Special Report

Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials

Consensus Recommendations and Further Research Priorities

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Background and Purpose—The Stroke Imaging Research (STIR) group, the Imaging Working Group of StrokeNet, the American Society of Neuroradiology, and the Foundation of the American Society of Neuroradiology sponsored an imaging session and workshop during the Stroke Treatment Academy Industry Roundtable (STAIR) IX on October 5 to 6, 2015 in Washington, DC. The purpose of this roadmap was to focus on the role of imaging in future research and clinical trials.

Methods—This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the US Food and Drug Administration to discuss STIR priorities in the light of an unprecedented series of positive acute stroke endovascular therapy clinical trials.

Results—The imaging session summarized and compared the imaging components of the recent positive endovascular trials and proposed opportunities for pooled analyses. The imaging workshop developed consensus recommendations for optimal imaging methods for the acquisition and analysis of core, mismatch, and collaterals across multiple modalities, and also a standardized approach for measuring the final infarct volume in prospective clinical trials.

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Conclusions—Recent positive acute stroke endovascular clinical trials have demonstrated the added value of neurovascular imaging. The optimal imaging profile for endovascular treatment includes large vessel occlusion, smaller core, good collaterals, and large penumbra. However, equivalent definitions for the imaging profile parameters across modalities are needed, and a standardization effort is warranted, potentially leveraging the pooled data resulting from the recent positive endovascular trials. **(*Stroke*. 2016;47:1389-1398. DOI: 10.1161/STROKEAHA.115.012364.)**

Key Words: angiography ■ clinical trial ■ ischemia ■ reperfusion ■ stroke

During the past 2 decades, an accumulated body of evidence from the stroke research community has led to incremental advances in the standardization of clinical trial methodologies and to the emergence of a central role for imaging in new treatment evaluations. The recent series of positive endovascular trials owe much of their success to the lessons learned from the many previous trials that failed to establish therapeutic efficacy.[1–5] These previous stroke trials have led to an understanding of the roles of vascular, core, penumbral, and collateral imaging and their relationships to treatment response and clinical outcome. The goal of this article is to report on neuroimaging biomarkers for treatment selection and for outcome.

It is beyond question that time from onset of focal cerebral ischemia to reperfusion is fundamental in determining therapeutic efficacy for reperfusion therapies.[6] The effect of early treatment of stroke with intravenous alteplase demonstrated in the hallmark National Institute of Neurological Disorders and Stroke (NINDS) trial[7] illustrates this principle; a robust and reliable benefit compared with placebo is related to time from onset to treatment.[8]

However, when time and brain imaging by standard noncontrast computed tomography (NCCT) imaging are insufficient to accurately test a therapeutic hypothesis, selection based on imaging of a biological target for treatment is a logical alternative (Table 1). Examples may be clinical trials in which the anticipated effect size is small (eg, comparing 2 thrombolytic medications or testing of a neuroprotective drug) or in which the treatment is relevant only for a subset of stroke types (eg, large-vessel occlusion). The Stroke Imaging Research (STIR) consortium has recommended the term treatment-related acute imaging target (TRAIT) to describe patient selection based on the biological target of a treatment. The responses of these biological targets to treatment may depend on time.[9] The series of positive endovascular trials confirmed the value of TRAIT selection and enrichment for endovascular reperfusion strategies (Table 1). The trials demonstrated that patient recruitment limited to an imaging-defined subset of stroke led to positive trials with smaller samples completed within reasonable periods of time. Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial (EXTEND-IA) illustrates how a greater enrichment results into a smaller sample and greater effect size, but potentially also decreased generalizability and excluded patients who may have benefited from treatment.

Imaging Selection in Recent Positive Acute Stroke Endovascular Clinical Trials

After 3 neutral endovascular trials in 2013 (Interventional Management of Stroke [IMS]-III, Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy [MR RESCUE], and Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke [SYNTHESIS EXP]),[10–13] the years 2014 to 2015 were marked by a historic series of positive acute stroke clinical trials (Table 2). The use of advanced imaging-based selection for patient recruitment in these recent trials is one of the most important factors in the success of these trials (Table 3). The imaging modalities required for each trial were different (Table 4). There is no evidence that the different imaging modalities resulted in different times from symptom onset to treatment (Table 5).

In the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN) trial,[1] the key imaging findings included a clear benefit of endovascular therapy for NCCT Alberta Stroke Program Early CT score (ASPECTS) scores of 5 to 10, but less certainty for ASPECTS score of 0 to 4. A post hoc analysis demonstrated that a good and moderate collateral score was also associated with a large benefit of endovascular therapy. However, although perfusion computed tomography (PCT) mismatch (cerebral blood volume and mean transit time thresholds) predicted functional outcome, the relative treatment effect in patients with and without mismatch was similar. The use of an ischemic core volume >70 mL on PCT criterion did identify a group of patients with low rates of independent outcome (1/13 [8%] endovascular-treated patients achieved modified Rankin Scale [mRS] score, 0–2) but there were relatively few patients and the interaction test was not significant.[14]

The EXTEND-IA trial[2] showed a robust effect of endovascular therapy over alteplase alone in patients with PCT-defined mismatch and core volume <70 mL. In this group of patients, near complete reperfusion (>90%) in target mismatch patients was strongly tied to favorable clinical outcome (regardless of the treatment strategy), and lack of reperfusion was associated with death or dependence in 70% of patients.

In the Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke (ESCAPE) trial,[3] an imaging strategy of NCCT ASPECTS scores of 6 to 10, as well as good and moderate collateral scores on computed tomography (CT) angiography, showed a robust effect favoring endovascular therapy. ASPECTS and collateral scores were highly correlated. Patients with higher clot burden assessed using the clot burden score demonstrated more treatment effect.

In the Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment (SWIFT PRIME) trial,[4] a target mismatch based on perfusion imaging combined with successful recanalization was associated with a favorable outcome. Final infarct volume (FIV) strongly correlated with

Table 1. Imaging Recommendations for Methods and Patient Selection for Clinical Reperfusion Trials

Baseline imaging markers that favor treatment response of thrombectomy	
TRAIT for thrombectomy	
Large artery occlusion	
Small core	
Large core-perfusion mismatch (penumbral marker)	
Good cerebral collaterals	
Imaging selection of patients for acute reperfusion trials (not limited to endovascular therapies): recommendations	
Imaging for defining the TRAIT is highly recommended for patient selection	
Additional time spent acquiring additional imaging information must be balanced against risk of delay in initiating reperfusion therapies	
Prerandomization vascular imaging should be obtained in acute endovascular trials. This would usually be done by CTA or MRA. Catheter angiography is included as a method for patient selection but it is understood that it is not likely the initial method for patient selection in a clinical trial	
Vascular, core, mismatch, and collateral imaging each have added value for identifying TRAIT and enriching sample toward greatest effect size. More than one imaging method and threshold criterion is acceptable for these purposes, but should be standardized within a trial	
Particularly in phase II trials with small sample sizes, both vascular and advanced tissue imaging may offer insights into patient populations that cannot be obtained from clinical data alone, and are recommended to assist characterization of patient populations and improve understanding of experimental therapies	
Proposed imaging methods for patient selection	
TRAIT	Proposed imaging methods
Artery occlusion	CTA
	MRA
	Catheter angiography
Core	ASPECTS on NCCT
	Volume of severely decreased CBV or CBF from PCT
	Volume of acute DWI lesion from MRI
Mismatch	Volume of perfusion lesion (by PCT, MRP, or ASL) to core volume
Cerebral collaterals	CTA source images
	Single- or multiphasic CTA
	Contrast-enhanced MRA
	Catheter angiography

ASL indicates arterial spin labeling; ASPECTS, Alberta Stroke Program Early CT score; CBF, cerebral blood flow; CBV, cerebral blood volume; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRP, magnetic resonance perfusion; NCCT, noncontrast computed tomography; PCT, perfusion computed tomography; and TRAIT, treatment-related acute imaging target.

clinical outcome in both treatment groups.[15] Baseline ischemic core volume predicted 27-hour infarct volume in patients who reperfused.[16] In target mismatch patients, the combination of baseline core and 27-hour hypoperfusion volume predicted FIV.

The Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptoms Onset (REVASCAT) trial[5] supported NCCT-based patient selection, only requiring ASPECTS score of ≥6, demonstrating a robust treatment effect. However, significant discrepancies were observed between the centralized core laboratory ASPECTS and the investigators' ASPECTS, and some benefit with lower ASPECTS scores (0–4) cannot be excluded. A pooled analysis of all patients with ASPECTS score of 0 to 4 across all endovascular trials is needed, but may be too small to draw reliable conclusions about endovascular treatment effects. Interestingly, there were also significant discrepancies between M1 versus M2 occlusions between the core laboratory and the investigators. It is important to note that, if the inclusion criteria were expanded to fully embrace the actual recruited subjects (eg, lower ASPECTS to 3–10 range) that a similar cohort would be enrolled and still show benefit.

Assess the Penumbra System in the Treatment of Acute Stroke (THERAPY) (ClinicalTrials.gov Identifier: NCT01429350), which required hyperdense clot length measurement ≥8 mm on NCCT for trial inclusion, suggested that the benefit of bridging endovascular therapy relative to intravenous thrombolysis alone increased with hyperdense clot length, and large infarcts as measured by final NCCT ASPECTS score of 0 to 4 to be associated with poor outcome providing further support for this threshold as a useful treatment exclusion criterion.

The Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke (THRACE) study

Table 2. Imaging characteristics in Medical Treatment and Endovascular Treatment Groups of Recent Positive Acute Stroke Clinical Trials

	MR CLEAN		EXTEND-IA		ESCAPE		SWIFT PRIME		REVASCAT		THERAPY	
	Medical Treatment (n=267)	Endovascular Treatment (n=233)	Medical Treatment (n=35)	Endovascular Treatment (n=35)	Medical Treatment (n=150)	Endovascular Treatment (n=165)	Medical Treatment (n=98)	Endovascular Treatment (n=98)	Medical Treatment (n=103)	Endovascular Treatment (n=103)	Medical Treatment (n=53)	Endovascular Treatment (n=55)
Site of vessel occlusion												
ICA	80/266 (30%)	61/233 (26.1%)	11/35 (31.4%)	11/35 (31.4%)	42/150 (28%)	48/165 (29.1%)	15/94 (16%)	17/93 (18.3%)	41/103 (39.8%)	45/103 (43.7%)	12/53 (22.6%)	18/55 (32.7%)
M1	165/266 (62%)	154/233 (66.1%)	18/35 (51.4%)	20/35 (57.2%)	103/150 (68.7%)	111/165 (67.3%)	72/94 (76.6%)	62/93 (66.7%)	65/103 (63.1%)	66/103 (64.1%)	36/53 (67.9%)	31/55 (56.4%)
M2	21/266 (8%)	18/233 (7.8%)	6/35 (17.2%)	4/35 (11.4%)	5/150 (3.3%)	6/165 (3.6%)	6/94 (6.4%)	13/93 (14%)	8/103 (7.8%)	10/103 (9.7%)	5/53 (9.4%)	6/55 (10.9%)
ASPECTS												
Mean±SD	8.4±2.0	8.3±1.8	9.1±1.0	9.2±0.9	8.7±1.4	8.6±1.4	8.5±1.4	8.4±1.5	7.2±2.1	7.4±2.0	7.4±1.7	7.1±2.1
Median (IQR)	9 (8–10)	9 (7–10)	9 (9,10)	9 (9,10)	8 (7–9)	9 (8,9)	9 (8–10)	9 (7–10)	8 (6–9)	7 (6–9)	8 (7–9)	7.5 (6–9)
Ischemic core volume, mL												
Mean±SD	46±44	42±33	20±17	19±19	n/a	n/a	11±11	11±16	n/a	n/a	n/a	n/a
Median (IQR)	32 (10–69)	36 (15–60)	18 (4–29)	12 (4–32)	n/a	n/a	9.0 (1–17)	6.5 (0–14)	n/a	n/a	n/a	n/a
Perfusion volume, mL												
Mean±SD	112±103	141±97	116±48	105±39	n/a	n/a	126±63	116±61	7.2±2.1		n/a	n/a
Median (IQR)	97 (41–181)	113 (60–190)	115 (72–158)	106 (76–137)	n/a	n/a	133 (79–162)	125 (66–149)	8 (6–9)		n/a	n/a
Clot length, mm												
Mean±SD	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	15.7±8.7	17.3±11.5
Median (IQR)	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	n/a	14.1 (10.1–18.6)	12.9 (9.4–22.2)
Collateral grade 0 (worst)/1/2/3/4 (best) or the ESCAPE trial collateral imaging criteria	9/72/111/71	17/64/88/64	n/a	n/a	145 adequate vs 5 poor	162 adequate vs 3 poor	n/a	n/a	n/a	n/a	7/6/10/16/6	7/9/11/11/6

ASPECTS indicates Alberta Stroke Program Early CT score; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; ICA, internal carotid artery; IQR, interquartile range; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; n/a, not applicable; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptoms Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; and THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke.

(ClinicalTrials.gov Identifier: NCT01062698) has not been published to date. This study required demonstration of an arterial occlusion but similar to MR CLEAN, did not use NCCT or other criteria to exclude patients with a large ischemic core.

Opportunities for Standardization

Although the above-listed stroke clinical trials had several elements in common (occlusion location and ischemic core size), they also had significant differences, which represents a unique opportunity for standardization. More specifically, the scoring systems used to characterize ischemic core and collateral circulation varied from trial to trial. The pooling of the imaging data from these trials offers great opportunities to refine the imaging selection of patients for acute reperfusion therapy and trials (last column in Table 4). A statistical analysis plan for the pooled analysis of all the endovascular trials has been published,[17] which will focus on ASPECTS, M1 versus other arterial occlusion sites, and good/moderate versus poor collaterals. The optimal set of imaging biomarkers to select patients with acute stroke may vary depending on the revascularization therapy being considered, the population being studied, and the time window under investigation, in agreement with the concept of TRAITs defined in STIR Roadmap II.[18] Imaging remains essential for phase II trials, and more than 1 imaging method is probably acceptable for patient selection purposes, as long as reasonable cross-modality concordance and within modality standardization and reliability are achieved. The Stroke Treatment Academy Industry Roundtable (STAIR)/STIR imaging workshop recommends imaging-based selection for acute stroke reperfusion clinical trials (not limited to endovascular therapies) as outlined in Table 1.

Table 3. Imaging Selection Criteria for Recent Positive Acute Stroke Clinical Trials

Imaging Selection Criteria	MR CLEAN	EXTEND-IA	ESCAPE	SWIFT PRIME	REVASCAT	THERAPY
Vessel occlusion	ICA, M1, M2, A1, A2 occlusion	ICA, M1, M2	ICA, M1, or functional M1 occlusion (both/all M2 occlusion)	ICA, M1	ICA or M1 occlusion	ICA, M1, or M2 occlusion -Hyperdense clot length ≥8 mm -Absence of tandem extracranial steno-occlusive disease requiring treatment before thrombectomy
Small core	Not required	RAPID perfusion infarct <70 mL (relCBF<30% threshold)	ASPECTS score 6–10	ASPECTS score 6–10 on NCCT or DWI, RAPID perfusion infarct <50 mL (relCBF<30% threshold)	ASPECTS score >6 on NCCT, ASPECTS score >5 on DWI (NCCT ASPECTS >8 for age 80–85)	Acute ischemic changes on NCCT less than one third of MCA territory
Penumbra	Not required	Target mismatch: RAPID perfusion ischemic core mismatch ratio >1.2, absolute mismatch >10 mL (T_{max}>6 s threshold)	Not required	Target mismatch: RAPID perfusion penumbra/ infarct ratio>1.8, penumbra absolute volume >15 mL (T_{max}>6 s threshold) -T_{max}>10 s Lesion ≤100 mL	Not required (clinical/core mismatch [NIHSS>5])	Not required
Collaterals	Not required	Not required	Adequate collateral circulation defined as some filling of 50% or greater of the ischemic territory pial circulation beyond occlusion on CT angiography (preferably multiphase CTA)	Not required	Not required	Not required

ASPECTS indicates Alberta Stroke Program Early CT score; CBF, cerebral blood flow; CT, computed tomography; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; ICA, internal carotid artery; MCA, middle cerebral artery; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; NIHSS, National Institutes of Health Stroke Scale; NCCT, noncontrast computed tomography; RAPID, Rapid Processing of Perfusion and Diffusion; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptoms Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; and THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke.

The specific imaging methods proposed for patient selection using each TRAIT are outlined in Table 1. Table 1 contains the acceptable options for patient selection in clinical trials and are not listed in any order of priority.

Exclusion of patients with large ischemic core was a feature of most of the recent positive acute stroke clinical trials. As the interaction of treatment with this imaging variable cannot be determined reliably because of the small numbers of subjects across all trials, neither safety nor efficacy of reperfusion therapies in this group is established. Future studies investigating the sensitivity and specificity of each method/modality used to define ischemic core is essential.[16,19] Furthermore, studies investigating the relationship between the ischemic core volume and collaterals[20] should be pursued. The definitions of ischemic core will need to be revisited in populations of patients with ultrafast reperfusion. The geographic distribution of the ischemic core may need to be considered in addition to its volume to reflect the eloquence of the infarcted region. Finally, future studies will need to determine whether treatment of patients with larger ischemic cores is associated with higher rates of symptomatic intracranial hemorrhage when treated. The research priorities for core and the other TRAITs are outlined in Table 6.

Standardization of the grading of collateral circulation on and between CT and magnetic resonance imaging (MRI) are needed. The importance of collateral circulation must also be more robustly validated in prospective acute ischemic stroke. Future studies comparing single-phase and multiphase CT angiography[21] for this purpose are warranted, considering that a dichotomous definition of collaterals (absent/poor versus good/moderate) is probably sufficient.

Perfusion-derived entities, such as the core and penumbra, are the imaging biomarkers that will require the largest effort in terms of standardization considering the number of existing definitions and the differences between imaging modalities. Core is defined generally as the irreversible ischemic area that

Table 4. Imaging Modalities Obtained at Baseline in Trial Patients (Required Imaging Indicated With an Asterisk)

Modality	MR CLEAN	EXTEND-IA	ESCAPE	SWIFT PRIME	REVASCAT	THERAPY	Total
NCCT	499/500 (99.8%)*	70/70 (100%)*	313/315 (99.4%)*	163/195 (83.6%)*	206/206 (100%)*	108/108 (100%)*	1359
PCT	333/500 (66.6%) 175/500 (35%) available	70/70 (100%)*	138/315 (43.8%)	139/195 (71.2%)	64/206 (31.1%)	40/108 (37.0%)	784
CTA	496/500 (99.2%)*	70/70 (100%)*	313/315 (99.4%)*	159/195 (81.5%)*	195/206 (94.7%)*	99/108 (91.7%)*	1332
DWI	19/500 (3.8%)	None	2/315 (0.006%)	34/195 (17.4%)*	11/206 (5.3%)*	3/108 (2.8%)	69
Perfusion-weighted MRI	None	None	None	34/195 (17.4%)*	5/206 (2.4%)	1/108 (0.9%)	40
MRA	2/500 (0.4%)	None	2/315 (0.006%)	32/195 (16.4%)*	11/206 (5.3%)*	2/108 (1.9%)	49

The last column indicates the total number of imaging studies available for pooling. CTA indicates computed tomography angiography; DWI, diffusion-weighted magnetic resonance imaging; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; NCCT, noncontrast computed tomography; PCT, perfusion computed tomography; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptoms Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; and THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke.

is injured beyond therapy benefit. Penumbra is defined generally as the at risk hypoperfused area surrounding the core that is the target for therapy to be salvaged. There are now data sets available to benchmark and compare processing of acute PCT against a concurrent diffusion-weighted imaging scan.[19] Also, much of the previous study to define optimal thresholding did not involve patients with ultra early reperfusion, and repeat study should be undertaken using the imaging data collected in these patients.

These efforts to refine and standardize imaging selection must also inform the concept of futility in stroke reperfusion therapy. A futile imaging profile should identify groups of patients in whom a therapy offers little to no clinical benefit particularly if an increased risk of harm is greater than any predicted benefit. A futile profile will depend on many considerations, including time from onset window, anatomic location of existing core infarction, type of treatment, and other clinical variables, such as patient age, NIH Stroke Scale

Table 5. Median Times (and Interquartile Range) for Imaging and to Treatment in Recent Positive Acute Stroke Clinical Trials, in Minutes

	MR CLEAN	EXTEND-IA	ESCAPE	SWIFT PRIME	REVASCAT	THERAPY
Multimodal CT acquisition time	n/a	6 min and 28 s (range: 3 min and 37 s–9 min and 0 s)	n/a	8 (4–21)	n/a	n/a
PCT postprocessing time	n/a	5 min and 20 s (range: 3–10 min)	n/a	3.9 (2.2–5.4)	n/a	n/a
Multimodal MR acquisition time	n/a	n/a	n/a	12 (7–15)	n/a	n/a
PWI/DWI postprocessing time	n/a	n/a	n/a	2 (1.5–2.7)	n/a	n/a
Door-to-arterial access time, min						
For entire IA cohort	n/a	109 (78–150)	76 (62–108)	90 (69–120)	109 (85–163)	142 (85–179.5)
For patients selected based on NCCT alone	n/a	n/a	n/a	n/a	n/a	96.5 (83.5–128.5) (n=4)
For patients selected based on NCCT+CTA	n/a	n/a	76 (62–108)	84 (55–102)	108.0 (85–163)	150.5 (121.5–200.5) (n=28)
For patients selected based on NCCT+CTA+PCT	n/a	109 (78–150)	n/a	90 (69–112)	103.0 (76–136)	101 (68–160) (n=18)
For patients selected based on MRI	n/a	n/a	n/a	84 (55–102)	114.0 (94–155)	114.5 (56–173) (n=2)

CTA indicates computed tomography angiography; DWI, diffusion-weighted imaging; CT indicates computed tomography; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; ESCAPE, Endovascular Treatment for Small Core and Proximal Occlusion Ischemic Stroke; EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits-Intra-Arterial; IA, intra–arterial; MR CLEAN, Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR, magnetic resonance; MRI, magnetic resonance imaging; n/a, not applicable; NCCT, noncontrast computed tomography; PCT, perfusion computed tomography; PWI, perfusion-weighted imaging; REVASCAT, Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within 8 Hours of Symptoms Onset; SWIFT PRIME, Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment; and THERAPY, Assess the Penumbra System in the Treatment of Acute Stroke.

Table 6. Research Priorities

Patient selection research priorities
Standardization of core, mismatch, and collaterals definitions
Standardizing acceptable methods and imaging parameters within and across modalities
Comparability of NCCT ASPECTS, DWI, PCT volume estimates and thresholds, collateral scores on multi- or single-phase CTA
Equivalent definitions and thresholds of mismatch across modalities including coregistration methods between core and perfusion imaging to precisely measure the mismatch volume
Acceptable variability, that is, inter-rater reliability, centralized review vs individual site review
Defining futility thresholds
Validation of semiautomated methods or fully automated methods of image quantification across vendor platforms, devices, and modalities
Final infarct volume research priorities
Recommended as outcome measure at phase II to assess biological effect of therapy
Comparison to baseline core volume preferred (volume of change or statistical adjustment)
Acceptable variability, that is, inter-rater reliability, centralized review versus individual site review
Optimal timing and modality/sequence
Correction for edema, shift due to mass effect, hemorrhagic transformation, atrophy, and preexisting chronic lesions

ASPECTS indicates Alberta Stroke Program Early CT score; CTA, computed tomography angiography; DWI, diffusion-weighted imaging; NCCT, noncontrast computed tomography; and PCT, perfusion computed tomography.

(NIHSS) score, and patient preferences.[22] One commonly used definition of unfavorable outcome, mRS score of 3 to 6, ignores potentially meaningful shifts from severe to moderate disability. The dichotomous approach has been modified to classify mRS score of 4 to 6 as poor clinical outcome (eg, hemicraniectomy for space occupying cerebral edema). However, an ordinal analysis approach using the full scale of the mRS to generate numbers needed to treat to achieve an improvement of at least 1 level on the mRS (perhaps combining 5 and 6 if that transition is not deemed meaningful) is an alternative approach that avoids arbitrary dichotomies. Similarly, patient-oriented outcomes, such as the NeuroQol or Patient-Reported Outcomes Measurement Information System (PROMIS), may also be considered. Recent small studies have shown that they correlate well with the mRS but have greater capacity to discriminate smaller but still meaningful change.[23,24] To address the issue of futility, future research efforts should use pooled analysis of data from recent trials as well as large imaging-based observational studies that enroll either patients without the TRAITs or all comers with a subsequent analysis of outcome by imaging profile to derive futility thresholds for current reperfusion therapy.[25]

Two ongoing trials, Promoting Acute Thrombolysis for Ischemic Stroke (PRACTISE) (ClinicalTrials.gov Identifier: NCT02360670) and Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE)-2, have been designed to better understand imaging selection strategy and the impact on treatment, rather than to test a specific treatment. PRACTISE is currently testing CT-based advanced imaging selection in intravenous thrombolysis decisions. PISTE-2 will have 2 arms, 1 with advanced imaging and 1 without advanced imaging selection, and it is hoped that these will provide information on the added value of advanced imaging.

Final Infarct Volume

FIV can potentially be a useful biomarker in phase II trials to provide an early signal of efficacy for a new treatment. The rationale is that FIV is a more direct measurement of biological effect of acute treatment compared with clinical outcome at 90 days or later which may depend heavily on infarct location and can be affected by unrelated pathology. However, it is not clear that FIV is an equivalent or more powerful measure of treatment effect than clinical measures of outcome. This is an important research question that has been addressed in earlier treatment trials of tissue-type plasminogen activator (imaging outcomes less powerful than clinical outcome measures to detect treatment effect with tissue-type plasminogen activator) but has yet to be investigated in the current endovascular trials. What is clear is that all FIV imaging approaches are known to correlate with long-term clinical outcome. However, what matters is not the degree of correlation but rather the ability to properly classify patients to predict accurately the long-term outcome.

The best approach and timing for measuring FIV requires further investigation. Measuring FIV early after stroke treatment (within 24–48 hours) has the advantage that the majority of patients remain in hospital, but the disadvantages that the lesion volume and signal intensity may still be changing or may be confounded by edema and by parenchymal hematomas. Early mortality at this time point is uncommon and becomes increasingly problematic with later imaging end points because it inevitably leads to missing data in a biased manner. Measuring FIV later (30–90 days) has the advantage of a more stable true final lesion, but the patient is less likely to be available for follow-up scan, tissue atrophy may underestimate the infarct volume, and distinguishing the index infarct from chronic ischemic damage may be impossible, or at least subjective. At all time points, lesion detection and contrast is superior for MRI than CT, making it the preferred modality for final lesion volume measurement. However, CT may be required when MRI is contraindicated or unavailable. The recommended MRI sequence to determine the FIV is diffusion-weighted imaging at 24 to 48 hours.[26] Performing diffusion-weighted imaging earlier than 24 hours risks underestimating lesion volume due to temporary postreperfusion reversal.[27] MRI with fluid attenuated inversion recovery imaging performed at 3 to 5 days or just before discharge is an alternative approach that reduces the potential risk of late infarct growth occurring in nonreperfused patients while minimizing loss to follow-up.[28] However, differentiating the acute lesion from chronic ischemia can be more challenging and edema is prominent at this time. The optimal timing for CT follow-up (when MRI is not available) needs further investigation (ie, 24–72 hours

versus 3–5 days). Research on confounding factors, including edema, hemorrhagic transformation, contrast staining on CT, fogging, etc, are necessary to increase validity of the use of FIV as a biomarker. Adjustment to account for the anatomic location and distribution of the final infarct relevant to clinical outcome whether it affects eloquent regions would clearly be relevant to models aiming to predict functional outcome. However, for assessment of biological treatment effect, removal of this potential confound may be a benefit rather than a pitfall. The research priorities for FIV are outlined in Table 6.

Imaging Technology Issues

Imaging selection for acute stroke could benefit from several technological improvements that would ensure that the requirement for speed does not result in reduced use of advanced imaging, which could impair future pathophysiologic insights and treatment advances.

MRI use could become more widespread with recent advances in rapid stroke imaging protocols but would require an effective fast safety screening process. The risk associated with the administration of gadolinium needs to be addressed, and alternative approaches to assess perfusion such as arterial spin labeling need to be further evaluated.

NCCT could benefit from a focus on improving image acquisition quality and workflow that would improve core detection, including characterization of ASPECTS score. A focus on standardizing optimal acquisition techniques, and the biophysics of image reconstruction algorithms, would be helpful, and should consider a wide range of CT technologies available, including the emerging availability of CT-equipped mobile stroke ambulances.

PCT would benefit greatly from increased signal contrast to noise through improved software and perhaps contrast agent approaches. Faster image reconstruction, transfer, and processing are critical, not just to produce standardized maps but to rapidly generate dynamic angiography. Minimum hardware requirements such as ability to operate at low kilovoltage of 80 kV (or 70 kV when available), volumetric coverage, and safety dose-check features should be considered. Rapid technological advances could open new horizons in terms of imaging selection of patients with acute stroke for treatment.

Conclusions

Recent positive acute stroke endovascular clinical trials have demonstrated the added value of neurovascular imaging. The optimal imaging profile for endovascular treatment includes large vessel occlusion, smaller core, good collaterals, and large penumbra. However, equivalent definitions for the imaging profile parameters across modalities are needed, and a standardization effort is warranted, potentially leveraging the pooled data resulting from the recent positive endovascular trials.

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Appendix

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Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials: Consensus Recommendations and Further Research Priorities

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