# Ischemic Stroke in the Neurocritical Care Unit

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## Introduction

Ischemic stroke is the most common severe neurologic disorder, the most common neurologic diagnosis leading to hospital admission, and the most common diagnosis prompting admission to the NCCU. Intravenous (IV) tPA (alteplase), the first successful therapy for acute ischemic stroke, was introduced in 1996. This therapy and advances since then, including strong evidence for the benefit of endovascular thrombectomy for rapid recanalization of occluded large intracranial arteries, have increased the demand for effective utilization of the NCCU to manage acute stroke. In this chapter, we discuss the current care of acute ischemic stroke, reviewing the clinical trials that support aggressive efforts to achieve early recanalization, the use of the NCCU to support optimal outcomes in this new treatment paradigm, and other issues pertaining to critical care for patients with unstable acute strokes.

## Need for NCCU Care for Patients with Ischemic Stroke

Urgent treatments for acute ischemic stroke are time-sensitive and are most commonly initiated before admission to the NCCU. Their successful application requires the collaboration of acute stroke teams, including stroke neurologists, neurointensivists, emergency room physicians, interventional neurologists or neurosurgeons or neuroradiologists, and the technical and nursing teams that support these urgent efforts. Neurointensivists frequently play a role in the early decision-making for such patients. Many patients treated with IV thrombolysis and endovascular thrombectomy for stroke will be best served by the close monitoring provided by the NCCU for aftercare that includes monitoring for hemorrhage, recurrent stroke, and malignant cerebral edema, when large strokes occur despite the treating team's best efforts. In addition, cerebellar infarcts present a particular concern with regard to deterioration due to the potential for edema and mass effect in the posterior fossa. Many patients with unstable symptoms due to vascular stenoses will benefit from close monitoring and interventions to optimize collateral blood flow. Finally, medically ill patients, such as those with infectious endocarditis, may present with acute strokes and require NCCU care. In all of these conditions, the expertise of NCCU nurses skilled in the early recognition of neurologic deterioration is a critical component of effective care. Some medications commonly used in the acute setting for ischemic stroke are summarized in Table 8.1.

## Intravenous Thrombolysis for Acute Ischemic Stroke

The National Institute of Neurological Disorders and Stroke (NINDS) trial of IV tPA established the benefit of this therapy for the first time in a large-scale clinical trial [4]. Therapy in this trial was limited to administration within 3 hours of symptom onset, setting the early standard for clinical implementation. Meta-analysis of data from the NINDS trial and other large trials suggested that clinical benefit might extend beyond this 3-hour window, and the European Cooperative Acute Stroke Study (ECASS) III trial provided evidence of benefit within a treatment window of 4.5 hours for selected patients [5–11]. Phase 4 post-marketing studies have demonstrated the successful implementation of protocols similar to those used in the NINDS and other trials in the community [12–15]. These clinical studies have established the standard of care for medical treatment of acute ischemic stroke [1–3]. Although the studies confirmed benefit for selected

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**Table 8.1** Medications commonly used for acute ischemic stroke

| Medication | Route | Dose | Indications | Major side effects |
|---|---|---|---|---|
| Alteplase | IV | 0.9 mg/kg; max 90 mg | Acute ischemic stroke within 4.5 hours | Systemic and intracranial hemorrhage, angioedema |
| | | 10% bolus over 1 minute | (see Table 8.2 for details) | |
| | | 90% infuse over 1 hour | (off label for 3–4.5 hours use) | |
| Tenecteplase | IV | Dose for stroke not established | Acute ischemic stroke (off label for stroke) | Systemic and intracranial hemorrhage, angioedema |
| Heparin | IV | Targeting aPTT 60–80 s: 80 U/kg bolus, start infusion at 18 U/kg/hour; targeting aPTT 50–70 s: 60 U/kg bolus, start infusion at 12 U/kg/hour; check aPTT in 6 hours and adjust target | Mechanical heart valve, hypercoagulable state, venous sinus thrombosis, DIC, etc. | Systemic and intracranial hemorrhage, heparin-induced thrombocytopenia (HIT) |
| | SC | 5000 U q 8–12 hours | DVT prophylaxis | Systemic and intracranial Hemorrhage, HIT |
| Enoxaparin (LMWH) | SC | 40 mg daily lower dose for renal insufficiency and low body weight | DVT prophylaxis | Systemic and intracranial hemorrhage, HIT |
| Enoxaparin (LMWH) | SC | 1 mg/kg q 12 hours; or 1.5 mg/kg daily | Treatment of DVT, PE, etc. | Systemic and intracranial hemorrhage, HIT |
| Fondaparinux | SC | 2.5 mg q 24 hours | DVT prophylaxis (e.g., with history of HIT) | Systemic and intracranial hemorrhage |
| Fondaparinux | SC | <50 kg: 5 mg q 24 hours | Treatment of DVT, PE, etc. | Systemic and intracranial hemorrhage |
| | | 50–100 kg: 7.5 mg q 24 hours | | |
| | | >100 kg: 10 mg q 24 hours | | |
| Argatroban | IV | Start: 1 mcg/kg/minutes; adjust to aPTT 1.5–3× initial value (with normal liver function) | IV anticoagulation in setting of HIT | Systemic and intracranial hemorrhage |
| Bivalirudin | IV | Start: 0.15 mg/kg/hour | IV anticoagulation in setting of HIT | Systemic and intracranial hemorrhage |
| | | Adjust to aPTT 1.5–3× initial value (with normal renal function) | | |
| Lepirudin | IV | Bolus: 0.4 mg/kg | IV anticoagulation in setting of HIT | Systemic and intracranial hemorrhage |
| | | max 110 mg | | |
| | | Infusion: 0.15 mg/kg/hour | | |
| | | Adjust to aPTT 1.5–2.5× initial value (with normal renal function) | | |
| Warfarin | PO | Targeting INR | Stroke prevention in AF, mechanical heart valve, hypercoagulable state, venous sinus thrombosis, etc. | Systemic and intracranial hemorrhage, acute hypercoagulability, skin necrosis, teratogenicity |
| Dabigatran | PO | 150 mg bid (adjust for CRI) | Stroke prevention in AF, DVT, PE | Systemic and intracranial hemorrhage, dyspepsia |
| Apixaban | PO | 5 mg bid (2.5 mg bid, if ≥2 of these: ≥80 y/o, ≤60 kg; SCr ≥ 1.5) | Stroke prevention in AF, DVT, PE | Systemic and intracranial hemorrhage |
| Rivaroxaban | PO | 20 mg daily (adjust for CRI) | Stroke prevention in AF, DVT, PE | Systemic and intracranial hemorrhage |
| Edoxaban | PO | 60 mg daily (adjust for CRI) | Stroke prevention in AF, DVT, PE | Systemic and intracranial hemorrhage |
| Cryoprecipitate | IV | Based on fibrinogen | Alteplase-related hemorrhage; low fibrinogen | Transfusion reaction |
| RiaSTAP | IV | Based on fibrinogen and weight | Alteplase-related hemorrhage; low fibrinogen | Thrombosis, allergic reaction |
| FFP | IV | Based on INR and weight | Reversal of INR elevation | Volume overload, transfusion reaction |
| PCC | IV | Based on INR and weight | Rapid reversal of INR elevation | Thrombosis, allergic reaction |
| ε-aminocaproic acid | IV | 1–5 g q 4–8 hours (rate 1 g/hour) | Alteplase-related hemorrhage | Thrombosis |
| Tranexamic acid | IV | Load: 1 g over 10 minutes | Alteplase-related hemorrhage | Systemic thrombosis |
| | | Infusion: 1 g q 8 hours given over 8 hours | | |

**Table 8.1** (continued)

| Medication | Route | Dose | Indications | Major side effects |
|---|---|---|---|---|
| 23% saline | IV | 30 cc and repeat adjusting to effect on serum Na and Osm | Cerebral edema | Volume overload, hypernatremia |
| Mannitol | IV | 0.25–2 g/kg; repeat adjusting to effect on serum Na and Osm | Cerebral edema | Dehydration, volume contraction hyponatremia, hypernatremia, renal failure |

*IV* intravenous, *AF* atrial fibrillation, *aPTT* activated partial thromboplastin time, *DIC* disseminated intravascular coagulation, *SC* subcutaneous, *DVT* deep vein thrombosis, *HIT* heparin-induced thrombocytopenia, *LMWH* low-molecular-weight heparin, *PE* pulmonary embolism, *PO* oral, *INR* international normalized ratio, *CRI* chronic renal insufficiency, *SCr* serum creatinine, *FFP* fresh frozen plasma, *PCC* prothrombin complex concentrate, *Osm* osmolality

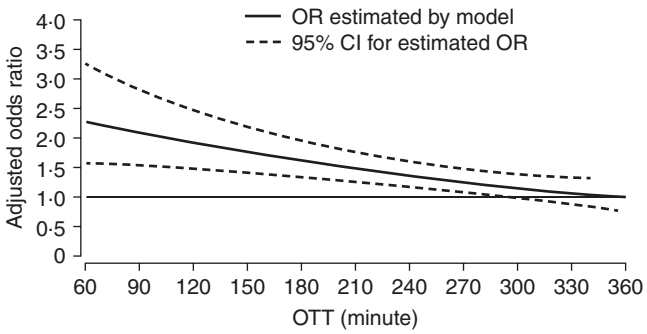


**Fig. 8.1** Estimated odds ratio for favorable outcome at 3 months in IV t-PA-treated patients compared to controls by time of onset to start of treatment (OTT). OTT onset to start of treatment, OR odds ratio. (Reprinted with permission from Hacke et al. [7])

patients treated within the 3- and 4.5-hour windows, it is important to emphasize that, in all cases, the chance of improved outcome is maximized by the most rapid treatment possible within these times windows (Fig. 8.1) [4, 7]. Standard inclusion and exclusion criteria for treatment with IV tPA are shown in Table 8.2. Tenecteplase offers some theoretical advantages over alteplase, and some studies suggest enhanced benefit and better safety in patients with coronary occlusion and stroke [16–20]. Further study of this agent will determine its possible future entry into clinical practice for acute stroke. Reteplase and abciximab, alternative thrombolytic and antiplatelet agents, respectively, are under investigation.

Based on the protocol used for the NINDS trial, recommendations for the first 24 hours after treatment with IV tPA include maintenance of systolic blood pressure (BP) below 180 mm Hg and diastolic BP below 105 mm Hg and avoidance of antiplatelet and anticoagulant agents and of interventions that present a risk of hemorrhage (see Tables 8.3 and 8.4).

The degree of systemic fibrinolysis conferred by IV tPA varies among patients [21]. Because the fibrinolytic state is transient, and we do not intervene unless the patient develops clinically significant hemorrhagic transformation, testing of international normalized ratio (INR), activated partial thromboplastin time (aPTT), and fibrinogen are not recommended except to address clinical needs. If patients are stable without significant hemorrhage after 24 hours, then antithrombotic or anticoagulant therapy and chronic antihypertensive therapy should be implemented as indicated by the clinical circumstances.

The ECASS study provided a classification system for hemorrhagic transformation after IV thrombolysis, vary-

**Table 8.2** Inclusion and exclusion criteria for intravenous thrombolysis [1–3]

| |
|---|
| *Major inclusion criteria*[a] |
| Age ≥18 years (for 3-hour window) |
| Severe or mild but disabling stroke |
| Blood pressure can be lowered to <185/110 mm Hg |
| Glucose >50 mg/dl (may consider therapy if focal deficit persists after correction of low glucose) |
| *Major exclusion criteria*[a] |
| Non-contrast head CT with extensive frank hypodensity of early infarction or with hemorrhage |
| Ischemic stroke within 3 months |
| Severe head trauma within 3 months |
| Intracranial or spinal surgery within 3 months |
| History of intracranial hemorrhage |
| Signs and symptoms of subarachnoid hemorrhage |
| Gastrointestinal malignancy or recent GI bleeding within 21 days |
| The following coagulation abnormalities: platelets <100,000, INR >1.7, aPTT >40 s, PT >15 s |
| Low-molecular-weight heparin given within 24 hours |
| Dose of direct thrombin inhibitor or direct factor Xa inhibitor with 48 hours, unless aPTT, INR, thrombin time, ecarin clotting time, or appropriate direct factor Xa activity are normal |
| Infective endocarditis |
| Aortic dissection |
| Intra-axial intracranial neoplasm |

*CT* computed tomography, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *PT* prothrombin time

[a]The following additional exclusions are recommended for use in the 3–4.5 hours window: (1) Age >80 years, (2) history of both diabetes mellitus and prior stroke, (3) National Institutes of Health Stroke Scale (NIHSS) >25, (4) use of oral anticoagulant regardless of INR or other laboratory tests, and (5) CT evidence of ischemic injury involving >1/3 of the MCA territory

**Table 8.3** Protocol for post-tPA management [1, 3]

| |
|---|
| Monitor closely and if severe headache, acute hypertension, nausea, vomiting, or worsening neurological examination occur, discontinue IV tPA, if still running; and obtain emergency head CT |
| Avoid nasogastric tube, urinary catheter, and arterial lines for 24 hours, if the patient can be managed without these |
| Maintain BP below SBP 180 and DBP 105 (see Table 8.4) |
| Obtain follow-up head CT or MRI 24 hours after treatment before starting antiplatelet or anticoagulant therapies |

*IV* intravenous, *CT* computed tomogram, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MRI* magnetic resonance imaging

**Table 8.4** Recommended management of high blood pressure before and after initiation of IV tPA [1, 3]

| |
|---|
| Pretreatment: If SBP >185 or DBP >110 |
| Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time |
| Nicardipine 5 mg/hour, titrate up by 2.5 mg/hour every 5–15 minutes; maximum 15 mg/hour |
| Clevidipine 1–2 mg/hour, titrate up by doubling the dose every 2–5 minutes; maximum 21 mg/hour |
| Or other agents, such as hydralazine, enalaprilat, etc. |
| Posttreatment: If SBP >180 or DBP >105 |
| Labetalol 10 mg IV followed by IV infusion 2–8 mg/minutes |
| Nicardipine, clevidipine, or other agents, as above |
| For DBP >140, consider sodium nitroprusside |

*SBP* systolic blood pressure, *DBP* diastolic blood pressure

**Table 8.5** Classification of hemorrhagic transformation [5]

| |
|---|
| Hemorrhagic infarction |
| HI1 – small petechiae along the margins of the infarct |
| HI2 – confluent petechiae within the infarcted area |
| Parenchymal hemorrhage |
| PH1 – hematoma not exceeding 30% of the infarcted volume with mild mass effect |
| PH2 – dense hematoma exceeding 30% of the infarcted volume with significant mass effect |

ing from scattered petechial hemorrhage with no mass effect to hematoma causing significant mass effect [5]. This nomenclature has come into common use (Table 8.5). Approximately 3–6% of patients treated with IV tPA will develop clinically significant hemorrhage [4–6, 8, 9, 11–15, 22]. Patients should be examined carefully to document neurologic function, including the National Institutes of Health Stroke Scale (NIHSS) before treatment and periodically for 24 hours (Table 8.3). Any deterioration in the examination (i.e., any increase in the NIHSS) should prompt discontinuation of IV tPA if it is still infusing and urgent imaging with non-contrast head computed tomography (CT) to look for cerebral hemorrhage. The serum half-life of tPA is very brief (<5 minutes), but tPA binds to thrombus and exerts its biological effects over many hours, hence the recommendation to avoid antiplatelet agents and anticoagulants for 24 hours. The risk of tPA-related hemorrhage correlates with depletion of plasma fibrinogen [21]. Patients with symptomatic

**Table 8.6** Protocol for treatment of symptomatic IV tPA-related hemorrhage [3]

| |
|---|
| 1. Discontinue IV tPA infusion |
| 2. Obtain STAT CBC, PT (INR), aPTT, fibrinogen, type, and cross-match |
| 3. Obtain urgent non-contrast head CT |
| 4. Give cryoprecipitate (includes factor VIII) 10 U IV over 10–30 minutes; repeat if fibrinogen <200 mg/dl |
| 5. Give tranexamic acid 1000 mg IV over 10 minutes or ε-aminocaproic acid 4–5 g over 1 hour, and then 1 g IV q 4–8 hours until bleeding is controlled |
| 6. Consult neurosurgery |
| 7. Support BP, ICP, CPP, and MAP, and control temperature and glucose |

*CBC* complete blood count, *PT* prothrombin time, *INR* international normalized ratio, *aPTT* activated partial thromboplastin time, *CT* computed tomography, *IV* intravenous, *BP* blood pressure, *ICP* intracranial pressure, *CPP* cerebral perfusion pressure, *MAP* mean arterial pressure

hemorrhage should undergo STAT laboratory testing, including fibrinogen, complete blood count (CBC) (which includes platelets), INR, and aPTT, and they should be treated with either cryoprecipitate or fibrinogen concentrate (RiaSTAP$^{T}$) until fibrinogen has been normalized. Elevated INR should be treated with prothrombin complex concentrate (PCC) or fresh frozen plasma (FFP), and thrombocytopenia should be treated with platelet transfusions. In the case of severe or uncontrolled bleeding, ε-aminocaproic acid or tranexamic acid, both agents that inhibit the conversion of plasminogen to plasmin, may be given to arrest hemorrhage. Once bleeding has been stopped, the patient should be managed by prioritizing efforts to avoid further hemorrhage and limit mass effect. Neurosurgical decompression may be offered in some cases after correction of measurable disorders of coagulation and, ideally, after a delay of at least 24 hours. The American Heart Association (AHA)/American Stroke Association (ASA) guidelines for the treatment of tPA-related hemorrhage are summarized in Table 8.6.

## Endovascular Thrombectomy for Acute Ischemic Stroke

Although the introduction of IV thrombolysis represented a breakthrough in the treatment of acute ischemic stroke, many patients, especially those with occlusion of large proximal arteries (e.g., internal carotid artery (ICA), middle cerebral artery (MCA) stem (M1), basilar artery), will not benefit from this therapy.

Aims of treatment with intra-arterial tPA are thus to optimize the state of cerebral blood flow (CBF) and to minimize the risk of recurrent thrombosis and hemorrhagic transformation. In patients who have a large stroke despite thrombolytic therapy, goals include minimizing the detrimental

effects of cerebral edema and mass effect. The Prolyse in Acute Cerebral Thromboembolism (PROACT) trial showed clinical benefit from endovascular administration of a thrombolytic agent, pro-urokinase, in patients with M1 occlusions [23]. However, the procedure studied in the PROACT II trial did not include mechanical disruption of the occluding thrombus, and, as technology advanced to include clot disruption and extraction with wires, snares, and suction devices, the intra-arterial administration of thrombolytics was never replicated in a large-scale trial. Along with the development of improved techniques for clot extraction, it has remained a goal of early stroke therapy to define patient eligibility not by time from stroke onset alone but based more directly on the state of the brain as defined by imaging of the infarct core and the penumbral territory at risk. The first large-scale trials to test the hypothesis that patients with large strokes will benefit from endovascular clot extraction with or without adjunctive intra-arterial thrombolysis were disappointingly negative. On March 7, 2013, three studies were published in *The New England Journal of Medicine*, all having failed to prove benefit [24–26]. With the perspective of the successful endovascular thrombectomy trials published in 2015, these failures likely had many explanations, including lack of angiographic proof of the target occlusive lesion leading to the enrollment of many patients without it, selective enrollment by many sites, and the lack of the availability of stent retriever devices, which later proved to be most efficacious, until the very end of enrollment in these 2013 trials. Subsequent trials addressed these shortcomings of design and technology, and in early 2015 and 2016, seven trials were published showing a large and consistent clinical benefit for endovascular clot retraction [27–33]. (Fig. 8.2). In particular, these studies established a clear benefit of endovascular thrombectomy with stent retriever devices in patients with proximal anterior circulation arterial occlusions (ICA, M1, M2) when treated within approximately 6 hours of symptom onset. The AHA/ASA updated their guidelines for the treatment of ischemic stroke incorporating this new evidence [3] (Table 8.7).

The 2015 studies left several open questions. These investigations did not include patients with distal MCA, anterior cerebral artery (ACA), or posterior circulation occlusions. Most practitioners and guidelines agree that it is most reasonable to extrapolate these results to include selected patients with occlusions of the M2 segment, ACA, basilar artery, vertebral arteries, and proximal posterior cerebral arteries (PCA), and that thrombectomy might be extended to some patients with pretreatment disability, large pretreatment infarcts, and milder but disabling strokes [3] (Table 8.7). In 2018, two studies were published extending the window of opportunity for treatment to 16–24 hours for patients with a small infarct core by imaging and evidence of significant tissue at risk, either by mismatch of a large clinical deficit to a small core or by mismatch of a perfusion imaging deficit to a small core [34, 35] (Fig. 8.2). The revised 2018 AHA/ASA guidelines for the management of acute ischemic stroke incorporate these new data (Table 8.7). Practitioners will surely also extend these indications to some patients who do not fall strictly within the studied populations.

Careful management of patients after intravenous thrombolysis or endovascular thrombectomy is essential to maintain the benefits of successful recanalization and to identify and treat complications of both the therapies and infarctions. Almost all patients will have some cerebral infarction after these therapies. Some patients will not achieve recanalization. Those who do may have small or large infarcts,

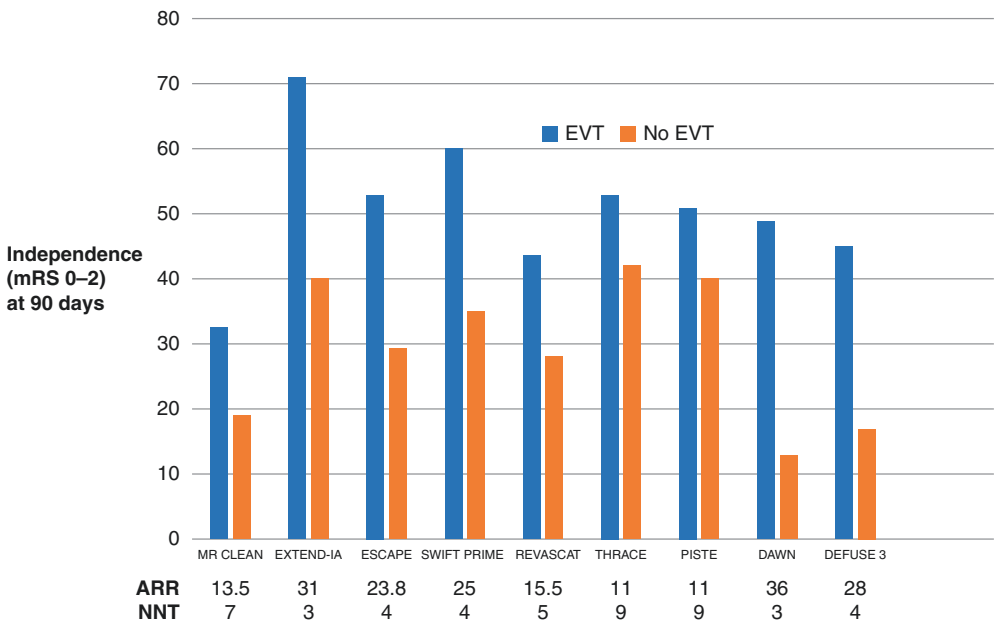


**Fig. 8.2** Independence at 90 days after endovascular thrombectomy for acute ischemic stroke. Notes: mRS modified Rankin Scale, ARR absolute risk reduction, NNT number needed to treat to achieve one additional good outcome

**Table 8.7** Guidelines for the treatment of acute ischemic stroke with endovascular thrombectomy [3]

| Patients should receive mechanical thrombectomy with a stent retriever device if: |
|---|
| Strong recommendation (I, A)[a] |
| 1. Pre-stroke mRS is 0–1 |
| 2. Causative occlusion is demonstrated in the internal carotid or MCA stem (M1) |
| 3. Age ≥18 years |
| 4. NIHSS ≥6 |
| 5. ASPECTS ≥6 |
| 6. Treatment can be initiated (groin puncture) within 6 hours of symptom onset |
| Less certain recommendations |
| 7. M2 and M3 occlusions (IIb, B-R) |
| 8. ACA, VA, BA, and PCA occlusions (IIb, C-EO) |
| 9. Pre-stroke mRS >1 (IIb, B-R) |
| 10. ASPECTS <6 (IIb, B-R) |
| 11. NIHSS <6 (IIb-B-R) |
| 16- to 24-hour window |
| 12. Selected patients with onset within 6–16 hours with LVO in the anterior circulation who meet DAWN and DEFUSE 3 eligibility criteria (I, A) |
| 13. Selected patients with onset within 6–24 hours with LVO in the anterior circulation who meet DAWN eligibility criteria (IIa, B-R) |

*MCA* middle cerebral artery, *M1, M2, M3* first, second, and third segments of MCA, respectively, *ACA* anterior cerebral artery, *VA* vertebral artery, *BA* basilar artery, *PCA* posterior cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *ASPECTS* Alberta Stroke Program Early CT Score, *mRS* modified Rankin Scale, *LVO* large vessel occlusion, *DAWN* DWI or CTP assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with trevo trial, *DEFUSE 3* endovascular therapy following imaging evaluation for ischemic stroke trial

[a]I, IIa, and IIb refer to strength of recommendations: strong, moderate, and weak, respectively; A, B-R, C-EO refer to level of evidence: A = high-quality (more than 1 randomized controlled trial), B-R (randomized) = moderate-quality (1 randomized controlled trial), C-EO = expert opinion in the absence of strong evidence

depending on the site of vascular occlusion, the duration of occlusion before recanalization, and the status of collateral vessels. Initial concerns are to maintain vascular patency and to minimize the risk of hemorrhagic transformation. For post-thrombectomy patients who have received IV tPA, we generally follow guidelines for post-thrombolysis management (Tables 8.3 and 8.4). For those who have not received IV tPA, we typically begin antiplatelet agents immediately to lower the risk of local reocclusion at the site of procedure-related endothelial trauma and retained thrombus. We allow moderate systolic BP elevation to the 160–180 range to promote perfusion but limit risk of reperfusion hemorrhage. Patients should be monitored closely with serial neurologic examinations for the first 24 hours after treatment. Those who deteriorate should undergo urgent head CT to look for hemorrhage or extension of infarction. Other potential complications after thrombectomy include reocclusion of a recanalized artery, arterial dissection, and groin site complications, including groin site hematoma and femoral artery dissection and pseudoaneurysm formation.

After angiography for acute stroke, it is common to see some extravasation of radiopaque contrast material into the irrigation field of the treated vessels. Such extravasation creates hyperdense areas of contrast staining on non-contrast CT that may be difficult to distinguish from acute hemorrhage, or such extravasation may be mixed with hemorrhage. Hounsfield unit (HU) measurements do not reliably clarify the cause of the hyperdensities, since low values consistent with blood (<90 HU) may be due to contrast that is not densely distributed in tissue, and high values (>90 HU) do indicate the presence of contrast but do not eliminate the possibility that contrast is mixed with blood. Susceptibility or gradient-echo magnetic resonance imaging (MRI) sequences might be expected to make the distinction, but the blooming artifact of small amounts of blood makes interpretation problematic in practice. Such extravasation does not seem to indicate increased risk of hemorrhage, although it does correlate with prior hemorrhage and infarct [36, 37]. Yet, not all areas of post-thrombectomy contrast staining are destined to progress to infarction (Fig. 8.3). If post-procedural hyperdensities are seen on CT without severe mass effect, a repeat CT in 6–12 hours will usually clarify the cause. The groin puncture site should be inspected for evidence of hemorrhage and palpated for evidence of a pseudoaneurysm, and distal pulses and capillary filling should be documented. A pseudoaneurysm may be found as a pulsatile mass near the puncture site or may be demonstrated by ultrasound. If found, consultation with a vascular surgeon should be obtained for arterial repair.

## Cerebral and Cerebellar Edema and Swelling After Infarction

Some patients will develop malignant edema during the first hours and days after large, usually MCA territory, infarcts. Cytotoxic edema resulting from infarction and the resultant brain swelling is the main cause of early death from ischemic strokes, and it threatens to extend the volume of stroke in those who survive. Such edema results from lysis of necrotic cells and the breakdown of the blood-brain barrier in areas of ischemic injury, although the reasons that one patient develops severe edema and another does not are not clear. A non-selective cation channel, the $NC_{Ca\text{-}ATP}$ channel, in neurons, astrocytes, and capillaries is opened by the adenosine triphosphate (ATP) depletion caused by stroke and trauma and promotes the development of cytotoxic edema. This channel is regulated by the sulfonylurea receptor 1 (SUR1) providing a possible therapeutic target [38].

Current therapy for edema depends on hyperosmolar agents and surgical decompression. Mannitol and/or

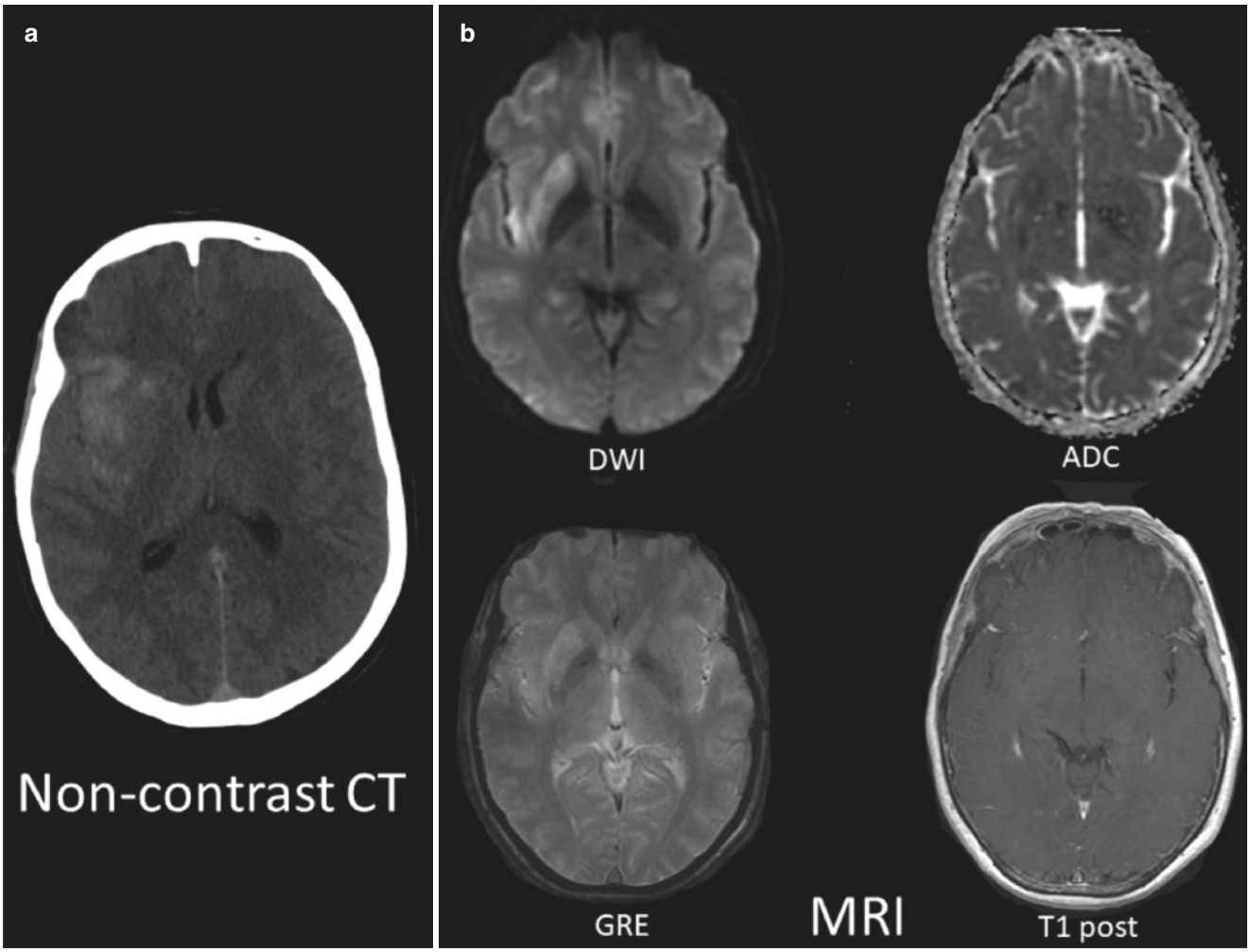


**Fig. 8.3** A 58-year-old woman presented with left hemiparesis and neglect and was found to have right M1 occlusion that was treated with endovascular thrombectomy 14 hours after she had been last seen well. Two stent-retriever passes achieved TICI 2b reperfusion. (**a**) Non-contrast head CT completed approximately 1 hour after recanalization shows contrast staining in the right frontal, temporal, and insular cortices. (**b**) MRI performed 3 ½ hours later demonstrates evidence of acute infarct in the right putamen on DWI and ADC sequences but no infarct in the areas of cortical contrast staining. GRE sequence shows no evidence of hemorrhage. T1 sequence after gadolinium administration reveals no enhancement in the same area. She had a near-full functional recovery with only minimal left facial weakness and subtle left pronator drift at discharge. TICI thrombolysis in cerebral infarction scale, DWI diffusion-weighted image, ADC apparent diffusion coefficient, GRE gradient echo

hypertonic saline may be given to reduce edema. We prefer the use of 23% saline to rapidly achieve a high osmotic gradient between the intravascular and intracranial space for best effect. Slow infusion of 3% saline does not clearly achieve an adequate gradient given that the injured blood-brain barrier does not effectively exclude the passage of sodium, and, even in the presence of an intact blood-brain barrier, the exclusion of mannitol and sodium from crossing the blood-brain barrier is time-limited. Clinical trials are now underway to test the effect of the SUR1-inhibitor glibenclamide on cerebral edema after large strokes [39, 40].

The permanent harm due to cerebral edema results from the swelling of the brain in the enclosed cranial space causing elevated intracranial pressure (ICP) with compromise of cerebral perfusion and herniation of brain tissue. These consequences are most effectively countered by decompressive hemicraniectomy. Several studies have convincingly shown that early hemicraniectomy decreases mortality and improves outcomes in patients 60 years of age or younger [41–44]. In older patients, hemicraniectomy reduces mortality without benefit in functional recovery in survivors [45].

Because most patients who survive after hemicraniectomy will have major neurologic deficits, and because the benefits are lost if surgery is delayed until after severe swelling and herniation have developed, it is important that those caring for such patients develop protocols for the proper consideration and application of this life-saving surgery. The goal is to define clinical features that will allow the prediction of

malignant edema within the first 24–48 hours and to precede any decision to act with a frank and open conversation with the patient's caretakers so that they can make an informed decision on the desirability of survival given the expected neurological deficits and disability. For this purpose, the STATE criteria, though not definitive, offer some direction, taking into consideration the degree of neurologic dysfunction on presentation (NIHSS) including level of consciousness, size of the infarct by CT or MRI, the patient's age, time since stroke onset, and, very importantly, expectations of the patient's health care proxy [46] (Table 8.8).

The issue of infarction-related cytotoxic edema in a closed space presents itself most urgently in the setting of large cerebellar strokes. The posterior fossa offers less space than the supratentorial compartment for swelling. Swelling after a cerebellar stroke can block the IVth ventricle and cerebral aqueduct causing acute hydrocephalus, and it can cause a rapid increase in pressure and compression of the vasculature and brainstem parenchyma, leading ultimately to secondary infarction of the brainstem. Progression of such edema will often lead to irreversible coma and death. The potential for such life-threatening complications must be considered in all patients with acute cerebellar infarcts. The larger the infarct, the more likely it is that threatening swelling will develop. Because the posterior inferior cerebellar arteries (PICA) supply the largest portion of the cerebellar hemispheres, most ominous lesions include infarctions in these territories. There is evidence that patients with cerebellar infarcts affecting 1/4 to 1/3 of the cerebellar volume with Glasgow Coma Scale (GCS) ≥9 and without deterioration of GCS before surgery benefit from suboccipital decompressive craniectomy (SDC), including achieving better functional outcomes and decreased mortality [47–50]. All patients with moderate-sized or large acute infarcts in the cerebellum should be closely monitored for such complications so that corrective interventions can be applied rapidly when needed and before progression to clinical deterioration. We monitor all such patients in the NCCU during the first several days after cerebellar infarction, and we engage our neurosurgical colleagues in anticipation of a potentially needed surgical decompression. All such patients should receive central venous access. Early use of hyperosmolar therapy with 23% saline and/or mannitol may prevent progression and forestall the need for surgery in some patients. Patients will often be fully alert on presentation and then deteriorate rapidly with the progression of edema and the development of obstructive hydrocephalus or brainstem compression. The first clinical signs of such deterioration are impaired upgaze and depression in level of consciousness. In patients with infarction of >1/4 of the cerebellar volume, or those with early compression of the IVth ventricle, SDC with or without external ventricular drain (EVD) should be performed before such clinical deterioration. If an EVD without SDC is placed in a patient with cerebellar infarction, continued close surveillance is critical, since many such patients will continue to progress due to direct brainstem compression or upward transtentorial herniation into the decompressed supratentorial compartment, and these patients will need urgent SDC. After surgery, patients are managed with hyperosmolar therapies as needed until swelling has subsided and catheters and EVDs can be safely removed.

**Table 8.8** STATE criteria for hemicraniectomy for malignant edema in patients with MCA stroke [46]

| | |
|---|---|
| Score | NIHSS item 1a ≥ 1 and NIHSS >15 |
| Time | Within 45 hours of onset |
| Age | 18–60 years old |
| Territory | MRI: DWI infarct volume >145 $cm^3$; CT: Infarct ≥50% of MCA territory |
| Expectations | Understanding that surgery improves survival, but the patient will probably still have major disability |

*MCA* middle cerebral artery, *NIHSS* National Institutes of Health Stroke Scale, *MRI* magnetic resonance imaging, *DWI* diffusion-weighted imaging, *CT* computed tomography

## Symptomatic Cervical and Intracranial Arterial Stenosis and Occlusion

Patients with severe vascular stenoses or occlusions, either intracranially or in the cervical internal or common carotid artery, may present with acute ischemic symptoms that prove to be reversible, either spontaneously or with augmentation of the BP to increase CBF.

The normal cerebral circulation has parallel channels that, if occlusions or stenoses are proximal to them, can provide immediate pathways of collateral flow. With occlusion or stenosis of the carotid artery below the origin of the ophthalmic artery, these channels include (1) the ophthalmic artery, which can reverse to provide flow from the external carotid to the distal ICA; (2) the posterior communicating artery, which can provide flow from the PCA to the distal ICA; and (3) the anterior communicating artery, which can provide crossing flow from the opposite carotid and ACA. Contrariwise, if basilar flow is blocked, an open posterior communicating artery can supply the distal basilar artery and its branches with flow from the anterior circulation. When such proximal channels are developmentally small or occluded by disease, or when blockage of flow is distal to these collateral connections, then collateral flow may be supplied by leptomeningeal branches filling from adjacent open vessels. For example, after occlusion of the MCA stem, leptomeningeal branches of the open anterior and posterior cerebral arteries may provide enough flow to penetrate deeply into the distal MCA branches. The effectiveness of such collateral flow to avert acute infarction depends on the size of the native collateral arteries and the CBF within them. CBF depends on

the equation for flow dynamics: CBF = CPP/CVR = MAP – CVP/CVR (where CPP = cerebral perfusion pressure, MAP = mean arterial pressure, CVP = cerebral venous pressure, and CVR = cerebral vascular resistance) (CVP, though not directly measured, should be nearly the same as the ICP when ICP is normal.). As this relationship shows, CBF varies directly with MAP. Hence, by driving up the MAP, we might augment flow from collateral channels allowing it to reach penumbral tissue at risk of infarction.

In addition to these standing collateral vessels, extended periods of oligemia will induce the growth of new vessels. This process is most important with longstanding stenoses, such as in moyamoya syndrome; however, some new vessel formation begins within days of oligemia onset [51, 52].

Although controlled studies have not shown the benefit of induced hypertension in large populations, clinical observations confirm its safety and benefit in many cases [53, 54]. Serving as his or her own control, a patient may demonstrate resolution of deficits with higher MAP and return of these deficits with lower MAP. When this relationship is reproducible in a patient with an appropriate vascular lesion, then the effect of augmenting collateral flow by induced hypertension is convincing. Such collateral flow can be demonstrated with various forms of flow and perfusion imaging. For example, transcranial Doppler (TCD) can show the directional change in the ophthalmic artery that accompanies ICA occlusion with external carotid artery/ophthalmic collateralization or in the ipsilateral ACA A1 segment that accompanies cross-filling from the anterior communicating artery. Also, vasoreactivity TCD studies can show the degree of compensatory vasodilation in potentially stressed tissues by showing a loss of capacity to dilate further with hypercarbia, and single photon emission computed tomography (SPECT) scans can similarly show lack of flow augmentation from acetazolamide (a vasodilatory stimulus) in vessels that have already reached their maximal caliber. CT and MR perfusion imaging can also be employed to show the extent of areas of delayed and poor blood flow. All of these modalities can be employed to show collateralization and flow augmentation that may be dependent on BP.

To capitalize on potential collateral flow in the setting of acute ischemic stroke, we hold antihypertensive agents (except beta-blockers in patients with coronary artery disease and sometimes in those with atrial fibrillation) to allow the systolic (and mean) BP to run high during the acute phase of stroke. Typically, the BP spontaneously rises acutely and remains high for several days after stroke onset before it begins to fall toward its baseline. We allow this autoregulatory rise to go untreated, unless hypertensive complications occur (heart failure, coronary ischemia, hypertensive encephalopathy, acute renal failure, or in cases of aortic dissection) or unless the protocol for post-IV tPA care demands the compromise of lowering to systolic BP <180. Acute ischemic stroke management guidelines typically recommend no treatment of BP unless it rises to 200–220/110–120, assuming that higher pressures will be no more effective above that high level and given concern for excessive elevations [1].

When a patient presents with stenosis or occlusion and a functional deficit larger than would be expected based on the volume and location of demonstrable infarction, then we proceed to a trial of induced hypertension. We place the head of bed flat; if tolerated, give IV fluids to optimize volume and BP and perfusion; and then using phenylephrine (or norepinephrine), we push the BP up in stages to a maximum of approximately systolic BP 200 or MAP 130 to see if function recovers at the higher BP. If it does not after a sustained interval of induced hypertension, then we consider that a failed trial and allow BP to autoregulate. However, if induced hypertension successfully improves function, then we will allow the BP to fall under close observation. If the symptoms re-emerge, then we will consider that a successful trial, and we will maintain BP augmentation at the lowest level needed for sustained maximal function.

In the best of situations, the endpoint of such induced hypertension will be spontaneous recanalization, which will allow the patient to tolerate normal BP. However, early recanalization is uncommon when acute recanalization has not been achieved by thrombolytic agents or endovascular thrombectomy. Commonly, patients who improve with induced hypertension will adapt to the occlusion over a period of days allowing withdrawal of vasopressors without functional deterioration. In patients whose deficits re-emerge when BP is allowed to autoregulate after a prolonged period of induced hypertension, we are left to consider surgical revascularization. Although we do recommend surgical revascularization in highly selected cases without satisfactory alternatives, the literature has not shown benefits of such procedures in controlled trials. So, before we discuss our approach, let us review the major trials.

Surgical bypass for symptomatic atherosclerotic disease has been studied in two large clinical trials. In 1985, the Extracranial-to-Intracranial (EC-IC) Bypass Study failed to show a benefit of EC-IC bypass [55]. This procedure was done infrequently after this study's publication. However, the techniques were improved, and an updated trial, the Carotid Occlusion Surgery Study (COSS), was completed in 2011 [56]. This trial, too, failed to show benefit from EC-IC bypass, arguing against its use in the manner built into the trial design. Endovascular angioplasty and stenting has also been studied in two clinical trials. Stenting of symptomatic intracranial stenoses was studied in the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial; this trial was stopped early due to poorer outcomes in the stented patients [57]. In fact, the patients in the medically treated group fared better than had been anticipated based on preliminary work.

A second similar trial, the Vitesse Intracranial Stent Study for Ischemic Stroke Therapy (VISSIT), also found poorer outcomes in stented patients [58].

Following these results, we also recommend optimal medical management for patients like those in the trials. However, in all of these trials, the enrolled subjects included mostly those who were stable ambulatory patients off vasopressors without induced hypertension. That is, patients who had proven themselves possessed of adequate collateral circulation to achieve that outcome. Left with a small subset of patients who are in the early phase of stroke or transient ischemic attack (TIA) and who cannot be weaned from induced hypertension without deterioration, we feel that favorable experience justifies surgical revascularization where proper neurovascular surgical expertise is available. This is usually done by grafting the superficial temporal artery to an M2 (insular) or M3 (opercular) branch of the MCA. Though not tested, by extension, other grafting procedures to the proximal PCA or by using venous grafts, can also be done based on surgical need. With this highly selective approach, we have had good outcomes with surgical revascularization of patients with unstable intracranial and cervical artery occlusions. We do not recommend stenting of intracranial stenoses, but rather treating such patients with dual antiplatelet therapy and intensive risk factor management as recommended by the relatively good outcome in the medical arm of the SAMMPRIS trial.

## Other Critical Care Issues

Any patient with acute stroke or high risk for acute stroke due to hemodynamic lability will need close monitoring in the NCCU during this period of instability. Patients with acute lacunar stroke syndromes may be unstable initially, sometimes with dramatically fluctuating symptoms alternating between sudden severe syndromes, such as hemiplegia and dysarthria, and then abrupt recovery of function. There is no established treatment for such small vessel strokes. However, rather than allowing such "stuttering lacunes" to recur and ultimately progress with only antiplatelet therapy given lack of proven treatments, we recommend optimization of BP and flattening the head of the bed, then a trial of induced hypertension, and, when these measures fail, heparinization. Anecdotal experience suggests that these measures may terminate fluctuations in some patients. Having stabilized the situation, we then move to validated therapies for long-term secondary prevention.

Patients with infectious endocarditis do not typically require NCCU care; however, monitoring in either a neurology or cardiac care intensive care unit is advised when patients present with neurologic complications, including hemorrhagic infarction, subarachnoid hemorrhage, recurrent cardio-embolism, or cardiac complications, such as valvular decompensation, heart failure, or conduction block, or systemic complications such as sepsis. Because neurologic complications are often the initial and most critical early signs of endocarditis, neurointensivists must be prepared to care for these patients in consultation with their cardiology, cardiac surgery, and infectious disease colleagues.

## References


1. Jauch EC, Saver JL, Adams HP, American Heart Association Stroke Council on Cardiovascular Nursing CoPVD, and Council on Clinical Cardiology, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44:870–947.
2. Demaerschalk BM, Kleindorfer DO, Adeoye OM, American Heart Association Stroke Council and Council on Epidemiology and Prevention, et al. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2016;47:581–641.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2018;2018:49.
4. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med. 1995;333:1581–7.
5. Hacke W, Kaste M, Fieschi C, ECASS Study Group, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). JAMA. 1995;274:1017–25.
6. Hacke W, Kaste M, Fieschi C, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). Lancet. 1998;352:1245–51.
7. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S, The ATLANTIS, ECASS, and NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. Lancet. 2004;363:768–74.
8. Clark WM. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. JAMA. 1999;282:2019–26.
9. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (Alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Stroke. 2000;31:811–6.
10. Davis SM, Donnan GA, Parsons MW, EPITHET Investigators, et al. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET): a placebo-controlled randomised trial. Lancet Neurol. 2008;7:299–309.
11. Hacke W, Kaste M, Bluhmki E, EPITHET Investigators, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–29.
12. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Atteplase to Reverse Stroke (STARS) Study. JAMA. 2000;283:1145–50.

13. Hill MD, Buchan AM. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. CMAJ. 2005;172:1307–12.
14. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. Lancet. 2007;369:275–82.
15. The IST-3 Collaborative Group. 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(9834):2352–63.
16. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012;366:1099–107.
17. Logallo N, Kvistad CE, Nacu A, et al. The Norwegian tenecteplase stroke trial (NOR-TEST): randomised controlled trial of tenecteplase vs. alteplase in acute ischaemic stroke. BMC Neurol. 2014;14:106.
18. Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase veraus teneteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol. 2015;14:368–76.
19. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017;16:781–8.
20. Anderson CS. NOR-TEST-ing tenecteplase in acute ischaemic stroke. Lancet Neurol. 2017;16:762–3.
21. Matosevic B, Knoflach M, Werner P, et al. Fibrinogen degradation coagulopathy and bleeding complications after stroke thrombolysis. Neurology. 2013;80:1216–24.
22. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008;359:1317–29.
23. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant prourokinase by direct arterial delivery in acute middle cerebral artery stroke. Stroke. 1998;29:4–11.
24. Broderick JP, Palesch YY, Demchuk AM, et al. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. N Engl J Med. 2013;368:893–903.
25. Kidwell CS, Jahan R, Gornbein J, et al. A trial of imaging selection and endovascular treatment for ischemic stroke. N Engl J Med. 2013;368:914–23.
26. Ciccone A, Valvassori L, Nichelatti M, et al. Endovascular treatment for acute ischemic stroke. N Engl J Med. 2013;368:904–13.
27. Berkhemer OA, Fransen PS, Beumer D, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372:11–20.
28. Goyal M, Demchuk AM, Menon BK, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. N Engl J Med. 2015;372:1019–30.
29. Campbell BC, Mitchell PJ, Kleinig TJ, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. N Engl J Med. 2015;372:1009–18.
30. Saver JL, Goyal M, Bonafe A, et al. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. N Engl J Med. 2015;372:2285–95.
31. Jovin TG, Chamorro A, Cobo E, et al. Thrombectomy within 8 hours after symptom onset in ischemic stroke. N Engl J Med. 2015;372:2296–306.
32. Bracard S, Ducrocq X, Mas JL, et al. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. Lancet Neurol. 2016;15:1138–47.
33. Muir KW, Ford GA, Messow CM, et al. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. J Neurol Neurosurg Psychiatry. 2017;88:38–44.
34. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. N Engl J Med. 2018;378:11–21.
35. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. N Engl J Med. 2018;378:708–18.
36. Nikoubashman O, Reich A, Gindullis M, et al. Clinical significance of post-interventional cerebral hyperdensities after endovascular mechanical thrombectomy in acute ischaemic stroke. Neuroradiology. 2014;56:41–50.
37. Parrilla G, Garcia-Villalba B, Espinosa de Rueda M, et al. Hemorrhage/contrast staining areas after mechanical intra-arterial thrombectomy in acute ischemic stroke: imaging findings and clinical significance. AJNR Am J Neuroradiol. 2012;33(9):1791–6. https://doi.org/10.3174/ajnr.A3044:1-6.
38. Simard JM, Chen M, Tarasov KV, et al. Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. Nat Med. 2006;12:433–40.
39. Simard JM, Yurovsky V, Tsymbalyuk N, Melnichenko L, Ivanova S, Gerzanich V. Protective effect of delayed treatment with low-dose glibenclamide in three models of ischemic stroke. Stroke. 2009;40:604–9.
40. Sheth KN, Taylor Kimberly W, Elm JJ, et al. Exploratory analysis of glyburide as a novel therapy for preventing brain swelling. Neurocrit Care. 2014;21:43–51.
41. Jüttler E, Schwab S, Schmiedek P, et al. Decompressive surgery for the treatment of malignant infarction of the middle cerebral artery (DESTINY): a randomized, controlled trial. Stroke. 2007;38:2518–25.
42. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6:215–22.
43. Hofmeijer J, Kappelle LJ, Algra A, et al. Surgical decompression for space-occupying cerebral infarction (the hemicraniectomy after middle cerebral artery infarction with life-threatening edema trial [HAMLET]): a multicenre, open, randomised trial. Lancet Neurol. 2009;8:326–33.
44. Vahedi K, Vicaut E, Mateo J, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL trial). Stroke. 2007;38:2506–17.
45. Juttler E, Unterberg A, Woitzik J, et al. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. N Engl J Med. 2014;370:1091–100.
46. Agarwalla PK, Stapleton CJ, Ogilvy CS. Craniectomy in acute ischemic stroke. Neurosurgery. 2014;74(Suppl 1):S151–62.
47. Kim MJ, Park SK, Song J, et al. Preventive suboccipital decompressive craniectomy for cerebellar infarction: a retrospective-matched case-control study. Stroke. 2016;47:2565–73.
48. Pfefferkorn T, Eppinger U, Linn J, et al. Long-term outcome after suboccipital decompressive craniectomy for malignant cerebellar infarction. Stroke. 2009;40:3045–50.
49. Ayling OGS, Alotaibi NM, Wang JZ, et al. Suboccipital decompressive craniectomy for cerebellar infarction: a systematic review and meta-analysis. World Neurosurg. 2018;110:450–9.. e455
50. Wijdicks EF, Sheth KN, Carter BS, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:1222–38.

51. Liman TG, Endres M. New vessels after stroke: postischemic neovascularization and regeneration. Cerebrovasc Dis. 2012;33:492–9.
52. Marti HJH, Bernaudin M, Bellail A, et al. Hypoxia-induced vascular endothelial growth factor expression precedes neovascularization after cerebral ischemia. Am J Pathol. 2000;156:965–76.
53. Rordorf G, Koroshetz WJ, Ezzeddine MA, Segal AZ, Buonanno FS. A pilot study of drug-induced hypertension for treatment of acute stroke. Neurology. 2001;56:1210–3.
54. Koenig MA, Geocadin RG, de Grouchy M, et al. Safety of induced hypertension therapy in patients with acute ischemic stroke. Neurocrit Care. 2006;4:3–7.
55. The EC-IC Bypass Study Group. Failure of extracranial-intracranial arterial bypass to reduce the risk of ischemic stroke: results of an international randomized trial. N Engl J Med. 1985;313:1191–200.
56. Powers WJ, Clarke WR, Grubb RL, et al. Extracranial-intracranial bypass surgery for stroke prevention in hemodynamic cerebral ischemia: the carotid occlusion surgery study randomized trial. JAMA. 2011;306:1983–92.
57. Derdeyn CP, Chimowitz MI, Lynn MJ, et al. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. Lancet. 2014;383:333–41.
58. Zaidat OO, Fitzsimmons BF, Woodward BK, et al. Effect of a balloon-expandable intracranial stent vs medical therapy on risk of stroke in patients with symptomatic intracranial stenosis: the VISSIT randomized clinical trial. JAMA. 2015;313:1240–8.