a.** Favorable with target mismatch profile **b.** Less favorable response for Non-Target Mismatch profile	conclusions on benefits or risks of endovascular therapy could not be made **b.** Small cohort of Non-Target mismatch patients that underwent endovascular therapy

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Table 2

Endovascular studies with stent retriever use

Study	Trial arms	Imaging selection	ASPECTS	Vascular Imaging	Recanalization status	Potential limitations
SWIFT	**a.** Solitaire FR stent retriever group **b.** Merci retriever group	**a.** Baseline NCCT or MRI brain **b.** DSA for LVO **c.** 24-hour NCCT or MRI	No	DSA	TIMI>2b/3 score: **a.** Solitaire FR stent retriever group: 69% **b.** Merci retriever group: 30%	**a.** Solitaire FR stent retriever were not compared with other stent retrievers or Penumbra aspiration device **b.** small sample size
TREVO EU	Trevo stent retriever group	**a.** Baseline NCCT or MRI brain **b.** DSA for LVO **c.** 24-hour NCCT or MRI	No	DSA	TICI ≥ 2a: 92% TICI ≥ 2b: 78%	Single arm trial with no comparison
TREVO 2	**a.** Trevo stent retriever group **b.** Merci retriever group	**a.** Baseline NCCT or MRI brain **b.** DSA for LVO **c.** 24-hour NCCT or MRI	No	DSA	TICI>2b/3 score: **a.** Trevo stent retriever group: 86% **b.** Merci retriever group: 60%	**a.** Randomization was not balanced for diastolic blood pressures and body mass index **b.** Internationalists and imaging core laboratory were not masked to device
IMS III	**a.** IV tPA + endovascular **b.** IV tPA alone	**a.** NCCT for ASPECTS **b.** CTA for LVO	<4	No	TICI 2b/3 grades: **a.** DSA: ICA (38%), M1 (44%), single M2 occlusion (44%), multiple M2 occlusions (23%) **b.** Follow-up CTA at 24 hours: ICA (81%), M1 (86%), M2 (88%)	**a.** Only 47% patients received CTA **b.** ~ 20% patients in endovascular group had catheter inaccessible thrombus or no LVO
MR RESCUE	**a.** Embolectomy, penumbral type **b.** Standard care, penumbral type	**a.** NCCT or MRI **b.** Multimodal CT/MR Perfusion for stratification of	No	CTA or MRA	TICI 2a to 3: **a.** Embolectomy, penumbral type: 67%	**a.** Underpowered study **b.** Only 25% of patients achieved TICI 2b/3

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Study	Trial arms	Imaging selection	ASPECTS	Vascular Imaging	Recanalization status	Potential limitations
	c. Embolectomy, non-penumbral type **d.** Standard care, non-penumbral type	favorable penumbral pattern: 1) predicted infarct core of ≤ 90 ml 2) predicted infarct tissue within the at-risk region of ≤ 70%			**b.** Standard care, penumbral type: 93% **c.** Embolectomy, non-penumbral type: 77% **d.** Standard care, non-penumbral type: 78%	**c.** Baseline-imaging prediction maps were developed from single time point frame **d.** Large infarct core volume noticed in patients who got NCCT v/s MRI.
SYNTHESIS EXPANSION	**a.** IV tPA **b.** Endovascular (IA tPA or mechanical thrombectomy or both)	**a.** NCCT **b.** DSA for LVO	No	No		**a.** No pre-procedural CTA performed to confirm LVO **b.** No defined lower threshold of NIHSS; 10% of patients randomly assigned to endovascular group had no LVO at DSA **c.** Failure to report revascularization score
MR CLEAN	**a.** Endovascular group (IA tPA, mechanical treatment, or both) + usual care (IV tPA if eligible) **b.** Usual care alone (IV tPA if eligible)	**a.** Baseline NCCT **b.** CTA or MRA or DSA **c.** 24 hour CTA or MRA for reperfusion status	No	CTA or MRA or DSA	**a.** mTICI >2b/3 on DSA: 58.7% **b.** No residual LVO on follow-up CTA: Endovascular group (75.4%), Usual care group (32.9%)	**a.** randomization was not balanced **b.** underestimation of recanalization rates due to unavailability of lateral DSA images **c.** wide inclusion criteria led to lower number of control group with mRS 0 to 2 at 90 days **d.** opinion bias as patients were aware of treatment groups
EXTEND-IA	IV tPA receiving patients divided into: **a.** Endovascular group using Solitaire FR stent-retriever	**a.** CTA for LVO **b.** CTP (RAPID) for penumbra	No	CTA or MRA	**a.** mTICI 2b/3 on DSA: 86% **b.** Recanalization on CTA at 24 hours: Endovascular group (94%), No	Patients excluded due to large ischemic core or absence of penumbra might have benefited from endovascular therapy

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Study	Trial arms	Imaging selection	ASPECTS	Vascular Imaging	Recanalization status	Potential limitations
	b. No further therapy group				further therapy group (43%)	
ESCAPE	IV tPA receiving patients divided into: **a.** Endovascular group (any mechanical thrombectomy devices) **b.** No further therapy group	**a.** NCCT for ASPECTS ≥ 6 **b.** single phase CTA for LVO **c.** Multiphase CTA and CT Perfusion for detection of core size	>6	CTA	**a.** TICI 2b/3 grade in endovascular group: 72.4% **b.** Arterial occlusive lesion in control group on repeat CTA at 2–8 hours interval: 31.2%	**a.** Limited generalizability of results due to implementation of efficient workflow and imaging processes **b.** no provision of data on ineligible patients based on imaging criteria
SWIFT PRIME	IV tPA receiving patients divided into: **a.** Endovascular group using Solitaire FR stent-retriever **b.** No further therapy group	**a.** NCCT for ASPECTS ≥ 7 **b.** CTA/MRA for LVO	>6	CTA or MRA	Substantial reperfusion with TICI 2b/3 in endovascular group (88%)	**a.** homogenous cohort **b.** limited generalizability of results due to implementation of efficient workflow and imaging processes
REVASCAT	IV tPA receiving patients divided into: **a.** Endovascular group using Solitaire FR stent-retriever **b.** Standard care including IV tPA	**a.** Baseline NCCT for ASPECTS or MRI **b.** CTA for LVO	>8	CTA or MRA	mTICI 2b/3 grade in intervention group: 66%	Discrepancies noted between central and investigator-adjudicated ASPECT scoring and site of LVO

Table Abbreviations: Alberta Stroke Program Early CT score; CTA computed tomography angiography; CTP computed tomography perfusion; DSA digital subtraction angiography; IA intra-arterial; IAT intra-arterial therapy; ICA internal carotid artery; ICH intracerebral hemorrhage; IV intravenous; NCCT non-contrast computed tomography; MCA middle cerebral artery; MR magnetic resonance; mTICI modified thrombolysis in cerebral infarction; LVO large vessel occlusion; tPA tissue plasminogen activator; TIMI thrombolysis in myocardial infarction; TICI thrombolysis in cerebral infarction