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Acute Stroke Imaging Research Roadmap II

A full list of authors and affiliations appears at the end of the article.

The STroke Imaging Research (STIR) group, the American Society of Neuroradiology and the Foundation of the American Society of Neuroradiology sponsored a series of working group meetings over 12 months, with the final meeting occurring during the Stroke Treatment Academy Industry Roundtable (STAIR) on March 9-10, 2013 in Washington, D.C. This process brought together vascular neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the U.S. Food and Drug Administration (FDA) to discuss stroke imaging research priorities, especially in the light of the recent negative results of acute stroke clinical trials that tested the concept of penumbral imaging selection. The goal of this process was to propose a research roadmap for the next 5 years. STIR recommendations include: 1) the use of standard terminology, aligned with the NINDS Common Data Elements (CDE); 2) a standardized imaging assessment of revascularization in acute ischemic stroke trials, including a modified Treatment In Cerebral Ischemia (mTICI) score; 3) a standardized process to assess whether ischemic core and penumbral imaging methods meet the requirements to be considered as an acceptable selection tool in acute ischemic stroke trials; 4) the characteristics of a clinical and imaging data repository to facilitate the development and testing process described in recommendation #3; 5) the optimal study design for a clinical trial to evaluate whether advanced imaging adds value in selecting acute ischemic stroke patients for revascularization therapy; and 6) the structure of a stroke neuroimaging network to implement and coordinate the recommendations listed above. All of these recommendations pertain to research, not to clinical care.

Stroke Imaging Terminology

STIR recommends the use of a standard terminology in compliance with the Common Data Elements (CDE) developed by NINDS (http://www.commondataelements.ninds.nih.gov/stroke.aspx#tab=Data_Standards).[1] In addition, the following refinements are proposed.

Perfusion imaging with CT (CTP) or MRI (MRP) needs to be accompanied by an explicit definition of the perfusion parameters that are going to be derived and used, e.g. cerebral

Address for correspondence and reprint requests: Max Wintermark, M.D., Associate Professor of Radiology, Neurology, Neurosurgery and Biomedical Engineering; Chief of Neuroradiology, UVA Department of Radiology, Neuroradiology Division, Box 800170, Charlottesville, VA 22908, Phone: (434) 982-1736, Fax: (434) 982-0943, Max.Wintermark@gmail.com.

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blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT), etc, and an explicit definition of the modality specific imaging acquisition parameters, e.g. scan techniques, scanner hardware, post-processing software and contrast agent characteristics.

Conceptually, "ischemic core" represents ischemic brain tissue that is irreversibly injured and cannot recover and will proceed to infarction even in the presence of immediate reperfusion. "Penumbra" represents functionally impaired ischemic brain tissue that has the potential to recover with early reperfusion, but is at high risk for irreversible injury (infarction) without early reperfusion.[2,3,4] The penumbra does not include benign oligemia, i.e., tissue with mild hypoperfusion unlikely to infarct even in the absence of reperfusion.

It is important to distinguish pathophysiological concepts from operational definitions that use CT or MR imaging to assess these concepts as part of research studies or clinical trials. CT and MR definitions of "ischemic core" and "ischemic penumbra" are probabilistic. Therefore, when the terms of *ischemic core* and *penumbra* are employed, there should be an *explicit qualification* in the publication as to the specific (i) *imaging technique*, (ii) *perfusion parameter(s)* and (iii) *threshold(s)* under discussion.

The term "malignant" should be reserved for "malignant edema", indicating rapidly progressive edema, mass effect, midline shift, and finally herniation with midbrain or brain stem compression. Use of the term "malignant" to refer to imaging features predictive of poor outcome or low probability of favorable response to therapy is potentially confusing and should be avoided.

Revascularization includes three separate concepts: 1) recanalization, which refers to arterial patency; 2) reperfusion, which refers to antegrade microvascular perfusion; and 3) collateralization, which refer to microvascular perfusion via pial arteries or other anastomotic arterial channels that bypass the primary site of vessel occlusion.

Imaging in Acute Ischemic Stroke Clinical Trials

In stroke clinical trials, imaging can be used as an efficacy and/or safety biomarker for patient selection or outcome assessment. Imaging in stroke clinical trials should be targeted to the specific treatment, trial requirements and goals. The understanding of appropriate imaging modalities, acquisition parameters, thresholds, and post-processing approaches is evolving as experience accrues. No single imaging approach addresses all issues.

Regardless of the imaging techniques used, some general recommendations should be incorporated in clinical trial design involving imaging (Table 1).

Treatment-Relevant Acute Imaging Targets (TRAITs)

Different imaging modalities may be optimal for different methods of treatment (intravenous (IV) versus endovascular or intra-arterial (IA)) and in distinct time windows (early versus late). Moreover, diverse modalities, perfusion parameters, and thresholds may have varying roles for determining potential treatment risks (e.g., hemorrhage) versus potential treatment benefits (e.g., functional recovery of ischemic brain tissue). "Treatment-Relevant Acute Imaging Targets" (TRAIT) is meant to capture imaging elements needed for inclusion (or

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exclusion) into specific treatment protocols. TRAITs acts as a shorthand term to describe the collection of specific imaging metrics used in protocols, and simultaneously reminds trial designers to ensure imaging is directed to the key anatomic or physiologic targets of their specific intervention. For revascularization therapies, the TRAIT could be an arterial occlusion, a perfusion defect causing neurological deficits, a penumbral pattern or some combination of these. In neuroprotective trials, the TRAIT might simply require CT or MRI to confirm the diagnosis of stroke. Research studies and clinical trials should ensure that the proposed imaging is aligned with the TRAITs and should be constant for both arms of the clinical trial.

Imaging for Patient Selection in Stroke Clinical Trials

Potential uses of imaging for patient selection in stroke clinical trials include the approaches listed in Table 2. These uses are not mutually exclusive.

Imaging Selection Biomarkers for Clinical Trials in the 0-4.5 Hour Time Window

The positive randomized placebo-controlled trials of IV alteplase have been based on risk-minimization using noncontrast CT (NCT) to exclude intracranial hemorrhage and excessive volume of established parenchymal hypoattenuation. There are many unresolved issues on the potential role of advanced imaging selection, particularly in the 0-4.5 hour time window (Table 3). When designing trials or studies to address the issues in this time window, the potential value of advanced imaging in this time window must be balanced against the detrimental impact of delaying treatment.

Imaging Selection Biomarkers in the Greater than 4.5 Hour Time Window

Reported and ongoing randomized acute stroke trials have been testing the benefit of reperfusion and revascularization in the greater than 4.5h time window. Differential treatment outcomes on different imaging selected subgroups have been shown in analyses of DEFUSE and DIAS/DEDAS samples. However, a differential treatment effect in imaging-selected subgroups compared to subgroups not undergoing imaging selection has not yet been demonstrated. Imaging paradigms have included MRI diffusion-perfusion mismatch (subgroups of MR RESCUE, DIAS 1&2, DEDAS, EPITHET, IST-3), CTA-confirmed occlusion (subgroups of IMS-3, IST-3) and CTP (subgroups of DIAS-2, IST-3).

Ongoing randomized controlled trials of late revascularization are employing a range of imaging selection criteria. In addition to proof of large artery occlusion (by CTA, MRA or thrombus detection on thin slice CT), these criteria are based either on ischemic core size assessment in the context of certain clinical deficits (clinical/ischemic core mismatch), on an estimated mismatch between ischemic core and ischemic penumbra, or on specific imaging findings that provide an estimate of the age of a given ischemic lesion (i.e. DWI-FLAIR mismatch).

Clinical trial to test the added value of imaging in selecting patients for acute revascularization therapy

Because there are several ongoing efforts to assess the optimal therapy for stroke in the different time windows, it is a complex matter to test the added value of advanced imaging

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in addition to testing different interventions. Currently, it is reasonable to obtain the same advanced imaging TRAIT in all arms of therapeutic clinical trials, which will allow secondary analyses addressing the value of imaging, while the primary focus of the trial is on therapy evaluation. Eventually, a clinical trial should be conducted to assess the added value of advanced imaging compared to what could have been extracted just from clinical information alone.

Imaging Biomarkers for Patients with TIAs and Minor Stroke

Imaging markers (including DWI positivity, intracranial and extracranial vessel occlusion) identify a subgroup of patients with TIA and minor stroke at higher-risk of future stroke or recurrent stroke and may represent trial enrichment selection criteria.[5,6] Transcranial Doppler (TCD) high-intensity transient signals (HITS) count has been used as a biomarker for antithrombotic drugs in phase 2 trials.[7]

Imaging as a Biomarker for Efficacy Outcome in Stroke Clinical Trials

Proof-of-concept phase 2 trials are typically of small size and may use imaging to test a mechanistic hypothesis or provide proof of therapeutic principle. Complete imaging data capture needs to be strictly enforced, as missing imaging data may mask a hazard (e.g., if a higher death or adverse event rate precluded follow-up scanning in this arm). The choice of imaging outcome biomarkers will influence clinical and imaging selection criteria. More restrictive selection criteria and greater complexity associated with pre-treatment imaging may provide more specific pathophysiological information, reducing sample size requirements and heterogeneity of the study population, but may reduce recruitment rate and generalizability of the results. If additional imaging data that are hypothesized to be TRAITs are used in trials primarily designed to test the efficacy of a therapeutic intervention, then the TRAIT can be evaluated only if it is not used as a selection criterion. Phase 2 trials using advanced imaging are optimally performed by collaborations among research centers with expertise in specific types of acute stroke imaging.

Imaging biomarkers of potential value in phase 2 studies include imaging of macrovascular, microvascular, and tissue outcomes (e.g. recanalization, reperfusion, ischemic core volume, and combinations of these). Imaging biomarker selection should take into account inter-observer reliability and measurement error for the selected technique.[8] Moreover, validation criteria for biomarker use in stroke trials should be established. Trials utilizing novel imaging biomarkers should include reporting to a reference standard method such as the STIR calibration described below.

Pivotal phase 3 trials with imaging selection aim at demonstrating effectiveness on a primary clinical endpoint.[9,10,11] As many of the treatments studied as well as imaging assessments are associated with substantial cost, incorporating cost effectiveness analyses into the design of acute stroke trials should be encouraged. Phase 3 trials with clinical endpoints typically involve many centers that may have limited experience and resources for acute specialized stroke imaging. Therefore, phase 3 trials must ensure that imaging protocols are sufficiently simplified and standardized, so that image acquisition is efficient, image interpretation for eligibility assessment can be performed by local investigators, and

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imaging is not an obstacle to enrollment. More sophisticated imaging selection criteria could confer benefits that may be partly or wholly negated by the additional time for acquisition, processing and interpretation. Local investigator certification should be required to insure accurate determination of patient eligibility and outcome assessment. A central core lab adjudication for imaging endpoints should be employed (local reading should also be incorporated for generalizability). Timing of central adjudication should be as close as possible to enrollment/imaging in order to allow for the timely detection of protocol violations.

Significant relationships between imaging biomarkers of infarct volume, lesion growth and penumbral salvage to clinical endpoints have been reported.[12,13,14,15] However, imaging biomarkers in stroke have not met criteria to be used as a surrogate of clinical outcome for Phase III clinical trials according to the FDA recommendations.[16]

Imaging as a Biomarker for Safety Outcome in Stroke Clinical Trials

Intracranial hemorrhage on post-treatment CT is widely used as a safety outcome in trials of revascularization therapies (drug or mechanical). Definitions are well established for CT, and STIR will propose in a separate manuscript an extension of the CT definitions to MRI that will accommodate differences between 1.5T and 3T MRI scanners, and between 2D gradient recalled echo (GRE) and 3D susceptibility-weighted imaging (SWI). Also, the definitions will be extended to include the patterns that can be seen on post-treatment CT scans, obtained after contrast has been administered, either for acute CTA/CTP or DSA. Hemorrhagic transformation should typically be assessed with imaging between 18 and 72 hours, or earlier if the patient demonstrates clinical deterioration. The timing of hemorrhagic transformation routine assessment should be consistent between all trial arms.

Infarct swelling or edema is another cause of early neurological deterioration. The infarct swelling generally peaks around three days after stroke onset, although it can produce symptoms much earlier in patients with malignant pattern.[17] Edema is a major confounder for using early subacute infarct/lesion volume as a surrogate for final infarct volume as it distorts actual infarct size substantially. Edema increases with infarct size (larger infarcts have more edema).[18] Visual scales that score the degree of infarct swelling separate from the infarct extent[19] appear to have good interobserver reliability.[20,21,22]

The role of blood-brain barrier (BBB) disruption as a risk factor for subsequent complications in patients undergoing acute stroke treatment has not been clearly established. Preliminary studies suggest that imaging markers of the BBB disruption are associated with risk of hemorrhagic transformation and adverse outcome.[23,24] Methods for measuring BBB disruption include post contrast parenchymal imaging, delayed gadolinium enhanced FLAIR, CTP, dynamic contrast-enhanced (DCE-MRP), and dynamic susceptibility contrast (DSC-MRP) imaging. The sensitivity of post-contrast imaging to BBB disruption can be enhanced using FLAIR instead of T1 weighted imaging. Post-contrast FLAIR imaging can depict the Hyperintense Acute Reperfusion Marker (HARM), due to enhancement in CSF spaces from contrast leak through the BBB associated with reperfusion.[25,26,27] DCE-MRP is the established measure of BBB disruption; however long acquisition times limit its use in acute stroke. DSC-MRP offers potential for identifying acute BBB disruption as it uses a

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sequence that is already part of the recommended acute stroke imaging protocol. Future research should focus on establishing reliable BBB permeability maps and assessing the utility of BBB markers for prevention of symptomatic ICH. Pooling of existing data will likely accelerate the development of this potential clinical tool.

Imaging Assessment of Revascularization

Standardization of vascular assessment in acute stroke research imaging

In trials of acute revascularization strategies, pathophysiology of acute ischemic stroke should be routinely documented at baseline angiography using systematic description of arterial occlusions and, ideally, collateral perfusion. In general, non-invasive vascular imaging with sufficient sensitivity and specificity for cerebral artery pathology should be performed prior to any invasive vascular imaging to limit the number of unnecessary invasive procedures. The same angiographic or tissue perfusion imaging modality should be used throughout the study design (i.e. baseline, post-treatment, next day), although more flexible use of different modalities (e.g. CT at baseline, MRI for follow-up) helps to limit radiation exposure.[28]

Revascularization imaging modalities

In ischemic stroke, early revascularization (which again encompasses both recanalization and reperfusion) remains the most critical process to impact positively on clinical outcome by restoring blood flow while salvageable brain still persists. A meta-analysis of 2,066 subjects with either spontaneous or therapeutic recanalization within 6 hours of symptom onset was associated with a 4-5 fold increase in the odds of an independent functional outcome and up to a 4 fold reduction in mortality.[29] The magnitude of effect may directly relate to the speed with which revascularization is achieved.[30] Recent randomized data from trials of endovascular treatment for acute ischemic stroke have confirmed that 3 month clinical outcome, as well as attenuated infarct growth, was associated with greater reperfusion and early revascularization.[31,32]

Arteriographic demonstration of revascularization has 3 important components (Table 4).[33] Distal reperfusion is the primary determinant of tissue fate and ultimately clinical outcome. Recanalization is necessary but not sufficient for tissue reperfusion (e.g., cases with distal embolization or no-reflow, in which contrast does not enter the affected tissue bed even though the parent artery may have reopened). Grading recanalization of the primary occlusion may provide prognostic information distinct to or in addition to tissue reperfusion in the setting of partial recanalization, where there may be a higher chance for reocclusion or distal embolization. Several diagnostic tools are capable of evaluating these components of revascularization.[34]

Conventional angiography with contrast injection in the extracranial arteries supplying the brain tissue is the reference standard for assessment of recanalization of the primary occlusion and restoration of blood flow into the distal arterial bed. It is available during and immediately after intra-arterial or endovascular treatment. Although catheter angiography has also been used to grade tissue reperfusion there are significant limitations. Prior trials have not had a uniform approach to grading either the arterial or the tissue bed components,

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and there are inherent challenges to quantifying the volume of tissue reperfusion on conventional angiography.

Non-invasive approaches are ideal for assessing revascularization after intravenous thrombolysis. Non-invasive angiographic imaging using CT- and MR-angiography (CTA and MRA) can assess recanalization but cannot accurately assess reperfusion which requires tissue imaging with CTP or MRP. CTA is generally more accurate than time of flight MRA for occlusion detection when compared to reference standard conventional angiography, particularly for second-order intracranial arteries.[35] However, the radiation exposure and contrast load associated with CTA and CTP should be considered in choosing imaging options. TCD evaluation is hampered by attenuation of energy through thick bone windows in the elderly and limited to the assessment of more proximal arteries because of difficulty distinguishing vessels on the cortical surface. However, it has been used for early diagnosis of large intracranial artery occlusion and does offer the advantage of bedside real-time monitoring of recanalization of large arteries for exact timing. CTP and MRP can assess tissue reperfusion. Flat-panel detector angiographic systems and Xpert-CT or dyna-CT scans have emerged as potential diagnostic tool for acute stroke patients. These systems might avoid delay in imaging of candidates for IA or endovascular therapy but currently they do not have enough spatial resolution to allow for the identification of early ischemic changes.

In some circumstances non-angiographic “thrombus imaging” may be an alternative to angiographic imaging. CTA and MRA do not precisely define occluded segments. These are displayed as gaps between contrasted non-occluded vessels and thus their shape is ambiguous. Furthermore, non-occluded segments close to the thrombus often do not show contrast due to slow flow or insufficient collaterals.[36] The hyperdense middle cerebral artery (MCA) sign on CT when clearly visible is highly predictive of an MCA main stem occlusion.[37] Hyperdense artery signs on CT involving other arteries have also shown high specificity.[38]

Until recently, clot imaging using the MCA sign on CT was considered impractical due to the sign’s low sensitivity. This problem can be overcome by reconstructing additional thin NCT slices. These allow for visualizing clots in the MCA main stem.[39,40] The length and location of the hyperdense artery sign may also predict response to IV tPA.[41,42] Length of hyperdense sign should be measured using a standardized thin section NCT. Similarly, an absent flow void or altered signal (susceptibility vessel sign (SVS) on GRE or SWI) on MRI can signify an intracranial occlusion.[43,44,45]

Limited literature is available concerning the use of non-angiographic thrombus imaging to assess revascularization. The disappearance of the hyperdense sign with IV tPA has been described and is associated with improved outcome (versus persistence of the sign)[46] although is not yet validated against angiographic imaging in a large population.

Timing of vascular assessments

Timing of assessments should be recorded and should be as closely matched in all arms of the trial to avoid disparities in revascularization assessment between treatment arms, which

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could bias the conclusions. The number of assessments should be relevant to the trial question to avoid unnecessary excess radiation/contrast load/disruption to patient care.

Timing should be relevant to assess re-occlusion where appropriate. Baseline (vascular status) should be as close in time as possible to the administration of treatment. Post-treatment assessment of revascularization should be early when "nutritional" reperfusion can still lead to salvage of significant regions of brain. If a comparison to endovascular treatment for revascularization is performed, this should take place within 2-6 hours of the treatment initiation, as long as this can be achieved without disrupting or compromising patient care. The timing of revascularization imaging could be later for systemic thrombolysis due to more gradual revascularization seen with such therapy. A late revascularization endpoint (next day/24 hour) could also be considered as a secondary revascularization endpoint. The relationship of this late revascularization endpoint to tissue salvage is less clear.

Recanalization-arterial patency and grading

The primary target lesion evaluated for recanalization should be the most proximal intracranial occlusive segment(s) that is likely to be the cause of recent stroke symptoms, and the target of the intervention. 'Occlusion' should be defined to include both complete and partial arterial obstruction. The primary target lesion should be described in detail: terminal ICA occlusions (T, L, or I types), proximal or distal M1 (first half and second half, respectively), M2 configuration. Of note, the M1 segment should be defined as the horizontal segment before the MCA bifurcation, accessible to endovascular treatment. When a large anterior temporal branch supplies brain tissue beyond the temporal pole, it is to be considered as an M2 equivalent, and the MCA segment between the anterior temporal branch and the MCA bifurcation is still M1. Secondary lesion(s) are occlusive segments involving: a) extracranial arteries proximal to the primary lesion; b) arterial segments distal to the primary lesion (i.e., M2/M3); or c) adjacent arteries involving other vascular territories (i.e. ACA) with smaller thrombus burden than the primary lesion. Of note, downstream territory for terminal ICA occlusions should be taken as the ACA and MCA territory unless there is clear evidence of ACA filling from the contralateral side.

Pial collaterals with retrograde flow should be routinely evaluated and scored with the ASITN/SIR grading system. [47] Other scoring systems, such as the Capillary Index Score, which focuses on capillary staining in the venous angiographic phase, show promise in predicting outcome prior to treatment, but have not been validated against the ASITN/SIR grading system.[48]

Patients with no angiographic evidence of intracranial occlusion should not be pooled with patients with angiographically-documented intracranial occlusion.

Normal variants of vasculature, such as hypoplastic or absent A1 ipsilateral to the occlusion, should be documented.

One reference standard recanalization grading scale should be used for each imaging modality (TCD, CTA, MRA, DSA) to assess patency of arteries. TCD recanalization grading is best assessed with the Thrombolysis in Brain Ischemia (TIBI) flow grading

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system now used in a number of TCD based clinical trials.[49,50] The TIBI score has also been slightly modified to assess recanalization using TCD technologies (Consensus On Grading Intracranial Flow obstruction, [COGIF] score).[51] No CTA or MRA based grading systems have been developed that are considered standard, although Thrombolysis in Myocardial Infarction (TIMI)/TICI/arterial occlusion lesion (AOL) scores have been used. AOL score has been applied to recanalization of the target arterial occlusive lesion. Such grading systems are variably applied and may perform poorly when conflating the scoring of the primary occlusion point, the distal arterial bed and the tissue level perfusion in one score. This is a source of confusion and should absolutely be avoided.[52] A STIR-revised version of the TICI score is detailed below.

Reperfusion grading could be performed by a visual scale or by quantifiable methods. Choice of method will depend on trial questions and trial phase.

Modified TICI score

DEFUSE 2 and IMS 3 provided data to support a correlation between modified TICI grades and clinical outcome at 3 months.[32,53] However, conventional TICI 2a and 2b grades, which comprised the majority of recent trial results, span a wide spectrum from marginal antegrade flow to substantial angiographic reperfusion, and the definition of the distinction between the two may be unclear. Substantial variability in partial perfusion thresholds with TICI was documented leading to different grading in approximately 20% of cases.[54] A TICI 2c grading has been proposed to further distinguish partial perfusion, but remains too new to recommend.

There are operational definitions for what constitutes effective revascularization. STIR recommends a modified TICI scale to measure the extent of capillary-level opacification (i.e., parenchymal blush) in the downstream territory after successful intra-arterial treatment on conventional angiogram (Table 5). This modified scale applies exclusivelyfor conventional angiography and for revascularization assessment. STIR recommends using the reperfusion scale without alteration for the location of the target arterial occlusive lesion.

The consensus definition of successful reperfusion is a mTICI score of 2b or 3, while mTICI of 0, 1 and 2a indicates a lack of successful reperfusion.

Future collaborative research

Studies of mTICI scale performance (including intra- and inter-observer reliability, and validity) should be conducted. The correlation between mTICI grades and clinical outcomes should be studied, including comparisons between mTICI 2b versus mTICI 3. Similarly, studies of the mTICI scale at distinct sites of target arterial occlusions (e.g. ICA vs M1 vs M2) should be conducted. There should be correlation studies between the mTICI grades and perfusion CT and MRI measurements, studies to correlate clot length, infarct size and collateral status, as well as studies to determine whether incorporating a time to reperfusion metric into the mTICI scale would further improve outcome prediction.

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STIR Calibration of Software Packages for Ischemic Core and Penumbral Imaging

STIR recognizes that imaging techniques continuously evolve, and that there will always be a newer, better ischemic core or penumbral imaging technique or processing software. Therefore, it is desirable to find a balance between continued attempts to improve on existing methods versus determining whether existing methods are good enough to be used in current clinical trials. For this discussion software package refers to the combination of imaging acquisition and post-processing algorithm.

STIR therefore has created a repository of shared stroke clinical and source imaging data available to the field of stroke researchers.[55,56] The STIR repository pools CT and MRI data from large datasets and stroke clinical trials that can be used to compare head to head different acquisition techniques and software packages in their attempts to define ischemic core and penumbra, and determine acceptability criteria.

This STIR calibration process described below *does not* assess or recommend how to use ischemic core and penumbra information for prognosis, prediction of response to treatment and/or selection of patients for reperfusion therapy. These are better answered in well-designed clinical trials or prospective validation studies. However, the data repository and analyses may be used to generate hypotheses and ischemic core/penumbra predictive/prognostic algorithms to be used in such clinical trials.

The clinical and imaging data to be included into the repository needs to meet specific criteria in order to allow rigorous analyses of the validity of software performance in defining ischemic core and penumbra. The selected data need to match the analyses proposed as part of the calibration process. If the required data for the analyses cannot be collected by compiling existing datasets (because of the strict criteria that the data need to satisfy), then the repository will need to be populated from prospective data collection.

The *first recommended analysis* is to use existing digital phantoms to produce goodness-of-fit metrics for perfusion maps created by CTP or MRP software.[57,58,59,60] The goodness-of-fit metrics will be evaluated against the digital reference object phantoms in terms of bias and variance as a function of signal-to-noise and simulation conditions. For each software package tested, the results of this analysis should be reported so that software users have objective information to select a software package for their research.

The *second recommended analysis* is a calibration/comparison of acute CTP and DWI to determine the optimal CTP parameter(s)/threshold(s) that produces a CTP abnormality that best matches the DWI abnormality (Table 6). It is assumed that most/all patients will have the CTP study done first, except perhaps in patients not eligible for reperfusion therapy. This will lead to some bias in the comparisons between the two imaging methods (CTP and DWI), such that CTP abnormality should, in general, underestimate the DWI abnormality. Post-reperfusion DWI reversal is not relevant to this dataset as patients with revascularization between the CTP and the MRI study will be excluded. Derivation and validation datasets should be established to prevent overfitting of the perfusion data.

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The *third recommended analysis* is another calibration effort between software packages. The goal of this calibration effort is that all acceptable software packages provide similar volume of ischemic core and penumbra independently of the underlying algorithms. This calibration step *does not* address the accuracy of the software packages for prediction of the tissue fate. Also, as mentioned above, this calibration process *does not* assess or recommend how to use ischemic core and penumbra information for prognosis, prediction of response to treatment and/or selection of patients for reperfusion therapy.

This calibration process will involve acute CT and MRI datasets to determine optimal parameters/thresholds to determine ischemic core and penumbra in two groups of patients: one with no revascularization and one with early revascularization (Table 7). The baseline dataset will include an advanced CT dataset: NCT (ideally with clot imaging), CTP, CTA (ideally dynamic CTA), and an MRI dataset: DWI, MRP, FLAIR, GRE or SWI, MRA. In the first group, patients should demonstrate persistent occlusion on follow-up CTA or MRA or complete lack of revascularization (persistent CTP or MRP lesion of similar size to baseline). In the second group ("early" revascularization), the issue is the timing of documentation of revascularization. The 'purest' group is evidence of complete revascularization on DSA after clot retrieval. But it is also important to assess and compare ischemic core parameter(s)/threshold(s) after IV tPA lysis. It is therefore desirable to have a second 'almost pure' group with evidence of complete revascularization between 2-8 hours after IV tPA lysis initiation. Finally, a third 'less pure' group with evidence of complete revascularization on CTA/MRA between 8 and 24 hours after revascularization initiation would also be acceptable. Since the STIR calibration process will consist of comparing the results of different software packages using the same dataset, the limitations of the 'less pure' dataset will be the same for all the software packages, and the comparison will be fair.

Final infarct volume needs to be assessed in both groups of patients. Final infarct volume assessment is a challenging issue because of the initial variation in the volumes of imaging abnormalities, contributed to by the superimposed edema in the initial phase and atrophy in the later phase, and because of logistic issues. Patients with persistent, complete, proximal occlusion have a very poor outcome and may be deceased by day 7. STIR *pragmatic* recommendation *for the purpose of this calibration process* is to use DWI (preferred) or NCT obtained between 18 and 36 hours to define the lesion to be used as the reference for the analyses described above. The 18-36 hour DWI is significantly associated with later infarct volume and is much easier to obtain than very late imaging (e.g. day 30).[61]

The *fourth recommended analysis* aims at standardizing collateral assessment, whether it is on angiographic data or noninvasive CTP/MRP data. Ideally, the collected dataset would be identical to the 'pure' DSA group in the second recommended analysis. The underlying idea is to define the 'most accurate' measure of collateral flow on non-invasive imaging datasets. The reference standard would be the DSA, and the tested imaging modalities would be the CTA or MRA performed prior and within 60 minutes of DSA, with confirmation of lack of recanalization between DSA and CTA/MRA. For this analysis, patients with baseline CTA and patients with baseline MRA will be analyzed as separate groups. Collateral assessment may be more accurate from time-resolved (or at least multi-phase) CTA data compared to static (single timepoint) CTA. This similarly applies to static MRA. Ideally, concurrent CTP

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or DWI/MRP should be obtained to assess quantitative perfusion measures against collateral status on DSA and non-invasive angiography.

For all the above recommended analyses, we will need a combination of sensitivity and specificity from receiver operator characteristic (ROC) curve analysis. At this time, we are not recommending any specific level of sensitivity or specificity to be achieved. Rather, we are recommending the four analyses detailed above be performed for all perfusion software packages available and the results published so as to serve as the initial benchmark. It is likely that the benchmark levels of sensitivity or specificity will increase over time, reflecting continuous improvements in the perfusion software packages.

For all datasets, a spread of the baseline imaging is needed in various time windows after stroke onset, e.g. - 0-3 hours, 3-4.5 hours, 4.5-6 hours, 6-12 hours. Similarly, a diverse population is desired, with patients who were not treated, patients treated with IV thrombolysis and patients treated with IA revascularization. All the datasets collected should ideally have appropriate clinical information collected as part of the protocol. If possible, NIH Stroke Scale scores at all imaging timepoints, mRS at day 90, time of onset, and acute treatment should be collected.

In terms of the imaging protocols used, two approaches can be considered. One would be to harmonize acquisition protocols as much as possible and for STIR to provide guidelines (as done previously).[62,63] However, a second, more pragmatic approach is to accept a broad range of acquisition protocols. A ‘good enough’ software should be able to deal with a broad range of image acquisition protocols. This makes the results more generalizable, but this approach requires validation.

The data submitted to the STIR repository should be anonymized and undergo a rigorous quality control process before being accepted into the repository, in order to ensure compliance with minimum basic acquisition standards.

Stroke Neuroimaging Network and Coordinating/Data Center

Similar to continuously evolving software tools, STIR recognizes that imaging techniques will continue to advance on the acquisition side as well. Promising emerging imaging techniques for providing even greater understanding into stroke sequelae include non-invasive measurement of cerebral blood flow (e.g. arterial spin labeling [ASL] MRI[64,65], oxygen extraction fraction MRI[66], pH-weighted MRI[67], vessel size imaging[68,69], vascular space occupancy (VASO) MRI[70], cerebrovascular reactivity measured with MRI[71], diffusion kurtosis MRI[72], diffusion-tractography[73], resting-state fMRI[74,75,76], dual-energy CT[77], and PET and SPECT tracers to assess inflammatory processes. New imaging techniques offer practical benefits such as less invasive methods that allow for repeat assessments or less motion sensitive approaches which are critical for imaging agitated and non-compliant patients who make up the majority of the acute stroke population. New contrast agents may offer practical benefits of patients’ exposure to less iodine or gadolinium. Beyond the likely increased specificity and sensitivity of identifying patients who may benefit from novel pathways for acute intervention, advanced imaging techniques can also potentially be used for trials of stroke prevention to assess vulnerable carotid

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atherosclerotic plaque and identify patients at high risk of stroke. Advanced imaging has also been posited to be potentially of use for monitoring functional changes in the brain recovery process and therefore may be used to evaluate physical and neurocognitive therapy after stroke.[78,79]

Although advanced neuroimaging techniques have the potential to impact all stages of stroke patient management, the practical translation of these potentially transformative techniques from research to clinical settings currently faces many challenges. Some of these include limited support for developing advanced imaging techniques in clinical trial environments and logistic issues regarding their feasibility in acute trial settings. Pragmatic issues such as scan duration are important especially in the acute revascularization trials as described above. For evaluating patients without pressing time constraints, e.g. chronic stroke patients and TIA patients, longer acquisitions may be feasible, and automatic motion correction would be extremely useful in this setting.

Critical to the acceptance of new techniques will be their performance. Depending on the patient population under investigation, there are many possible criteria by which new imaging techniques can be evaluated. As described above, for acute stroke patients, imaging techniques are typically evaluated on their ability to predict lesion volumes on follow-up imaging as a reference standard. The equivalent for at-risk patients would be prediction of future strokes. For acute stroke or at-risk patients, additional evaluation criteria should include prediction or measurement of clinical response to intervention or medication such as gray matter volume measurement relative to the contralateral unaffected brain could be evaluated against neurocognitive testing and be used for prediction of cognitive outcomes and response to rehabilitation therapy.[80] Ultimately, any new technique will need to impact clinical management of these patients, whether by making the imaging study less invasive or providing additional information on potential tissue salvage, tissue at risk or risk of complication with treatment. In addition, the evaluation of the utility of new imaging techniques for patient selection or as a biomarker of safety or efficacy of new treatments should follow the recommendations described above.

For translating new techniques from research settings to clinical settings, several study designs are possible. After the initial validation at a single site or small number of sites, the consensus is that multi-center, multi-vendor studies would be the most appropriate for successful translation of new techniques to non-academic hospital centers. There is still debate on whether to limit evaluation of new techniques to current state of the art technology, e.g. 3 Tesla scanners, or to emphasize generalizability, e.g. include 1.5 Tesla MRI scanners. For evaluating the clinical utility of new advanced imaging techniques, both acquisition and processing techniques, and contrast administration techniques will need to be standardized by expert panels, as is currently done for ASL by the Perfusion Study Group of the International Society for Magnetic Resonance in Medicine (ISMRM) and the European consortium ‘ASL in Dementia (AID)’ (funded through a grant from the European Union COST agency).

Mechanisms are therefore needed to translate and test advanced imaging methods across centers, to encourage the use of advanced imaging in acute settings, to stimulate closer

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academic-industry collaborations (such as for the Alzheimer's Disease Neuroimaging Initiative http://www.adni-info.org/[81]) and to promote the retrospective and prospective collection and pooling of imaging data, such as the one to create the STIR repository described above.

The two logistic priorities for promoting translation of new imaging research are: (1) population of the STIR imaging data repository with links to clinical metadata, and (2) establishment of a stroke trial imaging network.

Regarding the first priority, STIR recommends that worldwide government agencies can provide funding to centers to acquire a standard dataset using a common IRB-approved imaging-based study protocol matching the description above in the section about the STIR calibration process. Also, some government-funded acute stroke clinical trials could be required to collect a minimal basic imaging dataset, in addition to the clinical CDE. Promoting imaging as a required data element in some trials, and making these data available to the stroke community through a repository, would accelerate testing of the utility of advanced imaging for stroke research.

The second priority, an international stroke trial imaging network, will provide the infrastructure that facilitates advanced neuroimaging-based studies. An imaging network comprising international experts could track the clinical and imaging capabilities of potential participating centers, i.e. contact information for neurologists, neuroradiologists, interventionalists, imaging physicists and emergency physicians, ability to do acute CT, CTA, MRI as well as the number of acute stroke patients seen per year. In addition, scanner details (i.e. 1.5T MRI, 3T MR, manufacturer and software version) should be recorded. Having this information readily available will provide an easy mechanism for identifying potential centers that are capable of integrating advanced imaging into stroke clinical trials. Currently, every imaging-based multicenter trial repeats the same process for identifying eligible centers with the required technical capabilities to perform the study before startup. Having a centralized, regularly updated database of center capabilities could streamline the process and ultimately accelerate startup of these studies. Establishment of a stroke trial imaging network with a central coordinating/data group has the potential of both immediate and long-term impact on stroke research and public health by creating an infrastructure that reduces redundancy and increases efficiency of stroke imaging research, thereby allowing investigators to concentrate on clinical and scientific questions rather than implementation issues. In addition, such centers can promote scientific collaboration and education in a distributed fashion, and further advance software reuse, and data and model sharing.

Finally, worldwide governmental funding agencies can use their unique position to work with industry and academia to promote public-private partnerships to facilitate the distribution of proprietary techniques and software across multiple platforms and accelerate standardization and translation of advanced imaging technologies.

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Conclusion

The two main achievements of the STIR II are to provide specific terminology for acute stroke imaging, and a modified TICI scale. General guidance about the use of imaging in the design of stroke clinical trials is also provided.

The three main recommendations of STIR II for stroke imaging research directions include:

- the establishment of a STIR calibration process for measuring ischemic core and penumbral software,
- populate the STIR clinical and imaging data repository to facilitate the STIR calibration process, and
- the creation of a stroke neuroimaging network able to keep track of the clinical and imaging capabilities of centers, i.e. contact information for neurologists, neuroradiologists, interventionalists, imaging physicists and emergency physicians, ability to do acute CT, CTA, CTP, MRI, MRP, MRA as well as the number of acute stroke patients seen per year.

Collaboration among academia, industry, and funding and regulatory agencies is integral to the successful realization of these aims.

Authors

Max Wintermark, MD MAS,
Department of Radiology, Neuroradiology, University of Virginia, Charlottesville, VA & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Gregory W. Albers, MD,
Stanford University School of Medicine, Stanford, CA, USA

Joseph P. Broderick, MD,
Department of Neurology, University of Cincinnati Neuroscience Institute, Cincinnati, OH, USA

Andrew M. Demchuk, MD,
Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary; Calgary, AB Canada

Jochen B. Fiebach, MD,
Academic Neuroradiology, Center for Stroke Research Berlin, CharitéUniversitätsmedizin Berlin, Germany

Jens Fiehler, MD,
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

James C. Grotta, MD,
Department of Neurology, University of Texas Health Science Center, Houston, TX, USA

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Gary Houser,
The Stroke Group, Centennial, CO, USA

Tudor G. Jovin, MD,
Department of Neurology, University of Pittsburgh Medical Center, Stroke Institute and UPMC Center for Neuroendovascular Therapy, Pittsburgh, PA, USA

Kennedy R. Lees, MD,
Institute of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, UK

Michael H. Lev, MD,
Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

David S. Liebeskind, MD,
UCLA Stroke Center, Los Angeles, CA, USA

Marie Luby, PhD,
National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD, USA

Keith W. Muir, MD,
Institute of Neurosciences & Psychology, University of Glasgow, Southern General Hospital, Glasgow, Scotland, UK

Mark W. Parsons, MD PhD,
Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle, Australia

Rüdiger von Kummer, MD,
Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Joanna M. Wardlaw, MD,
Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

Ona Wu, PhD,
Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Albert J. Yoo, MD,
Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Andrei V. Alexandrov, MD,
Comprehensive Stroke Center, University of Alabama Hospital, Birmingham, AL, USA

Jeffrey Alger, MD PhD,
UCLA Stroke Center, Los Angeles, CA, USA

Richard I. Aviv, MD,
University of Toronto and Sunnybrook Health Science Centre, Toronto, Canada

Roland Bammer, PhD,

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NIH-PA Author Manuscript

Stanford University School of Medicine, Stanford, CA, USA

Jean-Claude Baron, MD ScD,
INSERM U894, Sorbonne Paris Cité, Paris, France, and Dept of Clinical Neurosciences, University of Cambridge, UK

Fernando Calamante, PhD,
The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Bruce C. V. Campbell, MD PhD,
Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

Trevor C. Carpenter, PhD,
Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Ediburgh, UK

Søren Christensen, PhD,
Stanford University School of Medicine, Stanford, CA, USA

William A. Copen, MD,
Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Colin P. Derdeyn, MD,
Washington University School of Medicine, St. Louis, MO, USA

E. Clarke Haley Jr, MD,
Department of Neurology, University of Virginia, Charlottesville, VA, USA

Pooja Khatri, MD,
Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

Kohsuke Kudo, MD PhD,
Department of Diagnostic Radiology, Hokkaido University Hospital, Sapporo, Japan

Maarten G. Lansberg, MD PhD,
Stanford University School of Medicine, Stanford, CA, USA

Lawrence L. Latour, PhD,
National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD, USA

Ting-Yim Lee, MD,
The University of Western Ontario, London, Ontario, Canada

Richard Leigh, MD,
Johns Hopkins University School of Medicine, Baltimore, MD, USA

Weili Lin, PhD,
Biomedical Research Imaging Center and Departments of Radiology, Neurology, Biomedical Engineering and School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Patrick Lyden, MD,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Cedars-Sinai Medical Center, Los Angeles, CA, USA

Grant Mair, MD,
Neuroradiology, Division of Neuroimaging Sciences, Western General Hospital, Edinburgh, UK

Bijoy K. Menon, MD,
Calgary Stroke Program, Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Patrik Michel, MD,
Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland

Robert Mikulik, MD, PhD,
Neurology Department, International Clinical Research Center, St. Anne's Hospital, Brno, Czech Republic

Raul G. Nogueira, MD,
Marcus Stroke & Neuroscience Center/Grady Memorial Hospital, Emory University School of Medicine, Atlanta, GA, USA

Leif Østergaard, MD PhD,
Center of Functionally Integrative Neuroscience, Aarhus University Hospital, Aarhus, Denmark

Salvador Pedraza, MD,
Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta, Girona, Spain

Christian H. Riedel, MD,
Department of Neuroradiology, University of Kiel, Kiel, Germany

Howard A. Rowley, MD,
Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Pina C. Sanelli, MD MPH,
Department of Radiology, Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY, USA

Makoto Sasaki, MD PhD,
Institute for Biomedical Sciences, Iwate Medical University, Yahaba, Japan

Jeffrey L. Saver, MD,
UCLA Stroke Center, Los Angeles, CA, USA

Pamela W. Schaefer, MD,
Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Peter D. Schellinger, MD,
Johannes Wesling Klinikum Minden, Minden, Germany

Georgios Tsivgoulis, MD,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Comprehensive Stroke Center, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA, Second Department of Neurology, School of Medicine, University of Athens, Athens, Greece

Lawrence R. Wechsler, MD,
Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Philip M. White, MD,
Institute for Ageing and Health, Newcastle University, UK

Greg Zaharchuk, MD PhD,
Stanford University School of Medicine, Stanford, CA, USA

Osama O. Zaidat, MD,
Department of Neurology, Neurosurgery, and Radiology, Medical College of Wisconsin and Froedtert Hospital, Milwaukee, WI, USA

Stephen M. Davis, MD,
Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

Geoffrey A. Donnan, MD,
The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Anthony J. Furlan, MD,
University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH, USA

Werner Hacke, MD PhD,
Department of Neurology, University of Heidelberg, Heidelberg, Germany

Dong-Wha Kang, MD PhD,
Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Chelsea Kidwell, MD,
Department of Neurology and the Stroke Center, Georgetown University, Washington, DC, USA

Vincent N. Thijs, MD PhD,
Laboratory of Neurobiology, Vesalius Research Center, VIB, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), University of Leuven (KU Leuven), Department of Neurology, University Hospital Leuven, Leuven, Belgium

Götz Thomalla, MD PhD, and
University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Steven J. Warach, MD PhD

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Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Austin, TX, USA

For the Stroke Imaging Research (STIR) and VISTA-Imaging Investigators

Affiliations

Department of Radiology, Neuroradiology, University of Virginia, Charlottesville, VA & Department of Radiology, Centre Hospitalier Universitaire Vaudois (CHUV), Lausanne, Switzerland

Stanford University School of Medicine, Stanford, CA, USA

Department of Neurology, University of Cincinnati Neuroscience Institute, Cincinnati, OH, USA

Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary; Calgary, AB Canada

Academic Neuroradiology, Center for Stroke Research Berlin, CharitéUniversitätsmedizin Berlin, Germany

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Department of Neurology, University of Texas Health Science Center, Houston, TX, USA

The Stroke Group, Centennial, CO, USA

Department of Neurology, University of Pittsburgh Medical Center, Stroke Institute and UPMC Center for Neuroendovascular Therapy, Pittsburgh, PA, USA

Institute of Cardiovascular and Medical Sciences, University of Glasgow, Western Infirmary, Glasgow, UK

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

UCLA Stroke Center, Los Angeles, CA, USA

National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD, USA

Institute of Neurosciences & Psychology, University of Glasgow, Southern General Hospital, Glasgow, Scotland, UK

Department of Neurology, John Hunter Hospital, Hunter Medical Research Institute, University of Newcastle, Australia

Neuroradiology and Dresden University Stroke Center, University Hospital Carl Gustav Carus, Technische Universität Dresden, Dresden, Germany

Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Edinburgh, UK

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

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Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Comprehensive Stroke Center, University of Alabama Hospital, Birmingham, AL, USA

UCLA Stroke Center, Los Angeles, CA, USA

University of Toronto and Sunnybrook Health Science Centre, Toronto, Canada

Stanford University School of Medicine, Stanford, CA, USA

INSERM U894, Sorbonne Paris Cité, Paris, France, and Dept of Clinical Neurosciences, University of Cambridge, UK

The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

Brain Research Imaging Centre, Division of Neuroimaging Sciences, Centre for Clinical Brain Sciences, University of Edinburgh, Ediburgh, UK

Stanford University School of Medicine, Stanford, CA, USA

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Washington University School of Medicine, St. Louis, MO, USA

Department of Neurology, University of Virginia, Charlottesville, VA, USA

Department of Neurology, University of Cincinnati, Cincinnati, OH, USA

Department of Diagnostic Radiology, Hokkaido University Hospital, Sapporo, Japan

Stanford University School of Medicine, Stanford, CA, USA

National Institute of Neurological Disorders and Stroke (NINDS), National Institutes of Health (NIH), Bethesda, MD, USA

The University of Western Ontario, London, Ontario, Canada

Johns Hopkins University School of Medicine, Baltimore, MD, USA

Biomedical Research Imaging Center and Departments of Radiology, Neurology, Biomedical Engineering and School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA

Cedars-Sinai Medical Center, Los Angeles, CA, USA

Neuroradiology, Division of Neuroimaging Sciences, Western General Hospital, Edinburgh, UK

Calgary Stroke Program, Departments of Clinical Neurosciences and Radiology, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada

Centre Hospitalier Universitaire Vaudois (CHUV) and University of Lausanne, Lausanne, Switzerland

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NIH-PA Author Manuscript

Neurology Department, International Clinical Research Center, St. Anne's Hospital, Brno, Czech Republic

Marcus Stroke & Neuroscience Center/Grady Memorial Hospital, Emory University School of Medicine, Atlanta, GA, USA

Center of Functionally Integrative Neuroscience, Aarhus University Hospital, Aarhus, Denmark

Radiology Department-IDI. IDIBGI. University Hospital Dr Josep Trueta, Girona, Spain

Department of Neuroradiology, University of Kiel, Kiel, Germany

Department of Radiology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

Department of Radiology, Weill Cornell Medical College, NewYork-Presbyterian Hospital, New York, NY, USA

Institute for Biomedical Sciences, Iwate Medical University, Yahaba, Japan

UCLA Stroke Center, Los Angeles, CA, USA

Massachusetts General Hospital and Harvard Medical School, Boston, MA, USA

Johannes Wesling Klinikum Minden, Minden, Germany

Comprehensive Stroke Center, Department of Neurology, University of Alabama at Birmingham, Birmingham, AL, USA, Second Department of Neurology, School of Medicine, University of Athens, Athens, Greece

Department of Neurology, University of Pittsburgh School of Medicine, Pittsburgh, PA, USA

Institute for Ageing and Health, Newcastle University, UK

Stanford University School of Medicine, Stanford, CA, USA

Department of Neurology, Neurosurgery, and Radiology, Medical College of Wisconsin and Froedtert Hospital, Milwaukee, WI, USA

Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia

The Florey Institute of Neuroscience and Mental Health, Melbourne, Australia

University Hospitals Case Medical Center, Case Western Reserve University, Cleveland, OH, USA

Department of Neurology, University of Heidelberg, Heidelberg, Germany

Department of Neurology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, South Korea

Department of Neurology and the Stroke Center, Georgetown University, Washington, DC, USA

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Laboratory of Neurobiology, Vesalius Research Center, VIB, Experimental Neurology and Leuven Research Institute for Neuroscience and Disease (LIND), University of Leuven (KU Leuven), Department of Neurology, University Hospital Leuven, Leuven, Belgium

University Medical Center Hamburg-Eppendorf, Hamburg, Germany

Seton/UT Southwestern Clinical Research Institute of Austin, Department of Neurology and Neurotherapeutics, UT Southwestern Medical Center, Austin, TX, USA

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References

1. Saver JL, Warach S, Janis S, Odenkirchen J, Becker K, Benavente O, et al. Standardizing the structure of stroke clinical and epidemiologic research data: The national institute of neurological disorders and stroke (ninds) stroke common data element (cde) project. Stroke; a journal of cerebral circulation. 2012; 43:967–973.
2. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia - the ischemic penumbra. Stroke; a journal of cerebral circulation. 1981; 12:723–725.
3. Baron JC. Mapping the ischaemic penumbra with pet: Implications for acute stroke treatment. Cerebrovasc Dis. 1999; 9:193–201. [PubMed: 10393405]
4. Lassen NA. Pathophysiology of brain ischemia as it relates to the therapy of acute ischemic stroke. Clinical neuropharmacology. 1990; 13(Suppl 3):S1–8. [PubMed: 2093413]
5. Coutts SB, Modi J, Patel SK, Demchuk AM, Goyal M, Hill MD. Ct/ct angiography and mri findings predict recurrent stroke after transient ischemic attack and minor stroke: Results of the prospective catch study. Stroke; a journal of cerebral circulation. 2012; 43:1013–1017.
6. Coutts SB, Simon JE, Eliasziw M, Sohn CH, Hill MD, Barber PA, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Annals of neurology. 2005; 57:848–854. [PubMed: 15929051]
7. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, et al. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using doppler embolic signal detection: The clopidogrel and aspirin for reduction of emboli in symptomatic carotid stenosis (caress) trial. Circulation. 2005; 111:2233–2240. [PubMed: 15851601]
8. Puntmann VO. How-to guide on biomarkers: Biomarker definitions, validation and applications with examples from cardiovascular disease. Postgraduate medical journal. 2009; 85:538–545. [PubMed: 19789193]
9. Schellinger PD, Bath PM, Lees KR, Bornstein NM, Uriel E, Eisert W, et al. Assessment of additional endpoints for trials in acute stroke - what, when, where, in who? International journal of stroke: official journal of the International Stroke Society. 2012; 7:227–230. [PubMed: 22405278]
10. Lees KR, Bath PM, Schellinger PD, Kerr DM, Fulton R, Hacke W, et al. Contemporary outcome measures in acute stroke research: Choice of primary outcome measure. Stroke; a journal of cerebral circulation. 2012; 43:1163–1170.
11. Howard G, Waller JL, Voeks JH, Howard VJ, Jauch EC, Lees KR, et al. A simple, assumption-free, and clinically interpretable approach for analysis of modified rankin outcomes. Stroke; a journal of cerebral circulation. 2012; 43:664–669.

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12. Johnston KC, Barrett KM, Ding YH, Wagner DP. Clinical and imaging data at 5 days as a surrogate for 90-day outcome in ischemic stroke. Stroke; a journal of cerebral circulation. 2009; 40:1332–1333.
13. Barrett KM, Ding YH, Wagner DP, Kallmes DF, Johnston KC. Change in diffusion-weighted imaging infarct volume predicts neurologic outcome at 90 days: Results of the acute stroke accurate prediction (asap) trial serial imaging substudy. Stroke; a journal of cerebral circulation. 2009; 40:2422–2427.
14. Parsons MW, Barber PA, Chalk J, Darby DG, Rose S, Desmond PM, et al. Diffusion- and perfusion-weighted mri response to thrombolysis in stroke. Annals of neurology. 2002; 51:28–37. [PubMed: 11782981]
15. Furtado AD, Smith WS, Koroshetz W, Dillon WP, Furie KL, Lev MH, et al. Perfusion ct imaging follows clinical severity in left hemispheric strokes. European neurology. 2008; 60:244–252. [PubMed: 18756089]
16. Katz R. Biomarkers and surrogate markers: An fda perspective. NeuroRx: the journal of the American Society for Experimental NeuroTherapeutics. 2004; 1:189–195. [PubMed: 15717019]
17. Davis SM, Broderick J, Hennerici M, Brun NC, Diringer MN, Mayer SA, et al. Hematoma growth is a determinant of mortality and poor outcome after intracerebral hemorrhage. Neurology. 2006; 66:1175–1181. [PubMed: 16636233]
18. Wardlaw JM, Dennis MS, Lindley RI, Warlow CP, Sandercock PAG, Sellar RJ. Does early reperfusion of a cerebral infarct influence cerebral infarct swelling in the acute stage or the final clinical outcome? Cerebrovasc Dis. 1993; 3:86–93.
19. Wardlaw JM, Sellar R. A simple practical classification of cerebral infarcts on ct and its interobserver reliability. AJNR. American journal of neuroradiology. 1994; 15:1933–1939. [PubMed: 7863945]
20. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the third international stroke trial [ist-3]): A randomised controlled trial. Lancet. 2012; 379:2352–2363. [PubMed: 22632908]
21. Wardlaw JM, Farrall AJ, Perry D, von Kummer R, Mielke O, Moulin T, et al. Factors influencing the detection of early ct signs of cerebral ischemia: An internet-based, international multiobserver study. Stroke; a journal of cerebral circulation. 2007; 38:1250–1256.
22. Yoo AJ, Sheth KN, Kimberly WT, Chaudhry ZA, Elm JJ, Jacobson S, et al. Validating imaging biomarkers of cerebral edema in patients with severe ischemic stroke. Journal of stroke and cerebrovascular diseases: the official journal of National Stroke Association. 2012
23. Hom J, Dankbaar JW, Soares BP, Schneider T, Cheng SC, Bredno J, et al. Blood-brain barrier permeability assessed by perfusion ct predicts symptomatic hemorrhagic transformation and malignant edema in acute ischemic stroke. AJNR. American journal of neuroradiology. 2011; 32:41–48. [PubMed: 20947643]
24. Aviv RI, d'Esterre CD, Murphy BD, Hopyan JJ, Buck B, Mallia G, et al. Hemorrhagic transformation of ischemic stroke: Prediction with ct perfusion. Radiology. 2009; 250:867–877. [PubMed: 19244051]
25. Latour LL, Kang DW, Ezzeddine MA, Chalela JA, Warach S. Early blood-brain barrier disruption in human focal brain ischemia. Annals of neurology. 2004; 56:468–477. [PubMed: 15389899]
26. Barr TL, Latour LL, Lee KY, Schaewe TJ, Luby M, Chang GS, et al. Blood-brain barrier disruption in humans is independently associated with increased matrix metalloproteinase-9. Stroke; a journal of cerebral circulation. 2010; 41:e123–128.
27. Batra A, Latour LL, Ruetzler CA, Hallenbeck JM, Spatz M, Warach S, et al. Increased plasma and tissue mmp levels are associated with bcsfb and bbb disruption evident on post-contrast flair after experimental stroke. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2010; 30:1188–1199.
28. Wardlaw J, Muir KW, Macleod MJ, Weir C, McVerry F, Carpenter T, et al. Clinical relevance and practical implications for trials of perfusion and angiographic imaging in patients with acute ischaemic stroke: a multicentre cohort imaging study. J Neurol Neurosurg Psychiatry. 2013 in press.

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29. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: A meta-analysis. Stroke; a journal of cerebral circulation. 2007; 38:967–973.
30. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. Neurology. 2009; 73:1066–1072. [PubMed: 19786699]
31. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. The New England journal of medicine. 2013; 368:914–923. [PubMed: 23394476]
32. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, et al. Endovascular therapy after intravenous t-pa versus t-pa alone for stroke. The New England journal of medicine. 2013; 368:893–903. [PubMed: 23390923]
33. Tomsick T. Timi, tibi, tici: I came, i saw, i got confused. AJNR. American journal of neuroradiology. 2007; 28:382–384. [PubMed: 17297017]
34. Zaidat OO, Yoo AJ, Khatri P, Tomsick T, von Kummer R, Saver JL, et al. Recommendations on Angiographic Revascularization Grading Standards for Acute Ischemic Stroke: A Consensus Statement. submitted for publication.
35. Bash S, Villablanca JP, Jahan R, Duckwiler G, Tillis M, Kidwell C, et al. Intracranial vascular stenosis and occlusive disease: Evaluation with ct angiography, mr angiography, and digital subtraction angiography. AJNR. American journal of neuroradiology. 2005; 26:1012–1021. [PubMed: 15891154]
36. Lev MH, Romero JM, Goodman DN, Bagga R, Kim HY, Clerk NA, et al. Total occlusion versus hairline residual lumen of the internal carotid arteries: Accuracy of single section helical ct angiography. AJNR. American journal of neuroradiology. 2003; 24:1123–1129. [PubMed: 12812937]
37. Leys D, Pruvo JP, Godefroy O, Rondepierre P, Leclerc X. Prevalence and significance of hyperdense middle cerebral artery in acute stroke. Stroke; a journal of cerebral circulation. 1992; 23:317–324.
38. Goldmakher GV, Camargo EC, Furie KL, Singhal AB, Roccatagliata L, Halpern EF, et al. Hyperdense basilar artery sign on unenhanced ct predicts thrombus and outcome in acute posterior circulation stroke. Stroke; a journal of cerebral circulation. 2009; 40:134–139.
39. Riedel CH, Jensen U, Rohr A, Tietke M, Alfke K, Ulmer S, et al. Assessment of thrombus in acute middle cerebral artery occlusion using thin-slice nonenhanced computed tomography reconstructions. Stroke; a journal of cerebral circulation. 2010; 41:1659–1664.
40. Riedel CH, Zoubie J, Ulmer S, Gierthmuehlen J, Jansen O. Thin-slice reconstructions of nonenhanced ct images allow for detection of thrombus in acute stroke. Stroke; a journal of cerebral circulation. 2012; 43:2319–2323.
41. Wolpert SM, Bruckmann H, Greenlee R, Wechsler L, Pessin MS, del Zoppo GJ, The rt-pa acute stroke study group. Neuroradiologic evaluation of patients with acute stroke treated with recombinant tissue plasminogen activator. AJNR. American journal of neuroradiology. 1993; 14:3–13. [PubMed: 8427107]
42. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: Successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. Stroke; a journal of cerebral circulation. 2011; 42:1775–1777.
43. Flacke S, Urbach H, Keller E, Traber F, Hartmann A, Textor J, et al. Middle cerebral artery (mca) susceptibility sign at susceptibility-based perfusion mr imaging: Clinical importance and comparison with hyperdense mca sign at ct. Radiology. 2000; 215:476–482. [PubMed: 10796928]
44. Kim HS, Lee DH, Choi CG, Kim SJ, Suh DC. Progression of middle cerebral artery susceptibility sign on t2*-weighted images: Its effect on recanalization and clinical outcome after thrombolysis. AJR. American journal of roentgenology. 2006; 187:W650–657. [PubMed: 17114520]
45. Schellinger PD, Chalela JA, Kang DW, Latour LL, Warach S. Diagnostic and prognostic value of early mr imaging vessel signs in hyperacute stroke patients imaged <3 hours and treated with recombinant tissue plasminogen activator. AJNR. American journal of neuroradiology. 2005; 26:618–624. [PubMed: 15764589]

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46. Kharitonova T, Thoren M, Ahmed N, Wardlaw JM, von Kummer R, Thomassen L, et al. Disappearing hyperdense middle cerebral artery sign in ischaemic stroke patients treated with intravenous thrombolysis: Clinical course and prognostic significance. Journal of neurology, neurosurgery, and psychiatry. 2009; 80:273–278.
47. Sanossian N, Ovbiagele B, Saver JL, Alger JR, Starkman S, Kim D, et al. Leukoaraiosis and collaterals in acute ischemic stroke. Journal of neuroimaging: official journal of the American Society of Neuroimaging. 2011; 21:232–235. [PubMed: 20977524]
48. Al-Ali F, Jefferson A, Barrow T, Cree T, Louis S, Luke K, et al. The capillary index score: Rethinking the acute ischemic stroke treatment algorithm. Results from the borgess medical center acute ischemic stroke registry. Journal of neurointerventional surgery. 2013; 5:139–143. [PubMed: 22266703]
49. Alexandrov AV, Wojner AW, Grotta JC. Clotbust: Design of a randomized trial of ultrasound-enhanced thrombolysis for acute ischemic stroke. Journal of neuroimaging: official journal of the American Society of Neuroimaging. 2004; 14:108–112. [PubMed: 15095554]
50. Saqqur M, Tsivgoulis G, Molina CA, Demchuk AM, Garami Z, Barreto A, et al. Design of a prospective multi-national clotbust collaboration on reperfusion therapies for stroke (clotbust-pro). International journal of stroke: official journal of the International Stroke Society. 2008; 3:66–72. [PubMed: 18705918]
51. Nedelmann M, Stolz E, Gerriets T, Baumgartner RW, Malferrari G, Seidel G, et al. Consensus recommendations for transcranial color-coded duplex sonography for the assessment of intracranial arteries in clinical trials on acute stroke. Stroke; a journal of cerebral circulation. 2009; 40:3238–3244.
52. Krafft PR, Bailey EL, Lekic T, Rolland WB, Altay O, Tang J, et al. Etiology of stroke and choice of models. International journal of stroke: official journal of the International Stroke Society. 2012; 7:398–406. [PubMed: 22712741]
53. Lansberg MG, Straka M, Kemp S, Mlynash M, Wechsler LR, Jovin TG, et al. Mri profile and response to endovascular reperfusion after stroke (defuse 2): A prospective cohort study. Lancet neurology. 2012; 11:860–867. [PubMed: 22954705]
54. Suh SH, Cloft HJ, Fugate JE, Rabinstein AA, Liebeskind DS, Kallmes DF. Clarifying differences among thrombolysis in cerebral infarction scale variants: Is the artery half open or half closed? Stroke; a journal of cerebral circulation. 2013; 44:1166–1168.
55. Ali M, Bath P, Brady M, Davis S, Diener HC, Donnan G, et al. Development, expansion, and use of a stroke clinical trials resource for novel exploratory analyses. International journal of stroke: official journal of the International Stroke Society. 2012; 7:133–138. [PubMed: 22264365]
56. [Accessed May 10, 2013] Stroke Imaging Repository (STIR) web site. http://stir.ninds.nih.gov/
57. Christensen S, Mouridsen K, Wu O, Hjort N, Karstoft H, Thomalla G, et al. Comparison of 10 perfusion mri parameters in 97 sub-6-hour stroke patients using voxel-based receiver operating characteristics analysis. Stroke; a journal of cerebral circulation. 2009; 40:2055–2061.
58. Kudo K, Christensen S, Sasaki M, Ostergaard L, Shirato H, Ogasawara K, et al. Accuracy and reliability assessment of ct and mr perfusion analysis software using a digital phantom. Radiology. 2013; 267:201–211. [PubMed: 23220899]
59. Wu, O. International stroke database: Perfusion simulation data. http://www.strokedatabases.org/pages/perfusion_sim_data.html
60. Ostergaard L, Weisskoff RM, Chesler DA, Gyldensted C, Rosen BR. High resolution measurement of cerebral blood flow using intravascular tracer bolus passages. Part i: Mathematical approach and statistical analysis. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 1996; 36:715–725.
61. Campbell BC, Tu HT, Christensen S, Desmond PM, Levi CR, Bladin CF, et al. Assessing response to stroke thrombolysis: Validation of 24-hour multimodal magnetic resonance imaging. Archives of neurology. 2012; 69:46–50. [PubMed: 21911654]
62. Wintermark M, Albers GW, Alexandrov AV, Alger JR, Bammer R, Baron JC, et al. Acute stroke imaging research roadmap. Stroke; a journal of cerebral circulation. 2008; 39:1621–1628.

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63. Wintermark M, Albers GW, Alexandrov AV, Alger JR, Bammer R, Baron JC, et al. Acute stroke imaging research roadmap. AJNR. American journal of neuroradiology. 2008; 29:e23–30. [PubMed: 18477656]
64. Williams DS, Detre JA, Leigh JS, Koretsky AP. Magnetic resonance imaging of perfusion using spin inversion of arterial water. Proceedings of the National Academy of Sciences of the United States of America. 1992; 89:212–216. [PubMed: 1729691]
65. Zaharchuk G, El Mogy IS, Fischbein NJ, Albers GW. Comparison of arterial spin labeling and bolus perfusion-weighted imaging for detecting mismatch in acute stroke. Stroke; a journal of cerebral circulation. 2012; 43:1843–1848.
66. An H, Liu Q, Chen Y, Lin W. Evaluation of mr-derived cerebral oxygen metabolic index in experimental hyperoxic hypercapnia, hypoxia, and ischemia. Stroke; a journal of cerebral circulation. 2009; 40:2165–2172.
67. Zhou J, Payen JF, Wilson DA, Traystman RJ, van Zijl PC. Using the amide proton signals of intracellular proteins and peptides to detect ph effects in mri. Nature medicine. 2003; 9:1085–1090.
68. Xu C, Schmidt WU, Villringer K, Brunecker P, Kiselev V, Gall P, et al. Vessel size imaging reveals pathological changes of microvessel density and size in acute ischemia. Journal of cerebral blood flow and metabolism: official journal of the International Society of Cerebral Blood Flow and Metabolism. 2011; 31:1687–1695.
69. Dennie J, Mandeville JB, Boxerman JL, Packard SD, Rosen BR, Weisskoff RM. Nmr imaging of changes in vascular morphology due to tumor angiogenesis. Magnetic resonance in medicine: official journal of the Society of Magnetic Resonance in Medicine / Society of Magnetic Resonance in Medicine. 1998; 40:793–799.
70. Donahue MJ, van Laar PJ, van Zijl PC, Stevens RD, Hendrikse J. Vascular space occupancy (vaso) cerebral blood volume-weighted mri identifies hemodynamic impairment in patients with carotid artery disease. Journal of magnetic resonance imaging: JMRI. 2009; 29:718–724. [PubMed: 19243067]
71. Mandell DM, Han JS, Poublanc J, Crawley AP, Fierstra J, Tymianski M, et al. Quantitative measurement of cerebrovascular reactivity by blood oxygen level-dependent mr imaging in patients with intracranial stenosis: Preoperative cerebrovascular reactivity predicts the effect of extracranial-intracranial bypass surgery. AJNR. American journal of neuroradiology. 2011; 32:721–727. [PubMed: 21436343]
72. Hui ES, Fieremans E, Jensen JH, Tabesh A, Feng W, Bonilha L, et al. Stroke assessment with diffusional kurtosis imaging. Stroke; a journal of cerebral circulation. 2012; 43:2968–2973.
73. Tournier JD, Calamante F, Connelly A. Robust determination of the fibre orientation distribution in diffusion mri: Non-negativity constrained super-resolved spherical deconvolution. NeuroImage. 2007; 35:1459–1472. [PubMed: 17379540]
74. Golestani AM, Tymchuk S, Demchuk A, Goodyear BG. Longitudinal evaluation of resting-state fmri after acute stroke with hemiparesis. Neurorehabilitation and neural repair. 2013; 27:153–163. [PubMed: 22995440]
75. Carter AR, Astafiev SV, Lang CE, Connor LT, Rengachary J, Strube MJ, et al. Resting interhemispheric functional magnetic resonance imaging connectivity predicts performance after stroke. Annals of neurology. 2010; 67:365–375. [PubMed: 20373348]
76. Shehzad Z, Kelly AM, Reiss PT, Gee DG, Gotimer K, Uddin LQ, et al. The resting brain: Unconstrained yet reliable. Cereb Cortex. 2009; 19:2209–2229. [PubMed: 19221144]
77. Gupta R, Phan CM, Leidecker C, Brady TJ, Hirsch JA, Nogueira RG, et al. Evaluation of dual-energy ct for differentiating intracerebral hemorrhage from iodinated contrast material staining. Radiology. 2010; 257:205–211. [PubMed: 20679449]
78. Carey LM, Seitz RJ. Functional neuroimaging in stroke recovery and neurorehabilitation: Conceptual issues and perspectives. International journal of stroke: official journal of the International Stroke Society. 2007; 2:245–264. [PubMed: 18705925]
79. Carter AR, Shulman GL, Corbetta M. Why use a connectivity-based approach to study stroke and recovery of function? NeuroImage. 2012; 62:2271–2280. [PubMed: 22414990]

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80. Stinear CM, Ward NS. How useful is imaging in predicting outcomes in stroke rehabilitation? International journal of stroke: official journal of the International Stroke Society. 2013; 8:33–37. [PubMed: 23280267]

81. [Accessed May 10, 2013] Alzheimer's Disease Neuroimaging Initiative website. http://www.adni-info.org/

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Table 1

General requirements for imaging in stroke clinical trials

Speed: In therapeutic trials, the benefits of additional imaging should be balanced against potential treatment delay; workflow should be optimised based on best practice.
Standardization: Acquisition parameters and perfusion post-processing should be standardized (by common software processing at centers or centralized processing) and should conform to minimum, protocol-defined, common standards.
Quality Control: A well-defined image quality control process should be implemented to ensure that the pre-defined study imaging protocol is respected and to minimize the number of protocol violations.
Reproducibility: If imaging is used to define patient selection then either a system for standardized central image processing and automated analysis, or appropriate training for neuroimaging raters at participating centers, should be undertaken. Imaging methods should have demonstrated acceptable interobserver and across-center reliability.
Centralization: Central analysis of imaging outcomes should be conducted as the reference standard in multicenter trials. A system for standardized central image processing and interpretation, blinded to clinical information and local investigator decision, should be implemented.

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Table 2

Uses of imaging in stroke clinical trials

Selection of patients with imaging confirmed diagnosis of stroke
Selection of patients appropriate to a mechanistic hypothesis: Treatment-Relevant Acute Imaging Target (TRAIT)
Exclusion of patients based on imaging defined risk of therapeutic intervention (e.g. hemorrhage if testing thrombolytic)
Exclusion of patients based on imaging defined futility of therapeutic intervention
Sample enrichment - selection of a sample likely to maximize a treatment effect
Assessment of therapeutic intervention on TRAIT (e.g., recanalization, reperfusion, infarct size/growth)

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Table 3

Unresolved issues with imaging selection biomarkers for clinical trials

Added value of vascular imaging
Added value of perfusion (penumbral) imaging
Whether additional imaging selects patients currently excluded from treatment
Whether additional imaging excludes patients from treatment who may otherwise benefit
Whether the additional time related to additional imaging is justified
Whether the 'optimal' additional imaging modality varies depending on the time window and the type of treatment
Clinical relevance of the signal intensity of the DWI abnormality
MRI versus CT in patient selection
Utility and use of extracellular contrast agents for CTP and MRP

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Table 4

Three components of revascularization

Recanalization or restoration of patency in the original or primary arterial occlusive lesion
Reperfusion past the primary occlusion into the distal arterial bed
Reperfusion of the affected tissue

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Table 5

Modified Treatment In Cerebral Ischemia (mTICI) scale

This relates to capillary-level reperfusion as measured on catheter angiography.

0	no reperfusion
1	flow beyond occlusion without distal branch reperfusion
2a	reperfusion of less than half of the downstream target arterial territory
2b	reperfusion of more than half, yet incomplete, in the downstream target arterial territory
3	complete reperfusion of the downstream target arterial territory, including distal branches with slow flow

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Table 6

Required characteristics for the dataset to be used in analysis to calibrate acute CTP to acute DWI abnormality

A maximum delay of 2 hours between the CTP and the DWI studies
Criteria for satisfactory data will be concurrent CTA (NCT assumed) and MRA to confirm lack of recanalization between exams
For cases where no baseline occlusion can be detected on the initial CTA, then follow-up MRP will be required to confirm the absence of reperfusion; ideally, MRI data should contain both MRA and MRP

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Table 7

Summary of imaging data characteristics to be collected for software calibration and collateral assessment

Baseline imaging study	- NCT/CTP/(dynamic) CTA or - DWI, MRP, FLAIR, T2* GRE or SWI, MRA
Revascularization imaging study, to confirm revascularization for the "ischemic core" calibration	- DSA after clot retrieval or - NCT/CTA (ideally dynamic/multiphase) and/or CTP between 2 and 24 hours after treatment or - DWI/FLAIR/GRE or SWI/MRA and/or MRP between 2 and 24 hours after treatment
Follow-up imaging study to determine the infarct volume	- 18- to 36-hour DWI (preferred regardless of baseline imaging modality) or 18-to 36-hour NCT