Developing practice recommendations for endovascular revascularization for acute ischemic stroke

ABSTRACT

Guidelines have been established for the management of acute ischemic stroke; however, specific recommendations for endovascular revascularization therapy are lacking. Burgeoning investigation of endovascular revascularization therapies for acute ischemic stroke, rapid device development, and a diverse training background of the providers performing the procedures underscore the need for practice recommendations. This review provides a concise summary of the Society of Vascular and Interventional Neurology endovascular acute ischemic stroke roundtable meeting. This document was developed to review current clinical efficacy of pharmacologic and mechanical revascularization therapy, selection criteria, periprocedure management, and endovascular time metrics and to highlight current practice patterns. It therefore provides an outline for the future development of multisociety guidelines and recommendations to improve patient selection, procedural management, and organizational strategies for revascularization therapies in acute ischemic stroke. Neurology® 2012;79 (Suppl 1):S243–S255

GLOSSARY

ACT = activated clotting time; AHA = American Heart Association; AIS = acute ischemic stroke; ASA = American Stroke Association; ASPECTS = Alberta Stroke Program Early CT score; CI = confidence interval; ECASS = European Cooperative Acute Stroke Study III; ED = emergency department; EMS = emergency medical services; ERT = endovascular revascularization therapy; FDA = US Food and Drug Administration; IA = intra-arterial; ICH = intracranial hemorrhage; IMS = Interventional Management of Stroke; J-MUSIC = Japan Multicenter Stroke Investigators’ Collaboration; MCA = middle cerebral artery; MELT = MCA-Embolism Local fibrinolytic intervention Trial; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; MR CLEAN = Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands; MR RESCUE = MR and Recanalization of Stroke Clots Using Embolectomy; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; NINDS = National Institute of Neurological Disorders and Stroke; OR = odds ratio; PROACT = Proplyse in Acute Cerebral Thromboembolism; rtPA = recombinant tissue plasminogen activator; sICH = symptomatic ICH; SYNTHESIS EXP = Intra-Arterial Versus Systemic Thrombolysis for Acute Ischemic Stroke; THERAPY = Assess the Penumbra System in the Treatment of Acute Stroke; VBO = vertebrobasilar occlusion.

In an effort to improve outcome in patients with acute ischemic stroke (AIS), recent initiatives have outlined the best medical management and developed protocols to facilitate timely identification and administration of the US Food and Drug Administration (FDA)–approved IV recombinant tissue plasminogen activator (rtPA) to eligible patients.1,2

Restoration of blood flow after AIS is associated with improved outcome and reduced mortality.3,4 A meta-analysis including over 2,000 patients in 53 studies confirmed a strong correlation between recanalization and good functional outcome at 3 months, in comparison with nonrecanalization (odds ratio [OR] 4.43; 95% confidence interval [CI] 3.32–5.91). A meta-analysis including over 2,000 patients in 53 studies confirmed a strong correlation between recanalization and good functional outcome at 3 months, in comparison with nonrecanalization (odds ratio [OR] 4.43; 95% confidence interval [CI] 3.32–5.91).4 Intra-arterial (IA) thrombolysis has not received FDA approval, but randomized trials and several case series have led to endorsements by multiple associations for select patients.5–9 Endovascular revascularization therapy (ERT) currently has a Class Ib recommendation for IA thrombolysis for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thrombus revascularization for select patients and a Level IIb recommendation for mechanical thromb
SAFETY AND EFFICACY OF ENDOVASCULAR REVASCULARIZATION THERAPY FOR ACUTE ISCHEMIC STROKE

Endovascular treatment options for intracerebral revascularization have evolved considerably over the past decade. Several trials evaluating the various therapies are summarized in Table 1. The Prolyse in Acute Cerebral Thromboembolism (PROACT) and PROACT II studies evaluated the use of IA thrombolysis with prourokinase in middle cerebral artery (MCA) occlusions. The initial phase 2 trial demonstrated higher recanalization rates with prourokinase. The phase 3 trial, PROACT II, demonstrated the effectiveness of IA thrombolysis with prourokinase in patients with an MCA occlusion treated within 6 hours from symptom onset. A minimum requirement NIH Stroke Scale (NIHSS) score of 4, except for isolated aphasia or hemianopia, was required for enrollment. Patients treated with prourokinase had a higher rate of recanalization (66% vs 18%; p < 0.001) and were more likely to have a good outcome (modified Rankin Scale [mRS] score of 0–2 at 90 days, 40% vs 25%; p = 0.04), despite a higher rate of symptomatic intracranial hemorrhage (sICH) (10% vs 2%; p = 0.06). The MCA-embolism local fibrinolytic intervention Trial (MELT) was a similarly designed trial comparing prourokinase to placebo in patients with MCA occlusions, which was terminated early because of the approval of the IV administration of rtPA in Japan. Although the MELT findings are underpowered, the results are consistent with those of the PROACT trials, suggesting higher recanalization rates (74%) with IA thrombolysis. A meta-analysis of these 3 trials and 2 additional smaller trials combined 395 randomized patients and showed that IA thrombolysis increased the odds of both nondisabled outcome (mRS score 0–1; OR 2.5; 95% CI 1.33–3.14; p < 0.001) and nondependent outcome (mRS score 0–2; OR 14; 95% CI 1.31–3.51; p < 0.003). A case-control analysis from Japan’s Multicenter Stroke Investigators’ Collaboration (J-MUSIC) compared 91 patients with an acute cardioembolic stroke treated with IA urokinase within 4.5 hours of symptom onset to a matched control group that did not receive IA therapy. The analysis showed that a favorable outcome (mRS score 0–2) was more frequently observed in the urokinase group (50.5% vs 34.1%; p = 0.0124), and there was no difference in mortality rate. Although confirmatory trials required for FDA approval of IA therapy have not been performed, these randomized trials and numerous case series support the use of IA thrombolysis in select patients who are ineligible for IV thrombolysis.

Mechanical devices for ERT have evolved as a means of achieving faster rates of recanalization in medium- to large-vessel occlusions. The Mechanical Embolus Removal in Cerebral Ischemia (MERCI) and Multi-MERCI were prospective, single-arm, multicenter trials designed to test the efficacy and safety of a corkscrew thrombectomy device in the treatment of medium- to large-vessel occlusions (anterior and posterior circulation) within 8 hours of symptom onset. A combined analysis of the 2 studies demonstrated a successful recanalization rate (defined as Thrombolysis in Myocardial Infarction 2 or 3 score) of 64.6%, with good clinical outcome (mRS score 0–2) in 32.4%, despite an sICH rate of 7.8% in the first study and 9.8% in the second. The Penumbra Pivotal Stroke Trial provided registry data on a novel aspiration-thrombectomy device, the Penumbra system, used within 8 hours for large-artery cerebrovascular occlusion. A quarter of the patients achieved an mRS score of less than or equal to 2 at 90 days. Different techniques for measuring recanalization preclude a direct comparison between the rates achieved with MERCI and Penumbra, but both exceed the natural history rate. Randomized trials are ongoing, such as the Local Versus Systemic Thrombolysis for Acute Ischemic
Table 1

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<tr>
<th>Intervention</th>
<th>Enrollment time, h</th>
<th>Design</th>
<th>No. of patients</th>
<th>Recanalization rate, % of treatment/control</th>
<th>Occlusion site</th>
<th>Mean NIHSS treated/untreated</th>
<th>SICH, % of treatment/control</th>
<th>mRS 0–2 at 90 days, % of treatment/control</th>
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<tr>
<td>Solitaire AB mechanical thrombectomy</td>
<td>&lt;6</td>
<td>Single arm, safety and feasibility</td>
<td>56/110</td>
<td>81</td>
<td>MCA, PCA</td>
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<td>&lt;6</td>
<td>Single arm, safety and feasibility</td>
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<td>91</td>
<td>MCA, PCA</td>
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<tr>
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<td>91</td>
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<td>6</td>
<td>6</td>
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<tr>
<td>PROACT II</td>
<td>&lt;6</td>
<td>Single arm, safety and feasibility</td>
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<tr>
<td>Multi-MERCI 2</td>
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<td>81</td>
<td>91</td>
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<tr>
<td>Penumbra PST 1</td>
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<td>MCA, PCA</td>
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Abbreviations: ACA = anterior cerebral artery; adjtx = adjunctive therapy; AICA = anterior inferior cerebellar artery; adjtx = adjunctive therapy; AI = an intracranial internal carotid artery; MCA = middle cerebral artery; MELT = Mechanical Embolus Retrieval for Combined Thrombolysis in Ischemic Stroke; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; MVA = middle vertebral artery; mRS = modified Rankin Scale; NIHSS = NIH Stroke Scale; PROACT = Prolyse in Acute Cerebral Thromboembolism trial; PST = Pivotal Stroke Trial; PROUK = Interventional Management of Stroke trial; RCT = randomized controlled trial; SCA = superior cerebellar artery; SICH = symptomatic intracranial hemorrhage; TICI = thrombolysis in cerebral infarction; TIA = thrombolytic in hemorrhage; TIMI = thrombolysis in myocardial infarction; TV = tissue plasminogen activator; UK = urokinase; VA = intracranial vertebral artery.

Designing a decision algorithm for patient selection for ERT in AIS is hindered by variable enrollment criteria in the trials cited previously. The presented outline for the development of a decision algorithm is based on findings from available randomized controlled trials and extrapolated from criteria from recent and ongoing clinical trials. This is an example of one possible algorithm, and further investigation is necessary prior to clinical use.

Outside of clinical trials, IV therapy remains first-line treatment for eligible patients presenting with clinical symptoms of AIS. Through a systematic review of the literature, the American Stroke Association (ASA) guidelines outline the best medical management as well as protocols to facilitate timely administration of IV rtPA to patients eligible for thrombolysis.1 For patients with moderate to severe deficits and minimal or no early ischemic changes on brain imaging, therapy triage is largely governed by time from symptom onset. There is strong evidence from multiple clinical trials to support the use of IV rtPA within 3 hours. 25,26 Current FDA approval exists for patients presenting up to 3 hours from symptom onset, and a science advisory from the ASA/AHA has recommended expanding the time
window to 4.5 hours in a subgroup of patients, on the basis of results of the European Cooperative Acute Stroke Study III (ECASS III).25,27

Patients presenting after 4.5 hours are not eligible for systemic thrombolysis; however, data exist, as cited previously, for the consideration of IA fibrinolytic administration up to 6 hours from symptom onset in patients with a large- to medium-vessel occlusion.6,12,28 For patients in whom endovascular therapy can be initiated within 8 hours from symptom onset, 2 mechanical revascularization device families have demonstrated safe and feasible rates of recanalization in single-arm, prospective trials.10,11,29

The optimal device for mechanical revascularization has not been identified, and the rapid growth of device technology will likely continue to challenge rigorous clinical evaluation.

Vertebrobasilar artery occlusion (VBO) has an invariably poor outcome if recanalization is not achieved early. The recent literature shows that mortality with acute VBO treated with nonthrombolytic drugs is 80% to 90%, although lower rates of 42% to 60% can be achieved with IA therapy.28,30,31 Success of recanalization and neurologic status before treatment are independent predictors of a favorable outcome after IA therapy.30,31 Multiple studies failed to establish a time window that would definitively exclude patients from IA therapy.28 One study found a significantly better clinical outcome in patients with acute VBO treated within 6 hours after symptom onset than in patients treated after 6 hours (favorable outcome of 36% vs 7%; mortality of 52% vs 70%; \( p = 0.005 \)).28 Other studies demonstrated trends toward better outcome, with shorter duration of symptoms, and no significant association between time to treatment and clinical outcome.30,31 When patients are in a coma or have had prolonged symptoms, additional imaging such as MRI with diffusion and perfusion or CT perfusion might help in identifying those who are likely to benefit from intervention. However, the current application of CT perfusion results to the posterior circulation may be limited.

The trials that shape the current decision patterns have been largely based on time from symptom onset. Data are lacking on the efficacy of ERT beyond 12 hours from symptom onset in patients with posterior circulation occlusion and beyond 8 hours in anterior circulation occlusion.10,11,29,31,32 Given the poor natural history of VBO, revascularization has been considered beyond 12 hours from symptom onset. Enthusiasm continues for a perfusion imaging–based decision algorithm, although rigorous data to support this approach are lacking.33 Further study of perfusion imaging may assist with selection of pa-
Inclusion criteria for ERT
Neurologic deficit attributable to a medium- to large-vessel occlusion
IA chemical thrombolysis can be initiated within 6 h of symptom onset
Mechanical thrombectomy treatment can be initiated within window of 8 h from time of onset for anterior circulation strokes
ERT can be initiated within window of 12 h from time of onset for posterior circulation strokes
Treatment beyond 6–8 h may be guided by advanced imaging results (DWI MRI, PWI, CTP) when available
Potentially disabling neurologic deficit
Persistent or worsening neurological deficits following IV rtPA administration
Exclusion criteria for ERT
Arterial stenosis precluding safe access
Suspicion of aortic dissection
Uncontrolled hypertension, defined as systolic blood pressure >185 mm Hg or diastolic blood pressure >110 mm Hg that cannot be reasonably treated with antihypertensive medication
Platelet count <30,000
Use of warfarin anticoagulation with INR >3.0
Known bleeding diathesis
Deficits attributable to glucose <50 mg/dL
Seizure at onset, if residual deficits are due to a postictal state rather than ischemia
Imaging findings
Significant mass effect with midline shift
Intracranial hemorrhage (ICH, SAH, subdural or epidural hematoma)
Subacute infarct on head CT/MRI that occupies >1/3 of the MCA territory or >100 cc of brain tissue
CNS lesion with high likelihood of hemorrhage should be excluded from IA pharmacologic thrombolysis (brain tumor, abscess, vascular malformation, aneurysm, contusion)
May consider IA thrombolysis in patients with small unruptured aneurysms or benign tumors with low vascularity
Relative contraindications for ERT therapy
Intracranial or spinal surgery, head trauma, or stroke in separate vascular territory within 3 months
History of ICH
Terminal illness with short life expectancy or severe comorbid illness
Pregnancy
Risk vs benefit of clinical symptoms and ability to shield patient must be considered
Known subacute bacterial endocarditis with or without mycotic aneurysm and stroke
Special consideration may be needed for patients on dabigatran
Relative contraindications for adjunctive ERT following IV rtPA
Glucose >400 mg/dL, based on increased ICH risk
Ongoing hemodialysis or peritoneal dialysis, due to possibly increased ICH risk

Abbreviations: CTP — CT perfusion; DWI MRI — diffusion-weighted MRI; ERT — endovascular revascularization therapy; IA — intra-arterial; ICH — intracerebral hemorrhage, INR — international normalized ratio; MCA — middle cerebral artery; NIHSS — NIH Stroke Scale; rtPA — recombinant tissue plasminogen activator; SAH — subarachnoid hemorrhage.

Table 2 Possible selection criteria for acute ischemic stroke endovascular revascularization therapy

In patients who would benefit from revascularization beyond 8 hours.34

At the very least, noncontrast head CT or diffusion- and susceptibility-weighted MRI are required to exclude hemorrhage and identify early ischemic changes that could pose increased hemorrhagic risk following revascularization. Larger regions of well-defined hypodensity (CT) or hyperintensity (MRI) indicating infarcted tissue may carry a considerably higher risk of hemorrhage following revascularization. Careful consideration may be needed for patients with CT hypodensity or MRI hyperintensity in greater than 1/3 of the MCA territory or with prominent sulcal effacement.35 Alternative standardized scoring systems may include the Alberta Stroke Program Early CT Score (ASPECTS).36

Future studies may show that for patients who receive IV rtPA and have a clinical presentation suggestive of a large-vessel occlusion, early consideration of ERT may be important. The limited efficacy of IV rtPA in large vessel occlusions is demonstrated by recanalization rates as low as 30% in the proximal MCA and 6% in the terminal internal carotid artery (ICA).37 Urgent noninvasive vascular imaging can identify patients with a large-vessel occlusion. The interval from a decision to pursue IA intervention to reaching the clot can be long, with time required to obtain consent, transport and prepare the patient, and negotiate tortuous anatomy. Accordingly, an efficient strategy may be to activate the neurointerventional team when a large-vessel occlusion is suspected, without delay in IV rtPA initiation. If dramatic clinical improvement occurs, patients can be rerouted to repeat noninvasive vessel assessment. One retrospective study has shown that in those patients with a contraindication to IV rtPA or whose IV therapy fails, the use of ERT within the first 3 hours after stroke symptom onset has a low sICH rate, of 5.3%.38

Patients with fluctuating deficits or continued mild deficits (NIHSS score ≤4) following rapid improvement from presentation carry a risk of harboring a large-vessel occlusion with tenuous collateral supply. Failure of collateral supply could lead to acute deterioration; therefore, emergent noninvasive angiography to identify vessel occlusions amenable to ERT may be considered. To date, no randomized clinical trial has compared the natural history of medical treatment alone to early recanalization with ERT in this subset of patients.

For patients in whom ERT is considered, inclusion and exclusion criteria will be needed. Based on the existing clinical trials and guidelines, a framework for the future development of criteria can be outlined (table 2).
### Table 3 Intra-arterial thrombolytic dosing and methods from selected trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>PROACT5</th>
<th>PROACT II6</th>
<th>MELT12</th>
<th>IMS I75</th>
<th>IMS II90</th>
<th>IMS III81</th>
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<tbody>
<tr>
<td>Agent</td>
<td>ProUK</td>
<td>ProUK</td>
<td>UK</td>
<td>rtPA</td>
<td>rtPA</td>
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<tr>
<td>Max dose</td>
<td>Two-tier dose 6 mg and 12 mg</td>
<td>9 mg</td>
<td>600,000 IU</td>
<td>IV rtPA 0.6 mg/kg, 60 mg max, IA rtPA 22 mg</td>
<td>IV rtPA 0.6 mg/kg, 60 mg max, IA rtPA 22 mg</td>
<td>IV rtPA – 0.6 mg/kg, 60 mg max, possibly IA rtPA 22 mg</td>
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<tr>
<td>Median dose, mg</td>
<td>6 and 12</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>12</td>
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<td>Infusion duration, h</td>
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<tr>
<td>Infusion location</td>
<td>At proximal one-third of thrombus</td>
<td>At proximal one-third of thrombus</td>
<td>Distal to thrombus</td>
<td>2 mg distal to thrombus, then 2 mg into thrombus, then infusion</td>
<td>At site of thrombus, with or without Ekos ultrasound catheter</td>
<td>1 mg distal and 1 mg proximal, then 20 mg over maximum of 2 h</td>
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<tr>
<td>Mechanical disruption</td>
<td>Prohibited</td>
<td>Prohibited</td>
<td>Only with guidewire</td>
<td>Only with guidewire or microcatheter</td>
<td>Only with guidewire or microcatheter</td>
<td>Merci device, Ekos, or penumbra device with IA rtPA infusion or microcatheter/IA rtPA infusion</td>
</tr>
<tr>
<td>Intraprocedural systemic thromboprophylaxis</td>
<td>Heparin 2,000 IU bolus and 500 IU/h infusion for 4 h</td>
<td>Heparin 2,000 IU bolus and 500 IU/h infusion for 4 h</td>
<td>Heparin 5,000 IU bolus</td>
<td>Heparin 2,000 IU bolus and 450 IU/h infusion</td>
<td>Heparin 2,000 IU bolus and 450 IU/h infusion</td>
<td>Heparin 2,000 IU bolus and 450 IU/h infusion until the end of the procedure</td>
</tr>
<tr>
<td>Adjunct antithrombotic agents</td>
<td>Prohibited in first 24 h</td>
<td>Prohibited in first 24 h</td>
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<td>Prohibited in first 24 h</td>
<td>Prohibited in first 24 h</td>
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</table>

Abbreviations: IA = intra-arterial; IMS = Interventional Management of Stroke trial; IU = international units; MELT = Middle cerebral artery Embolism Local Fibrinolytic intervention Trial; PROACT = Prolyse in Acute Cerebral Thromboembolism trial; rtPA = IV recombinant tissue plasminogen activator; UK = urokinase.

lored interventions. For example, greater efficacy and safety may be demonstrated in distal vessel revascularization by use of IA fibrinolytic therapy, vs a mechanical device that may be more difficult to deliver. Alternatively, in large proximal vessel occlusions, greater benefit may be achieved with mechanical thrombectomy. Furthermore, carotid occlusion at the origin of the ICA may be better treated with balloon angioplasty and stent implantation.

**Pharmacologic thrombolysis.** Local IA thrombolysis efficacy was demonstrated in PROACT II.5 This led to an AHA Class I, level of evidence B recommendation that IA thrombolysis is an option for the treatment of selected patients who have AIS under 6 hours duration due to occlusions of the MCA and who are not otherwise candidates for IV rtPA.4 Although variability in study designs prohibits direct comparison of the data, theoretically there may be a higher risk of intracerebral hemorrhage (ICH) with chemical IA thrombolysis than with mechanical revascularization. However, increased ICH was not substantiated in a multicenter study.39

Microcatheter position during thrombolytic infusion may also theoretically affect recanalization rates. The microcatheter position varies among the studies; in some instances it is placed distal to the thrombus, within the thrombus, or proximal to the thrombus. Some operators will use multiple locations to infuse rtPA throughout the thrombus. The maximum safe dose for IA rtPA is not known; however, if we extrapolate from large clinical trial experience, then a maximum dose of 22 mg, as in the IMS trials, may be a reasonable initial limit.31,40

**Bridging therapies.** Bridging therapy trials evaluating the combined approach have shown better recanalization rates for medium- to large-vessel occlusions. However, they have shown only trends toward better outcomes in comparison with the IV rtPA–treated subjects in the National Institute of Neurological Disorders and Stroke (NINDS) rtPA Stroke Study or a database registry.40,41 Potential benefit of bridging therapy increases when the target population is limited to IV rtPA nonresponders (40% IV-IA patients reached functional independence at 3 months, vs 14.9% of recipients of only IV rtPA, among the nonresponders \( p = 0.012\)). This benefit came at the cost of a higher morbidity associated with the bridging therapy (OR 2.14; 95% CI 0.58–7.83 for sICH).42 The early Emergency Management of Stroke Bridging Trial/IMS trials used a protocol of 0.6 mg/kg IV rtPA with up to an additional maximum of 22 mg IA rtPA, which in most patients allowed for the total dose to remain below the NINDS maximum amount of 90 mg (table 3). However, newer bridging studies and the amended IMS III are using full-dose IV rtPA in the combined IV-IA treatment arm.20,21

**Mechanical revascularization.** Mechanical techniques for ERT, including thrombectomy, clot retrieval, and thromboaspiration, have shown comparable or slightly higher recanalization rates than IA thrombol-
### Table 4: Treatment times in selected studies, in minutes

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<tr>
<td>Time-to-CT/MRI scan: mean (median)</td>
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<td>Imaging-to-GP</td>
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<td>CT scan-to-microcatheter</td>
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<td>Time-to-ERT initiation or angiography or GP</td>
<td>SO (330)</td>
<td>SO (318)</td>
<td>SO 217 (212)</td>
<td>SO 123.7/25.2</td>
<td>SO a (188)³</td>
<td>SO 227</td>
<td>SO 258c</td>
<td>SO 151b</td>
<td>SO 324 (330)</td>
<td>SO 321</td>
<td>Door (130)</td>
<td>SO 244</td>
<td>SO (226)</td>
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<td>GP-to-max TIMI/TICI</td>
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<td>SO-to-max TIMI/TICI</td>
<td>a(378)</td>
<td>b(342)</td>
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**Abbreviations:** EMS = Emergency Management of Stroke; ERT = endovascular revascularization treatment; GP = groin puncture; IA = intra-arterial; IAT = intra-arterial therapy (includes thrombolysis and mechanical techniques); IMS = Interventional Management of Stroke trial; MELT = Middle cerebral artery Embolism Local Fibinolytic Intervention Trial; MERCI = Mechanical Embolus Removal in Cerebral Ischemia; PROACT = Prolyse in Acute Cerebral Thromboembolism trial; PST = Pivotal Stroke Trial; RECANALISE = Recanalisation using Combined intravenous Alteplase and Neurointerventional Algorithm for acute Ischemic Stroke; RS = retrievable stent; rtPA = recombinant tissue plasminogen activator; SO = symptom onset; TICI = thrombolysis in cerebral infarction; TIMI = thrombolysis in myocardial infarction; UK = urokinase.
times. The Brain Attack Coalition has recommended that IV rtPA be administered within 60 minutes from arrival to the emergency department (ED) for eligible patients. The established time intervals target a multidisciplinary goal. Each component of the process—ED physicians, ancillary staff, laboratory and radiology services, neurology team, and radiology staff—is essential for the time goal. As such, ERT time intervals should integrate into the existing model, beginning with patient arrival to the ED. Separate time intervals can be established for patients transferred from another institution and patients who receive adjunctive ERT following IV rtPA therapy. Because vascular anatomy can add unpredictable delays in procedural times, the endpoint should reflect the fact that the patient requires more time-consuming neurologic 

In the limited case series discussing time intervals to ERT, there is variability in which interval is utilized (table 4). Randomized trials show feasibility in achieving time intervals of approximately 4 to 5 hours from stroke onset to IA rtPA administration. In PROACT II, median time from stroke onset to randomization and IA rtPA administration was 282 minutes, whereas the IMS study demonstrated an interval of 231 minutes from stroke onset to IA rtPA administration. Time from CT scan to microcatheter placement in the cerebrovasculature had a mean time of 174 ± 60 minutes in 91 patients undergoing ERT for AIS, demonstrating wide variability and a need for time standards. Transferred patients whose laboratory tests and CT scan have already been completed may still have a door-to-puncture time of up to 60 minutes. Further study is needed to identify barriers to rapid access to endovascular therapy.

Currently, the American College of Cardiology and the AHA recommend that door-to-balloon time in ST segment elevation myocardial infarction should be within 90 minutes. A similar future proposal could be made for ERT in AIS, with a goal door-to-puncture time of 90 minutes (table 5). This would include activation of the stroke team, technologists, and nurses. Adjunctive time benchmarks can be developed, including puncture-to-clot and clot-to-close goals. This target is more difficult to achieve for cerebral than cardiac revascularization, as stroke patients require more time-consuming neurologic interventions.
evaluation and brain imaging before proceeding to the angiography laboratory.

Achieving a 90-minute door-to-puncture time would likely require the neurointerventionalist to play an integral part in the stroke team, because the decisions on treatment strategy may evolve as the patient proceeds through the AIS protocol and IV rtPA evaluation pathway. The ERT protocol should integrate into the IV rtPA pathway. For interhospital transfers, the completed imaging and laboratory studies as well as additional lead time may reduce the target time interval to 60 minutes for door-to-puncture. However, significant delay in hospital transfer may warrant repeat neuroimaging when the patient arrives at the recipient institution. Benchmark times will need to be established for IV nonresponders, with special consideration for additional delay when clinical deterioration following IV rtPA requires a repeat brain imaging prior to ERT.

**Triage and transfer strategies.** The considerable decline in efficacy of revascularization therapies at around 6 to 8 hours from symptom onset demands well-organized triage and transfer strategies. Emergency department reorganization has been an area of focus to improve early identification of stroke patients. Tracking door-to-thrombolysis times, positioning a CT/MRI scanner within the department, and having emergency medical services (EMS) send a prehospital notification are steps that have improved thrombolysis access. However, given the limited availability of Comprehensive Stroke Center infrastructure, few centers in a given geographic region will have capabilities for providing comprehensive stroke care and 24/7 ERT. This will lead to a high proportion of patients eligible for ERT arriving by interhospital transfer. Transfer delay has been shown to be a major factor limiting the use of ERT in stroke patients, accounting for an estimated odds of treatment decrease by 2.5% for every minute of transfer time. To avoid transfer delay, regional protocols for triage of AIS patients by EMS personnel to designated stroke centers has become a focus of prehospital stroke triage policy.

Alternative strategies include initiation of IV thrombolysis in a referring hospital prior to transfer “drip-and-ship,” followed by further management at the accepting hospital, which may include ERT. A described model of “drip, ship, and retrieve” used full-dose IV rtPA (0.9 mg/kg) followed by ERT with mechanical thrombectomy and thrombo-aspiration, suggesting feasibility in basilar artery occlusion. Different models may evolve where the patient receives ERT in an outside hospital and is transferred for further care at a comprehensive stroke center where neurosurgery, neurocritical care, and vascular neurology expertise are available, known as “retrieve-and-ship.” Pay-for-performance measures similar to those for acute myocardial infarction could help facilitate transfer of appropriate patients from primary to comprehensive stroke centers (the hub-and-spoke model).

**GENERAL PREPROCEDURAL AND INTRAPROCEDURAL MANAGEMENT**

**Anesthesia and monitoring.** The type of anesthesia for ERT has been a topic of controversy, with recent reports suggesting worse outcome with use of general endotracheal anesthesia, possibly due to treatment delays and complications from intubation. Alternatively, conscious sedation may pose a different set of risks related to patient cooperation, especially in those with severe aphasia or neglect, which may negatively influence time to revascularization and procedural success. Furthermore, ancillary monitoring requiring invasive arterial access for blood pressure monitoring and central IV access may also be of limited value and add delay to initiation of therapy. Further study is needed to evaluate sedation methods for ERT. Sedation methods may currently vary among centers.

**Thromboprophylaxis with systemic anticoagulation.** Arterial catheterization carries a risk of thrombembolism, often requiring systemic anticoagulation. Randomized clinical trials of ERT report variable protocols for thromboprophylaxis, including bolus IV heparin infusion of 2,000 to 5,000 units at procedure onset, followed by continuous infusions of approximately 500 units of IV heparin per hour for the procedure duration. Alternatively, activated clotting time (ACT) values can be obtained with heparin boluses to maintain an ACT at a therapeutic goal. Limited data exist on the safety of heparin anticoagulation during ERT procedures. A subgroup analysis of the MERCI trial showed no association with hemorrhage or 90-day mortality and heparin use. A reasonable ACT range may be 250 to 300 seconds during ERT.

**Renal prophylaxis.** Patients with AIS may also have chronic renal impairment, which may worsen with contrast administered during angiography. Interventions designed to prevent contrast-induced nephropathy have not been rigorously studied. Reasonable prophylaxis strategies include hydration with isotonic saline. Recent data have not provided strong support for the administration of N-acetylcysteine. The use of sodium bicarbonate infusion may be reasonable for patients with renal insufficiency, but it can be limited by the large volume and time to acquire the solution from the pharmacy. Periprocedural renal prophylaxis for...
ERT in select AIS patients is an important area in need of further investigation.

**POSTPROCEDURAL MANAGEMENT** Imaging. Patients may benefit from postprocedural imaging, including noncontrast head CT or susceptibility-weighted MRI within 16 to 32 hours from ERT. Given the associated risk of hemorrhagic complications with revascularization therapy, urgent head CT or MRI may be needed for clinical deterioration in the postprocedure period. Intraprocedure imaging is also possible in many angiography suites and can offer rapid diagnostic information.

**Neuromonitoring.** Intensive care unit monitoring with staff trained in neurologic patient care may be important for postprocedure neuromonitoring, including frequent neurologic examination assessments by nursing staff experienced and trained in neurovascular diseases. Intensive monitoring would also include surveillance for groin-access complications and the appropriate management. Stroke severity and outcome scales may be important in performance monitoring.

**Blood pressure management.** Patients in whom revascularization was successful may be at risk of reperfusion hemorrhage, thereby warranting aggressive blood pressure control. Common practice has followed a protocol similar to that for post IV rtPA administration with vigilant blood pressure monitoring for at least the first 24 hours. Blood pressure is measured every 15 minutes for 2 hours, then every 30 minutes for 6 hours, and every hour for 18 hours. Goal blood pressure is targeted to remain below 180/105 mm Hg. Bolus dosing of labetolol or continuous infusion of nicardipine has been used to achieve target blood pressure. Adjustments in blood pressure parameters may be necessary to achieve clinical stability.

**Antithrombotic regimen.** Postprocedure antithrombotic regimen will likely follow a similar pathway to that in general AIS management. Antithrombotics are usually avoided in the first 24 hours following IV and IA administration of a thrombolytic agent. Certain procedures may present exceptions, such as patients receiving stent implantation, in which the respective preferred regimen will need to be implemented. This may include loading doses of 325 to 650 mg of aspirin (orally or rectally) and 300 to 600 mg of clopidogrel with subsequent dual antiplatelet therapy with daily aspirin (325 mg) and clopidogrel (75 mg) for 4 to 12 weeks, followed by indefinite single-antiplatelet therapy with aspirin 325 mg daily or tailored to the underlying etiology. A potential hazard of dual antiplatelet therapy for acute stent implantation in a patient with a recent large stroke includes hemorrhage.

**Glycemia management.** Hyperglycemia may be associated with an increased risk of hemorrhagic transformation of the cerebral infarction. An appropriate glycemic-control regimen will likely be modeled after existing management strategies developed for AIS.

**Statin therapy.** Comprehensive management strategies for patients with AIS who undergo ERT will likely also adopt statin therapy regimens modeled after those developed for AIS patients in general.

**CLINICAL OUTCOME MEASUREMENTS** Monitoring clinical outcomes following ERT is important for quality metrics. Thresholds and benchmarks for acceptable stroke severity–weighted sICH and mortality rates need to be established. The proportion of patients completing 90-day clinical follow-up (from those who are eligible) needs to be established. Similarly, consensus on rates of 90-day good functional mRS outcome (score of 0–2) following ERT needs to be established.

**DISCUSSION** This outline can be used as a framework for the development of future practice recommendations and as an interim tool that the practicing neurovascular specialist can use to assess the rapidly evolving management strategies. This evolving field is marked by ongoing intense investigation of various therapies for acute revascularization, which will demand frequent reevaluation and modification of these strategies.

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DISCLOSURE

Dr. Lazzaro reports no disclosures. Dr. Novakovic performs endovascular treatments for acute ischemic strokes (has not used a retrievable stent). Dr. Alexandrov serves as an Associate Editor for Frontiers in Interventional Neurology; has a patent for Therapeutic Methods and Apparatus for Use of Sonication to Enhance Perfusion of Tissue; has received publishing royalties for Cerbrovascular Ultrasound in Stroke Prevention and Treatment (first and second editions); has served as a consultant for Cerevast Therapeutics; spends 60% effort on clinical stroke service at Comprehensive Stroke Center, UAB Hospital, monitoring endovascular procedures and evaluating success of recalibration with imaging; has received research support from Cerevast Therapeutics, Inc.; has received research support from NINDS; has received compensation from Cerevast Therapeutics, Inc.; and has received license fee payments from Therapeutic Methods and Apparatus for Use of Sonication to Enhance Perfusion of Tissue. Dr. Darakhbani reports no disclosures. Dr. Edell serves as an Associate Editor for Frontiers in Interventional Neurology. Dr. English has served on the scientific advisory board of Concentric Medical Inc., Clinical Events Committee; serves on the editorial boards of Neurohospitalist and The Stroke Interventionalist; and serves as Medical Scientific Advisor for Silk Road Medical. Dr. Frei has served as a consultant to Penumbra, Inc. Dr. Jameson has served as a consultant to Bayer and Boehringer-Ingelheim; served on the speakers bureau for Boehringer-Ingelheim and Merck; served on the scientific advisory board for Bayer and on the Adjudication Committee for ARRIVE trial; and serves as an Associate Editor for Neurology: Alert. Dr. Janardhan reports no disclosures. Dr. N. 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Dr. Linfante serves as a consultant for Codman Neurovascular and Stryker; holds stock options in Surpass Limited; serves on the Scientific Advisory Board for Codman Neurovascular; serves on the editorial boards for Stroke and Journal of Neurointerventional Surgery; and serves on the speakers bureau for Codman. Dr. Nguyen serves as Associate Editor of Frontiers in Vascular and Interventional Neurology and Editor of SVIN newsletter The Care; performs intra-arterial stroke procedures; and serves as a consultant for Penumbra. Dr. Saver serves on the editorial boards of Stroke, Reviews in Neurologic Disease, Journal of Neuroimaging, and Journal of Stroke and Cerebrovascular Disease; is an employee of the University of California (UC), which holds a patent on retriever devices for stroke; serves on scientific advisory boards, for which the UC Regents receive payments, for CoAxia, Inc., Concentric Medical, Talaris Biotherapeutics, Ferrer, AGA Medical Corporation, BrainGate, PhotoThera, Ev3, and Synapsis Bioscience GmbH & Co. KG; is an unsed site investigator in multicenter clinical trials sponsored by AGA Medical Corporation, Lundbeck, Inc., and Ev3, for which the UC Regents received payments based on clinical trial contracts for the number of subjects enrolled; is an unpaid site investigator in the NIH IRIS, CLEAR, IMS 3, SAMMPRIS, and VERITAS multicenter clinical trials, for which the UC Regents receive payments based on clinical trial contracts for the number of subjects enrolled; receives research support from the NIH and NINDS; receives research support from the AHA; and performs acute stroke care (35%). Dr. Shutter serves on the scientific advisory board for Neuren Pharmaceuticals; receives funding for travel or speaker honoraria from Codman, J&J, and NIH; serves as a consultant for Cincinnati Bengals; receives research support from Department of Defense and NIH (NINDS); receives research support from the Mayfield Education and Research Fund; and holds stock options in UCB Pharma. 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Dr. Zaidat serves on the scientific advisory board for Talecris; served on the adjudication committee for Stryker; received speaker honoraria from Stryker; served on the editorial board of Frontiers in Neurology (Endovascular & Interventional Neurology Section); serves as Editor of The Journal of Neurointerventional Surgery, and serves as Associate Editor and is a member of the Editorial Board of Journal of Stroke & Cerebrovascular Disease; served as a consultant for Stryker Neurovascular, Codman Neurovascular, and Microvention, Inc; and has received research support from Society of Vascular & Interventional Neurology (SVIN) for this educational activity. Go to Neurology.org for full disclosures.

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