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Imaging and Treatment of Patients with Acute Stroke: An Evidence-Based Review

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Summary

Evidence-based medicine has emerged as a valuable tool to guide clinical decision-making, by summarizing the best possible evidence for both diagnostic and treatment strategies. Imaging plays a critical role in the evaluation and treatment of patients with acute ischemic stroke, especially those who are being considered for thrombolytic or endovascular therapy. Time from stroke-symptom onset to treatment is a strong predictor of long-term functional outcome after stroke. Therefore, imaging and treatment decisions must occur rapidly in this setting, while minimizing unnecessary delays in treatment. The aim of this review was to summarize the best available evidence for the diagnostic and therapeutic management of patients with acute ischemic stroke.

In this era of health care reform and cost containment, major concerns have been raised regarding inappropriate medical expenditures and the lack of data to support the necessity of such high levels of health care spending. It is becoming ever more difficult to justify diagnostic imaging and other medical procedures with anecdotal evidence, expert opinion, or experience. Instead, great emphasis has been placed on the necessity for evidence-based practice to guide clinical decision-making, especially in light of limited financial resources and increased public awareness of imaging-related safety concerns, including risks from radiation and contrast administration.

Evidence-based practice is defined as “integration of the best research evidence with clinical expertise and patient values.” This necessitates the balance of scientific evidence, clinical expertise, and judgment. When strong evidence is available and integrated in a methodical fashion, practice guidelines can emerge, eventually shaping new standards of care. However, when strong evidence is not available, clinical expertise and judgment play a major role in medical decision-making.

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The aim of this review is to summarize the best available evidence for the diagnostic and therapeutic management of patients with acute ischemic stroke. The first part of this review synthesizes the most current evidence on the appropriate indications and modalities to consider in the diagnostic work-up of patients with acute stroke. The second part examines the efficacy of medical and mechanical interventions in acute stroke. Summary statements along with strength of evidence are provided for each section as a quick reference. Table 1 describes the classification scheme used to determine the strength of evidence in the literature.

Evidence-Based Imaging in Acute Ischemic Stroke

Because acute ischemic stroke and intracranial hemorrhage may have similar clinical presentations, the primary imaging goal is to differentiate these 2 entities. Because thrombolysis and endovascular therapy are associated with an increased risk of hemorrhage, an additional imaging goal includes confirming the diagnosis while excluding stroke mimics so that patients are not treated unnecessarily. Finally, for patients who do not meet the criteria for IV thrombolysis but who arrive at the hospital relatively early after stroke onset, emerging imaging goals also include identifying brain tissue that is still viable and identifying the location of vascular occlusion when endovascular therapy is considered.

Imaging Evidence to Assess Intracranial Hemorrhage

CT—Although it is accepted that CT is sensitive in detecting acute ICH, surprisingly few studies have been conducted to support this belief.[1] One of the original studies on a first-generation scanner in the 1970s identified 66 hemorrhages with CT, but the data lacked postmortem confirmation. Subsequently, in a postmortem series of 79 patients, in 4 of 17 patients, CT missed ICHs—all of which were located in the brain stem.[2] While there is little doubt that the third-generation scanners are far superior today, the precise accuracy of CT for the detection of ICH is unknown.

MR Imaging—MR imaging was reported to detect ICH within 6 hours and as early as 23 minutes from symptom onset.[3,4] One study evaluated 62 patients with ICH within 6 hours of onset and 62 controls, with 3 experienced readers using CT as the reference standard.[5] The readers, blinded to clinical and CT results, identified all acute hemorrhages on MR imaging, yielding 100% sensitivity and specificity. A subsequent study comparing CT and MR imaging for detection of hemorrhagic stroke within 6 hours of onset, using the discharge diagnosis as the reference standard, found 86% sensitivity and 100% specificity for both CT and MR imaging. Of 29 acute hemorrhages on CT, 25 were identified on MR imaging (in 3 of 4 cases, blood was misclassified as chronic instead of acute).[6] Similarly, 4 cases of ICH identified on MR imaging were not seen on CT (all were ischemic infarcts with hemorrhagic transformation). Therefore, it appears that rare cases of early intracranial hemorrhage may be missed on either CT or MR imaging. However, susceptibility-weighted sequences have improved sensitivity in the detection of cerebral microbleeds that are not otherwise detected on CT. Thus far, studies suggest that neither the presence nor number of microbleeds is associated with an increased risk of hemorrhagic transformation in either tPA-treated or untreated patients.[7-9]

Summary of Evidence—In the evaluation of patients with acute stroke for IV thrombolysis, CT has become the technique of choice for exclusion of ICH, based on randomized controlled trials (strong evidence). Recent studies indicate that the accuracy of MR imaging in detecting ICH is likely equivalent to that of CT even in the hyperacute setting (within 6 hours of ictus) and is even more accurate for detection of chronic cerebral microbleeds (moderate evidence).

Imaging Evidence to Assess Ischemia and Exclude Stroke Mimics

CT—The diagnosis of acute stroke is primarily based on the clinical history and physical examination. At times, patients may present with strokelike symptoms due to nonstroke etiologies. Stroke mimics may account for up to 19% of patients initially diagnosed with stroke and up to 14% of patients treated with IV tPA.[10,11] An additional goal of imaging is to confirm diagnosis and to evaluate the extent of ischemic changes. Large ischemic strokes may demonstrate early signs of ischemia on CT, including loss of gray-white differentiation, hyperattenuated clot in the proximal MCA, sulcal effacement, and local mass effect. Such signs were found in 31% and 81% of patients within 3 and 5 hours after symptom onset, respectively.[12,13] Early CT signs involving more than one-third of the MCA distribution have been associated with large strokes, increased risk of hemorrhagic transformation, and poor outcome.[14-16] The Alberta Stroke Program Early CT Score (ASPECTS), a 10-point scoring system to detect early ischemic changes on NCCT, was developed as a tool that would be more reliable than the MCA rule.[17] While ASPECTS was found to have superior interobserver agreement, it only modestly improved accuracy for predicting functional outcome and performed the same as the MCA rule for predicting symptomatic hemorrhage.[17,18]

MR Imaging—DWI is more sensitive for detecting ischemic changes within minutes of stroke onset and ischemic lesions as small as 4 mm in diameter compared with CT.[19-21] As time from symptom onset increased, the sensitivity of DWI for the diagnosis of ischemic stroke also increased 73%, 81%, and 92% for <3 hours, 3–12 hours, and >12 hours, respectively, whereas CT had only 12%, 20%, and 16% sensitivity at these respective time intervals. The sensitivity for MR imaging to detect ischemia within 6 hours of onset is 81%–91%; therefore, the absence of a DWI lesion does not completely exclude ischemic stroke. DWI may be falsely negative in very early stroke and in patients with small subcortical or vertebrobasilar infarctions or in patients with low stroke severity (NIHSS score < 4).[21-24] Therefore, stroke timing, location, size, and perfusion status contribute to the visualization of a DWI lesion.

Summary of Evidence—DWI is superior to CT for identifying acute ischemic stroke within the first 12 hours of symptom onset (strong evidence). However, MR imaging does not necessarily have a greater influence than CT on decision-making or clinical outcomes in the acute setting, given its limited availability and the need for patient screening. Early CT signs of ischemia involving more than one-third of the MCA distribution have been associated with large strokes, increased risk of hemorrhagic transformation, and poor outcome (strong evidence).

Imaging Evidence to Determine Brain Tissue Viability

MR Imaging—An emerging goal of acute stroke imaging is to identify patients who may benefit from treatment outside the current therapeutic window for IV thrombolysis. Thus, identifying tissue that may be rescued with therapy (ie, the ischemic penumbra) has been a major focus of clinical research. Using multimodal MR imaging, DWI is postulated to delineate irreversibly injured tissue (infarct core), and PWI is postulated to delineate critically hypoperfused tissue that will evolve into infarction if not reperfused in a timely manner (ischemic penumbra). When DWI and PWI are superimposed, the nonoverlapping "mismatched" region has been proposed to represent the penumbra.[25,26] Consistent with the idea of an evolving ischemic core, the DWI lesion may grow into a final infarct approximating the early PWI abnormality.[27] The DWI-PWI mismatch has been rapidly translated into clinical trials under 3 categories of study design: 1) to select patients for enrollment in the therapeutic trial, 2) to validate DPM as a biomarker of the penumbra, and 3) both (Table 2).

Within the first category, the Desmoteplase in Acute Ischemic Stroke trial (DIAS),[28] the Dose Escalation for Ischemic Stroke trial (DEDAS),[29] and the DIAS-II[30] have been completed. These trials examined a novel thrombolytic agent, desmoteplase, compared with placebo in patients demonstrating DPM between 3 and 9 hours after stroke onset. While the initial phase-2 studies, DIAS and DEDAS, demonstrated safety and early signs of efficacy for desmoteplase, the phase-3 study, DIAS-II, showed unexpectedly high mortality and no overall clinical benefit. Unfortunately, these negative results did not permit an analysis of which component of the study failed—the therapeutic agent or the DPM criteria.

Within the second category, the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) trial aimed to validate DPM by comparing clinical outcomes in patients with DPM and reperfusion with outcomes in patients without DPM and reperfusion; patients in both groups were treated with tPA between 3 and 6 hours of stroke onset.[31] Of 74 patients enrolled, 75% had DPM and 25% did not. In patients with DPM, reperfusion was associated with better clinical outcome than no reperfusion. However, due to the small number of patients without DPM (n = 11), the converse that nonmismatch patients did not improve with reperfusion could not be proved. The high ratio of mismatch to nonmismatch patients made it clear that the definition for DPM was too liberal, resulting in a relatively unselected group of patients with stroke.

On the basis of the DEFUSE results, the DPM definition was refined for the DEFUSE-2 study.[32,33] However, a subset of patients with DPM with "target mismatch" was selected, which excluded patients with a "malignant profile" (large baseline DWI and PWI lesions) because DEFUSE indicated that these patients have worse outcomes. Thus far, selection of patients with the "target mismatch" definition demonstrated improved clinical outcome and reduced infarct growth compared with the nontarget mismatch group.

Studies giving information about both the utility of the imaging biomarker and the efficacy of treatment include the Echo-Planar Imaging Thrombolytic Evaluation Trial (EPITHET)[34] and MR and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE).[35] In EPITHET, patients with stroke after 3 hours from symptom onset were serially imaged at 3

time points: 1) before administration of tPA versus placebo, 2) at 3–5 days, and 3) at 90 days after treatment. With its similarity to the DEFUSE protocol, most (86%) of enrolled patients were categorized as having DPM, making conclusions regarding nonmismatch patients difficult. The primary end point showed no difference in geometric mean infarct growth between the tPA and placebo groups. MR-RESCUE,[35] an ongoing study, aims to test both a similar DPM protocol in combination with treatment by using the Merci retriever (Concentric Medical, Mountain View, California) versus placebo up to 8 hours after stroke onset.

Taking advantage of the endogenous susceptibility of deoxyhemoglobin on T2*-weighted images is an active investigation into imaging oxygen metabolism by using MR imaging (eg, MR-oxygen metabolic index),[36-38] a parameter similar to PET-derived cerebral metabolic rate of oxygen. If these physiologic measures of oxygen metabolism accurately delineate the ischemic penumbra, they may yield ischemic thresholds that are time-invariant,[38] unlike diffusion and perfusion thresholds, which vary with elapsed time between stroke onset and imaging.[19,39] These relatively new imaging approaches will require validation in well-designed trials.

CT—Similar to PWI, CTP is capable of providing maps of tissue perfusion. In a prospective multicenter study, patients with acute stroke were imaged < 12 hours from stroke onset with CT and MR imaging.[40] The CTP parameter most accurately reflecting the ischemic core (compared with DWI) was absolute CBV < 2 mL/100 g, while the parameter most accurately reflecting the penumbra was a relative mean transit time of > 145% of the contralateral hemisphere. However, in more recent studies, relative CBF was found to be more predictive of the ischemic core and final infarct volume than absolute CBV.[41-43] Recently, CTP mismatch with PWI used for both core (CBF) and penumbra (MTT, CBV) in combination with intracranial vessel occlusion on CTA was used to select patients for entry into a randomized controlled trial of IV tenecteplase versus IV tPA administered within 6 hours of stroke onset.[44] This trial was positive for its co-primary end points, improvement in the NIHSS score and percentage reperfusion at 24 hours. However, it is currently unknown whether tenecteplase is superior to tPA in unselected patients because treatment without CTA and CTP screening would save time and perhaps broaden the applicability of tenecteplase.

Summary of Evidence—Determination of tissue viability by using advanced imaging has the potential to individualize therapy and extend the therapeutic time window for some patients with acute stroke. Several imaging modalities, including MR imaging, CT,and PET, have been examined in this role. Operational hurdles have limited the use of some of these modalities in the acute stroke setting (eg, PET), while others such as MR imaging have been studied in large clinical trials. Randomized controlled trials have not demonstrated a benefit of thrombolytic treatment in patients who are selected by using MR imaging–based criteria such as DPM (moderate evidence); however, studies are ongoing. Clinical trials with positive results will be needed before the use of penumbral imaging techniques in routine clinical decision-making.

Imaging Evidence to Determine the Location of Vascular Occlusion

CTA—An advantage of CTA is that it can be performed immediately after the prerequisite NCCT in patients with stroke. In several small case series, the sensitivity and specificity of CTA for trunk occlusions of the circle of Willis were 83%–100% and 99%– 100%, respectively, compared with DSA.[45-48] A study with 2 blinded observers comparing CTA with DSA measured 475 short segments of intracranial arteries in 41 patients.[47] For detection of ≥50% stenosis, CTA had 97.1% sensitivity and 99.5% specificity. A similar study of 672 vessel segments in 28 patients found excellent sensitivity and specificity for intracranial stenosis of 98% and 98%, respectively, with 100% sensitivity and 100% specificity for intracranial occlusion.[48] This study also compared time-of-flight MRA with CTA and found CTA to have significantly higher sensitivity and positive predictive value compared with MRA (see below).

MRA—While MRA appears to be a useful tool for measuring stenosis in large extracranial vessels, its sensitivity decreases for smaller caliber intracranial vessels. For time-of-flight, complete or partial signal voids in regions of high and/or turbulent flow may occur, leading to an overestimation of the extent of stenosis. Therefore, cautious interpretation of the lumen caliber is warranted. In a study of intracranial disease comparing CTA and MRA with DSA in 28 patients (in 672 vessel segments), time-of-flight MRA had a sensitivity of 70% and 81% and a specificity of 99% and 98% for intracranial stenosis and intracranial occlusion, respectively.[48] The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial was a prospective multicenter study comparing the diagnostic accuracy of transcranial Doppler and MRA with DSA.[49] The SONIA study found that both transcranial Doppler and MRA have high negative predictive values (86% and 91%, respectively) but low positive predictive values (36% and 59%, respectively). Sensitivity and specificity could not be obtained in this study because not every patient underwent DSA.[49]

Summary of Evidence—CTA and MRA have high diagnostic accuracy for detecting large-vessel occlusion compared with DSA (strong evidence). However, evidence supporting these imaging modalities in acute stroke management is lacking (limited evidence). Prospective studies examining the accuracy of acute non-invasive vascular imaging and whether it alters clinical outcome after stroke are needed.

Evidence-Based Treatment in Acute Ischemic Stroke

IV Thrombolytic Therapy

The National Institute of Neurological Disorders and Stroke (NINDS) stroke study proved the efficacy of the use of IV alteplase within 3 hours of stroke onset in patients with MCA stroke and no hemorrhage on NCCT.[50] At 3 months, patients treated with alteplase were at least 30% more likely to have minimal or no disability compared with those treated with a placebo. The benefit occurred despite higher rates of ICH in alteplase-treated patients compared with controls (6.4% versus 0.6%). Treatment with IV alteplase within 3 hours of stroke onset was endorsed early by the Special Writing Group of the Stroke Council, American Heart Association.[51]

A number of studies followed that failed to prove the efficacy of IV alteplase in the 3- to 6-hour time window. More recently, a meta-analysis was undertaken evaluating data from trials with negative results only in the 3- to 4.5-hour time window. The meta-analysis showed the efficacy of treatment with IV alteplase from 3 to 4.5 hours after MCA stroke onset in patients with no hemorrhage and no signs of significant early infarct on NCCT.[52] Multiple registries have been established, and these results further support the safety and efficacy of IV alteplase in the 4.5-hour window.[53-55]

In general, IV thrombolysis is regarded as less effective in recanalizing large occlusive clots, such as those of the terminal ICA or M1 MCA.[56-60] The presence of a hyperdense MCA sign on CT, indicating complete vessel occlusion, bodes poorly for patients treated with IV tPA,[58,59] which yields recanalization rates of 30% for proximal MCA occlusion and 10% for ICA occlusion.[60] On the basis of a subgroup analysis of the NINDS stroke study, despite low rates of recanalization with proximal occlusions, IV tPA improved outcome in large strokes.[61] Presumably, much of the benefit of IV treatment derives from recanalization of smaller more distal branches.

Summary of Evidence—IV thrombolysis is the standard-of-care treatment for acute ischemic stroke in the anterior circulation within 4.5 hours of symptom onset (strong evidence). Larger more proximal clots (ICA, M1 MCA) exhibit lower recanalization rates with IV thrombolytic treatment, and such patients tend to have worse prognosis (strong evidence).

IA Thrombolytic Therapy

Based on preliminary experience with IA therapy, the Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial was implemented to determine the clinical efficacy and safety of intra-arterial r-proUK in patients with acute stroke.[62] Only patients with MCA infarct of <6 hours from onset and no evidence of hemorrhage or early signs of major infarct on CT were included. Angiographic inclusion criteria were either complete occlusion (TIMI 0) or contrast penetration with minimal perfusion (TIMI 1) of either an M1 or M2 division of the MCA. Following angiography, 180 patients met the criteria. These patients were randomized in a 2:1 ratio to receive IA r-proUK plus heparin or heparin only. The results indicated benefit for the treated group with 40% of r-proUK patients compared with 25% of control patients achieving the primary outcome measure of a modified Rankin Scale score of 0–2, with similar mortality rates. Improved outcome in the treated group was noted despite increased frequency of early symptomatic hemorrhage (within 24 hours, 10% versus 2%). The recanalization rate was 66% for the r-proUK group and 18% for the control group ($P < .001$). Treated and control patients with less severe strokes (NIHSS score ≤ 10) did equally well. Patients with more severe strokes (NIHSS score > 10) were twice as likely as controls to achieve the desired outcome measure. Considering the limitations of this study, many investigators suspect that the demonstrated PROACT II benefit represents a lower limit for IA treatment efficacy.

Combined IV and IA Thrombolysis

Recognizing the trade-offs between IV and IA thrombolytic therapy, researchers have studied combined therapy consisting of IV treatment followed by IA treatment.[63] The Interventional Management of Stroke (IMS) II trial compared combined IV/IA thrombolysis with historical controls of IV thrombolytics alone and placebo from the NINDS stroke study.[64] Eighty-one patients who could be treated with IV alteplase within 3 hours from symptom onset were enrolled. IV treatment consisted of two-thirds the usual alteplase dose administered as a 15% bolus during 1 minute followed by the remainder for 30 minutes. Once IV treatment had been initiated, the patient was transferred to the angiography suite. If an IA treatment-amenable clot was identified, the remaining one-third of the alteplase dose was administered in the clot. If no IA-amenable clot was identified, the remaining one-third of the alteplase dose was administered IV. Of 81 patients, 55 under-went combined treatment with the remainder receiving IV treatment alone. The combined IV/IA-treated patients exhibited a better outcome than the NINDS alteplase-treated subjects by the Barthel Index but not by other outcome measures. The patients with combined treatment had significantly better outcome at 3 months than NINDS patients with placebo on all outcome measures (odds ratio > 2). The 3-month mortality for IMS patients with combined treatment (16%) trended lower than NINDS placebo- (24%) and alteplase-treated subjects (21%). The difference was not statistically significant. A subsequent trial, IMS III, compared combined IV alteplase alone with combined IV/IA treatment including mechanical devices. In April 2012, an independent data safety monitoring board placed the trial on hold because the interim analysis indicated a very low likelihood of improved outcome with combined treatment.

A prospective registry (RECANALISE [REcanalisation using Combined intravenous Alteplase and Neurointerventional ALgorithm for acute Ischemic StrokE] study) compared recanalization rates, 24-hour improvement, and 3-month functional outcome between patients in 2 time intervals who underwent different thrombolytic protocols.[65] In the first time period, patients within 3 hours of symptom onset were treated with IV alteplase according to standard protocol. In the second time interval, patients were treated with a combined technique similar to that in IMS II. Early neurologic recovery (defined as NIHSS 0 or 1 or a 4-point improvement) occurred in 60% of patients with combined treatment compared with 39% of those with IV treatment ($P = .07$); and 3-month functional outcome (mRS 0–2) occurred in 57% of those with combined treatment compared with 44% of those with IV treatment ($P = .35$). The 90-day mortality and symptomatic intracranial hemorrhage rates were not appreciably different. The most pronounced difference observed was in the recanalization rate: 87% in patients with combined treatment and 52% of those with IV treatment ($P = .0002$).

Mechanical Endovascular Intervention

Mechanical clot removal has not been evaluated in a randomized controlled fashion. The Merci retriever (Concentric Medical) and the Penumbra aspiration system (Penumbra, Alameda, California)[66-69] were evaluated in prospective multicenter single-arm design trials. A historical control from PROACT II was often used, and the patients were treated for up to 8 hours. In the Multi MERCI trial,[67] mechanical thrombectomy was used in large-

vessel stroke, in both anterior and posterior circulations, within 8 hours of onset. Patients with persistent large-vessel occlusion after IV alteplase were also included. Successful recanalization was reported in 57.3% (75 of 131) and a higher rate of 69.5% (91 of 131) after adjunctive therapy consisting of IA alteplase. The study also showed improved efficacy in recanalization with the new-generation devices. Significant complications were defined as those procedural complications resulting in an NIHSS decline of ≥4 or death or groin complication necessitating surgery and/or blood transfusion. Such clinically significant complications were observed in 9 patients (5.5%). Symptomatic ICH occurred in 16 patients (9.8%).

In the Penumbra Pivotal trial, patients with treatable large-vessel stroke <8 hours from onset were enrolled.[66] This study observed high recanalization rates (TIMI 2 or 3) of 81.6%. However, 12.8% of patients (18 of 125) endured procedural complications with 2.4% (3 patients) considered serious, resulting in a significant negative impact on the patient.

Two stent retrievers have been developed and compared with the Merci system (Solitaire FR Revascularization Device; Covidien, Irvine, California; and Trevo Pro Retrieval System; Stryker, Kalamazoo, Michigan). Patients treated with both retriever systems showed markedly improved rates of recanalization and reasonable safety.[70,71] As with the MERCI and Penumbra studies, safety was demonstrated along with high rates of recanalization; however, the clinical efficacy data are lacking. Both devices received FDA approval in 2012.

Summary of Evidence—IA thrombolysis may be used at a qualified stroke center to treat patients with major stroke due to MCA occlusion in <6 hours who cannot receive IV alteplase (strong evidence). The FDA has approved several mechanical devices for intracranial clot removal in appropriately selected patients up to 8 hours from symptom onset (strong evidence). Although considered appropriate for emergency stroke treatment, the effect on outcomes has not been established.

Conclusions

CT has been used as the first-line imaging to assess ICH in patients with acute stroke. Although MR imaging has equivalent accuracy in detecting ICH and is superior to CT within the first 24 hours for detection of ischemia, it should be used only if treatment is not delayed because the time from stroke-symptom onset to treatment is a strong predictor of long-term functional outcome. Non-invasive vascular imaging (CTA, MRA) to assess the location and extent of clot and perfusion imaging to assess viable tissue are promising imaging techniques that may be used to select patients for novel thrombolytic agents and interventional devices. Therefore, further studies assessing their accuracy and impact on clinical outcomes are greatly needed. Regarding treatment of acute ischemic stroke, strong evidence exists proving the efficacy of IV and IA thrombolysis up to 4.5 and 6 hours, respectively, from stroke symptom onset. Mechanical thrombectomy has been approved in selected patients up to 8 hours.

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Abbreviations

DPM	diffusion-perfusion mismatch
IA	intra-arterial
ICH	intracranial hemorrhage
r-proUK	recombinant prourokinase
TIMI	Thrombolysis in Myocardial Infarction

Table 1
Classification scheme for the strength of evidence

Strength of Evidence	Criteria Used
Strong	Studies with broad generalizability to most patients suspected of having the disease; include prospective, blinded comparison of a diagnostic test with a well-defined final diagnosis in an unbiased sample when assessing diagnostic accuracy or blinded randomized control trials when assessing therapeutic impact or patient outcomes; also included are well-designed meta-analyses
Moderate	Prospective or retrospective studies with narrower spectrum of generalizability, with only a few flaws that are well-described so that their impact can be assessed but still include a blinded study of diagnostic accuracy on an unbiased sample (well-designed cohort or case-control studies) and randomized trials for therapeutic effects or patient outcomes
Limited	Diagnostic accuracy studies with several flaws in research methods, small sample sizes, incomplete reporting, or nonrandomized comparisons for therapeutic impact or patient outcomes
Insufficient	Studies with multiple flaws in research methods, case series, descriptive studies, or expert opinions without substantiating data

Table 2
Clinical studies testing penumbral imaging markers

Study Name	Validation of the Imaging Biomarker	Testing a Treatment on the Basis of Selection of Patients with an Imaging Biomarker
DIAS,[28] DEDAS,[29] DIAS-2,[30] IV tenecteplase,[44,a]	No	Yes
DEFUSE,[31] DEFUSE-2,[32,33]	Yes	No
EPITHET,[34] MR-RESCUE[35]	Yes	Yes

[a] This trial required intracranial vessel occlusion on CTA and CTP mismatch for randomization.