Stroke

AHA/ASA GUIDELINE

# 2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association

*Endorsed by the American Association of Neurological Surgeons/Congress of Neurological Surgeons, Neurocritical Care Society, the Society for Academic Emergency Medicine, the Society of NeuroInterventional Surgery, and the Society of Vascular and Interventional Neurology.*

*The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.*


## Guideline Writing Group

Shyam Prabhakaran, MD, MS, FAHA, Chair; Nestor R. Gonzalez, MD, MSCR, FAHA, Co-Vice Chair; Kori S. Zachrison, MD, MSc, FAHA, Co-Vice Chair*; Opeolu Adeoye, MD, MS, FAHA; Anne W. Alexandrov, PhD, AGACNP-BC, ANVP-BC, ASC-BC; Sameer A. Ansari, MD, PhD, FAHA†; Sherita Chapman, MD, FAHA; Alexandra L. Czap, MD; Oana M. Dumitrascu, MD, MSc, FAHA; Koto Ishida, MD, FAHA‡; Ashutosh P. Jadhav, MD, PhD, FAHA§; Brenda Johnson, DNP, MSN, FNP-BC, ANVP, FAHA; Karen C. Johnston, MD, MSc, FAHA; Pooja Khatri, MD, MSc, FAHA; W. Taylor Kimberly, MD, PhD, FAHA; Vivien H. Lee, MD, FAHA; Thabele M. Leslie-Mazwi, MD; Brian Mac Grory, MB BCh BAO, MHSc, MRCP, FAHA; Tracy E. Madsen, MD, MCTR, PhD, FAHA‖; Bijoy Menon, MD; Eva A. Mistry, MBBS, MSCI, FAHA#; Soojin Park, MD, FAHA**; Stephanie Parker, MHA, BSN, RN; Natalia Pérez de la Ossa, MD, PhD; Mathew Reeves, BVSc, PhD, FAHA; Tania Saiz††; Phillip A. Scott, MD, MBA, FAHA; Dana Schwartzberg††; Sunil A. Sheth, MD; Peter B. Sporns, MD, MHBA; Sabrina Times, DHSc, MPH; Stavropoula Tjoumakaris, MD, MBA‡‡; Stacey Q. Wolfe, MD; Shadi Yaghi, MD, FAHA

## Peer Review Committee

Enrique C. Leira, MD, MS, FAHA, Chair; Joseph P. Broderick, MD, FAHA Vice Chair; Antonio Arauz, MD, PhD; Agnieszka Ardelt, MD, PhD, MBA, FAHA; Mona Bahouth, MD, PhD*; Anna Finley Caulfield, MD**; Colin P. Derdeyn, MD, FAHA; Layne Dylla, MD, PhD‖; Michael Frankel, MD; Heather J. Fullerton, MD, MAS; Waldo R. Guerrero, MD§; Edward C. Jauch, MD, MS, MBA, FAHA; Kimberly P. Kicielinski, MD, MSPH; Yvonne Labram, PharmD, BCPS††, Patrick Lyden, MD, FAHA; Elisabeth B. Marsh, MD, FAHA; William J. Meurer, MD; J. Mocco, MD, MS, FAHA; Aditya Pandey, MD‡‡; Alejandro A. Rabinstein, MD, FAHA; Karen Rapp, RN, BSN; Christopher T. Richards, MD, MS; Marcelo Rocha, MD, PhD; Regina Royan, MD, MPH; Edgar A. Samaniego, MD, MS; Navdeep S. Sangha, MD‡; Clemens Schirmer, MD, PhD, FAHA†; Alexis N. Simpkins, MD, PhD, MS, FAHA; Christopher Streib, MD, MS; David Tirschwell, MD, MSc, FAHA; Elizabeth Zink, PhD, RN






*AHA Stroke Council Scientific Statement Oversight Committee Liaison. †Society of NeuroInterventional Surgery Representative. ‡American Academy of Neurology Representative. §Society of Vascular and Interventional Neurology Representative. ‖Society for Academic Emergency Medicine Representative. #Stroke Performance Measures Oversight Committee liaison. **Neurocritical Care Society Representative. ††Patient Representative. ‡‡American Association of Neurological Surgeons/Congress of Neurological Surgeons Representative.

AHA Stroke Council Scientific Statement Oversight Committee members, see page e•••.

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CLINICAL STATEMENTS AND GUIDELINES

**AIM:** The "2026 Guideline for the Early Management of Patients With AIS" replaces the "2018 Guidelines for the Early Management of Patients With AIS" and the 2019 update to reflect recent advances in evidence. This updated guideline is intended to provide a comprehensive, up-to-date, evidence-based set of recommendations, advising management from prehospital evaluation through acute treatment and early in-hospital management of complications and initiation of early secondary prevention measures. The intended audience includes prehospital care professionals, physicians, allied health professionals, and hospital administrators.

**METHODS:** A search for literature derived from research principally involving human subjects, published in English since the last AIS guideline in 2018 and the 2019 update, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases relevant to this guideline, was conducted between September and December 2024. Additional high impact studies and articles published through March 2025 were added later, where appropriate.

**STRUCTURE:** This guideline represents the most current and comprehensive evidence available in AIS care. Key updates include the incorporation of new evidence related to thrombolytic choice and eligibility, determination of eligibility for endovascular thrombectomy, and management of hyperglycemia and dysphagia; a focused consideration of the pediatric population; and modification of the approach to thrombolysis contraindications. Although this guideline reflects significant advances, it also highlights gaps in knowledge and underscores the urgent need for continued research to further refine and improve treatment strategies.

**Key Words:** AHA Scientific Statements ■ endovascular procedures ■ guideline ■ ischemic stroke ■ stroke ■ thrombolytic therapy

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## TOP TAKE-HOME MESSAGES

1. Mobile stroke units (MSU) enable rapid identification and treatment of thrombolytic-eligible patients with acute ischemic stroke (AIS). Recent studies have highlighted the benefit of MSUs over conventional emergency medical services and, when available, the guideline now includes recommendations related to the implementation of MSUs, based on their safety and benefit.
2. Identification of appropriate transport destination for patients with suspected stroke in the prehospital setting remains challenging. Previous guidelines recommended transport to the nearest thrombolytic-capable facility. Given recent evidence, this guideline endorses consideration of the characteristics of the local system of care and direct transport to the closest endovascular thrombectomy (EVT)-capable hospital in the absence of well-functioning systems with rapid interhospital transfer processes.
3. Intravenous thrombolysis (IVT) is a mainstay of medical management for patients with AIS. Given numerous international trials showing noninferiority and the potential advantages of intravenous tenecteplase compared with alteplase, the new guidelines endorse the use of either alteplase or tenecteplase in the 4.5-hour thrombolytic treatment window. Furthermore, we emphasize rapid thrombolytic treatment in eligible patients with disabling deficits, regardless of National Institutes of Health Stroke Scale (NIHSS) score, within the 4.5-hour window without advanced imaging selection. In addition, the guidelines provide support for extended window thrombolysis for select patients with stroke of unknown onset or 4.5–9 hours from onset using advanced imaging criteria (eg, diffusion weighted imaging-fluid attenuated recovery or perfusion-based mismatch).
4. For patients with non-disabling (eg, isolated sensory syndrome) deficits in the 4.5-hour window, trials have failed to demonstrate benefit of thrombolysis. Dual antiplatelet therapy is preferred and recommended in this population.
5. New studies have examined the role of adjuvant antithrombotic therapy, such as argatroban and eptifibatide, concurrently with IVT. These studies have shown no benefit and, therefore, adjuvant antithrombotic drugs are not recommended to enhance the outcomes from thrombolytic therapy.
6. EVT has been established as a standard treatment for patients with AIS with large vessel occlusion (LVO) based on numerous randomized controlled trials. Recent evidence supports expanding EVT to populations previously considered ineligible. Specifically, several studies indicate that EVT benefits some patients with larger ischemic core strokes as determined by diagnostic imaging.
7. Based on several trials showing improvement in functional outcomes compared with medical management alone, the guidelines also provide a strong recommendation for EVT in patients with basilar artery occlusion presenting within 24 hours of symptom onset and NIHSS score ≥10.
8. For the first time, the guidelines include recommendations for interventional treatment in pediatric patients with AIS. Although much work remains to adapt prehospital and hospital stroke protocols for pediatric patients, expert consensus and recent studies highlight the importance of early stroke recognition in children and support the safety and potential benefit of endovascular interventions in select pediatric patients with AIS. These recommendations serve as a foundation for future recommendations and address the phases of pediatric acute stroke care.
9. Glycemic management in patients with AIS has been updated since the prior guidelines such that intensive glucose control to the range of 80 to 130 mg/dL is not recommended to improve clinical outcome and increases the risk of severe hypoglycemia.
10. Several new trials have assessed the efficacy and safety of blood pressure (BP) lowering after IVT and EVT in adult patients, providing new evidence that more intensive BP reduction does not improve functional outcome after IVT and may result in harm after EVT. Therefore, intensive systolic BP lowering to <140 mm Hg is not recommended even in the setting of complete reperfusion (eg, Thrombolysis In Cerebral Infarction grade 3 flow).

## PREAMBLE

Since 1990, the American Heart Association (AHA) and American Stroke Association (ASA) have translated scientific evidence into clinical practice guidelines with recommendations to improve cerebrovascular health. These guidelines, which are based on systematic methods to evaluate and classify evidence, provide a foundation for

the delivery of quality cerebrovascular care. The AHA and ASA sponsor the development and publication of clinical practice guidelines without commercial support, and members volunteer their time to the writing and review efforts.

Clinical practice guidelines for stroke provide recommendations applicable to patients with or at risk of developing cerebrovascular disease. The focus is on medical practice in the United States, but many aspects are relevant to patients throughout the world. Although it must be acknowledged that guidelines may be used to inform regulatory or payer decisions, the core intent is to improve quality of care and align with patients' interests. Guidelines are intended to define practices meeting the needs of patients in most, but not all, circumstances, and should not replace clinical judgment; furthermore, the recommendations set forth should be considered in the context of individual patient values, preferences, and associated conditions.

The AHA and ASA strive to ensure that guideline writing groups contain requisite expertise and are representative of the broader medical community by selecting experts from a broad array of backgrounds, representing underrepresented populations, intellectual perspectives, geographic regions, and scopes of clinical practice, by inviting organizations and professional societies with related interests and expertise to participate as endorsers. The AHA and ASA have rigorous policies and methods for development of guidelines that limit bias and prevent improper influence. The complete policy on relationships with industry and other entities can be found at https://professional.heart.org/-/media/phd-files/guidelines-and-statements/policies-devolopment/aha-asa-disclosure-rwi-policy-5118.pdf?la=en.

Numerous modifications to the AHA and ASA guidelines have been implemented to make them shorter and to enhance user friendliness. Guidelines are written and presented in a modular knowledge chunk format, in which each chunk includes a table of recommendations, a brief synopsis, recommendation-specific supportive text and, when appropriate, flow diagrams or additional tables. Other modifications to the guidelines include the addition of Knowledge Gaps and Future Research segments in most sections.

*Nerissa Ko, MD, MAS*
*Chair, AHA Stroke Council Scientific Statement Oversight Committee*

## WHAT IS NEW AND OF HIGH IMPACT

This Table highlights selected new and practice-changing recommendations since the last iteration of the guideline and is not a comprehensive list of all updates.

| Section title | 2025 Recommendation |
|---|---|
| **New and impactful pediatric recommendations** | |
| 2.3. Prehospital Assessment and Management | COR 2b. In pediatric patients with suspected stroke transported by ambulance, the usefulness of common adult stroke screening tools is uncertain because they perform poorly for identification of stroke. Newer pediatric stroke screening tools demonstrate good interrater reliability; however, their sensitivity, specificity, and predictive value in the prehospital setting remain to be determined, and their usefulness is unknown. |
| 3.2. Initial, Vascular, and Multimodal Imaging Approaches | COR 2a. In pediatric patients with suspected AIS, emergent brain and vascular imaging with MRI/MRA of the cervical and intracranial vessels is reasonable to identify patients with large vessel occlusion and to differentiate arterial ischemic stroke from hemorrhagic stroke or stroke mimics. |
| 3.2. Initial, Vascular, and Multimodal Imaging Approaches | COR 2a. In pediatric patients with suspected AIS, emergent brain and vascular imaging with CT/CTA of the cervical and intracranial vessels is reasonable if MRI/MRA imaging is not available immediately (within 25 minutes) to identify patients with large vessel occlusion. |
| 4.6.1. Thrombolysis Decision-Making | COR 2b. In pediatric patients aged 28 days to 18 years with confirmed AIS presenting within 4.5 hours of symptom onset and disabling deficits, IVT with alteplase may be considered as it is safe, but efficacy is uncertain. |
| 4.7.5. Endovascular Thrombectomy in Pediatric Patients | COR 2a. In pediatric patients ≥6 years with acute neurological symptoms and ischemic stroke due to LVO and within 6 hours from symptom onset, EVT can be effective if performed by experienced neurointerventionalists to improve functional outcomes. |
| 4.7.5. Endovascular Thrombectomy in Pediatric Patients | COR 2a. In pediatric patients ≥6 years with acute neurological symptoms and ischemic stroke due to LVO, 6 to 24 hours from symptom onset, and with potentially salvageable brain tissue, EVT can be effective to improve functional outcomes. |
| 4.7.5. Endovascular Thrombectomy in Pediatric Patients | COR 2b. In pediatric patients aged 28 days to 6 years with acute neurological symptoms, including first-time seizure and AIS due to LVO, within 24 hours from symptom onset, and with potentially salvageable brain tissue, EVT performed by neurointerventionalists with pediatric experience may be reasonable to improve functional outcomes. |
| **New and impactful general recommendations** | |
| 2.4. EMS Destination Management | COR 3: No Benefit. In areas with well-coordinated SSOC and local hospital(s) proficient in thrombolysis delivery and secondary interhospital transfer, direct transport of patients with suspected LVO to a distant (eg, 45–60 min) TSC compared with transport to a local stroke center does not improve 3-month clinical outcomes. |
| 2.4. EMS Destination Management | COR 1. Hospitals and EMS professionals should establish agreements and protocols to prioritize interhospital transfer of patients with acute stroke needing a higher level of care to reduce door-in-door-out (DIDO) times. |
| 2.5. Role of Mobile Stroke Units | COR 1. In patients with suspected AIS, the use of MSUs over conventional EMS where available is recommended for the transport and management of thrombolytic-eligible patients to ensure the fastest achievable onset-to-treatment time and improve functional outcomes. |

(*Continued*)

| Section title | 2025 Recommendation |
|---|---|
| 2.9. Organization and Integration of Components | COR 1. Hospitals caring for patients with acute stroke that provide EVT (ie, TSC, CSC hospitals) should develop a system to comprehensively track key time metrics and other care processes relevant to thrombectomy (eg, door-to-puncture time, successful reperfusion), as well as long-term patient outcomes. |
| 2.9. Organization and Integration of Components | COR 1. Hospitals caring for patients with acute stroke that provide EVT (ie, TSC, CSC hospitals) should credential neurointerventionalists using established and agreed upon training and certification standards. |
| 4.3. Blood Pressure Management | COR 3: No Benefit. In patients with mild to moderate severity AIS who have been treated with IVT, intensive SBP reduction (target of <140 mm Hg compared with <180 mm Hg) is not recommended because it is not associated with an improvement in functional outcome. |
| 4.3. Blood Pressure Management | COR 3: Harm. In patients with AIS with LVO of the anterior circulation who have been successfully recanalized by endovascular therapy (mTICI 2b, 2c, or 3) and without other indication for blood pressure management target, intensive SBP reduction target of <140 mm Hg for the first 72 hours is harmful and not recommended. |
| 4.5. Blood Glucose Management | COR 3: No Benefit. In hospitalized patients with AIS with hyperglycemia, treatment with IV insulin to achieve blood glucose levels in the range of 80 to 130 mg/dL is not recommended to improve 3-month functional outcomes. |
| 4.6.1. Thrombolysis Decision-Making | COR 1. In adult patients with AIS who are eligible for IVT within 4.5 hours of symptom onset, treatment should be initiated as quickly as possible, assuring safe administration and avoiding potential delays associated with additional multimodal neuroimaging, such as CTA/MRA, and CT/MR perfusion imaging. |
| 4.6.2. Choice of Thrombolytic Agent | COR 1. In adult patients with AIS presenting within 4.5 hours of symptom onset or last known well and eligible for IVT, tenecteplase at a dose of 0.25 mg/kg body weight (max 25 mg) or alteplase at a dose of 0.9 mg/kg body weight is recommended to improve functional outcomes. |
| 4.6.3. Extended Time Windows for Intravenous Thrombolysis | COR 2a. In patients with AIS who have salvageable ischemic penumbra detected on automated perfusion imaging and who (a) awake with stroke symptoms within 9 hours from the midpoint of sleep or (b) are 4.5–9 hours from last known well, IV thrombolysis may be reasonable to improve functional outcomes. |
| 4.7.2. Endovascular Thrombectomy for Adults | COR 1. In patients with AIS from anterior circulation proximal LVO of the ICA or M1, presenting within 6 hours from onset of symptoms, with NIHSS score ≥6, prestroke mRS score of 0 to 1, and ASPECTS 3 to 10, EVT is recommended to improve functional clinical outcomes and reduce mortality. |
| 4.7.2. Endovascular Thrombectomy for Adults | COR 1. In selected patients* with AIS from anterior circulation proximal LVO of the ICA or M1, presenting between 6 and 24 hours from onset of symptoms, with age <80 years, NIHSS score ≥6, prestroke mRS score 0 to 1, ASPECTS 3 to 5, and without significant mass effect on imaging, EVT is recommended to improve functional clinical outcomes and reduce mortality. |
| 4.7.2. Endovascular Thrombectomy for Adults | COR 2a. In selected patients† with AIS from anterior circulation proximal LVO of the ICA or M1 presenting within 6 hours from onset of symptoms, with age <80 years, NIHSS score ≥6, prestroke mRS 0 to 1, ASPECTS 0 to 2, and without significant mass effect on imaging, EVT is reasonable to improve functional clinical outcomes and reduce mortality. |
| 4.7.2. Endovascular Thrombectomy for Adults | COR 2a. In patients with AIS from anterior circulation proximal LVO of the ICA or M1 presenting within 6 hours from onset of symptoms, with NIHSS score ≥6, and ASPECTS ≥6, who have a prestroke mRS score of 2, EVT is reasonable to improve functional clinical outcomes and reduce accumulated disability. |
| 4.7.3. Posterior Circulation Stroke | COR 1. In patients with AIS, with basilar artery occlusion, a baseline mRS score of 0 to 1, NIHSS score ≥10 at presentation, and PC-ASPECTS ≥6 (mild ischemic damage), EVT within 24 hours from onset of symptoms is recommended to achieve better functional outcome and reduce mortality. |
| 4.7.4. Endovascular Techniques | COR 3: No Benefit. In the management of patients with AIS in the setting of LVO, preoperative administration of tirofiban before EVT is not useful to improve 90-day functional outcome. |
| 4.8. Antiplatelet Treatment | COR 2a. In patients with minor (NIHSS score ≤5) noncardioembolic AIS or high-risk TIA (ABCD$^2$ score ≥4) within 24 to 72 hours from stroke onset, or NIHSS score of 4 to 5 within 24 hours from onset, who did not receive IVT, with presumed atherosclerotic cause (≥50% stenosis of intracranial or extracranial stenosis that was likely to have accounted for clinical presentation or acute new infarctions on imaging of presumed large artery atherosclerosis origin), DAPT (clopidogrel and aspirin) for 21 days followed by SAPT is reasonable to reduce the 90-day risk of recurrent stroke. |
| 4.9. Anticoagulants | COR 2a. In carefully selected (eg, milder severity) patients with AIS with atrial fibrillation, a strategy of early oral anticoagulation poststroke is low risk and is reasonable compared with a strategy of delayed anticoagulation, although the efficacy of early anticoagulation for prevention of early recurrent stroke is not established. |
| 5.2. Dysphagia | COR 2a. In patients with stroke with dysphagia, treatment with pharyngeal electrical stimulation (PES), can be beneficial to reduce dysphagia severity and decrease the risk of aspiration. |
| 6.2. Brain Swelling (Medical Management) | COR 3: No Benefit. In patients with large hemispheric infarction 18 to 70 years of age, the use of IV glibenclamide does not result in improved functional outcome and is not recommended. |

AIS indicates acute ischemic stroke; CT, computed tomography; CTA, computed tomography angiography; CSC, comprehensive stroke center; DAPT, dual antiplatelet therapy; DIDO, door-in-door-out (time metric for stroke transfers); EMS, emergency medical services; EVT, endovascular thrombectomy; ICA, internal carotid artery; IV, intravenous; IVT, intravenous thrombolysis; LVO, large vessel occlusion; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; mTICI, modified thrombolysis in cerebral infarction (scale for reperfusion success); NIHSS, National Institutes of Health Stroke Scale; SAPT, single antiplatelet therapy; SBP, systolic blood pressure; SSOC, stroke system of care; TIA, transient ischemic attack; and TSC, thrombectomy-capable stroke center.

## ABBREVIATIONS

| Abbreviation | Meaning |
|---|---|
| AF | atrial fibrillation |
| AHA | American Heart Association |
| AIS | acute ischemic stroke |
| AKI | acute kidney injury |
| ARD | absolute risk difference |
| ASA | American Stroke Association |
| ASRH | acute stroke-ready hospital |
| AUC | area under the receiver operating characteristic curve |
| BP | blood pressure |
| CBF | cerebral blood flow |
| CI | confidence interval |
| CMB | cerebral microbleed |
| cOR | common odds ratio |
| COR | class of recommendation |
| CRAO | central retinal artery occlusion |
| CSC | comprehensive stroke center |
| CSF | cerebrospinal fluid |
| CT | computed tomography |
| CTA | computed tomographic angiography |
| CTP | computed tomographic perfusion |
| DAPT | dual antiplatelet therapy |
| DBP | diastolic blood pressure |
| DIDO | door-in–door-out |
| DOAC | direct oral anticoagulant |
| DSM | Diagnostic and Statistical Manual of Mental Disorders |
| DTAS | direct triage to the angiography suite |
| DTN | door-to-needle |
| DVT | deep vein thrombosis |
| DWI | diffusion-weighted imaging |
| ECG | electrocardiogram |
| ED | emergency department |
| EMS | emergency medical services |
| EVT | endovascular thrombectomy |
| FLAIR | fluid-attenuated inversion recovery |
| GPC | graded compression stockings |
| GTN | glyceryl trinitrate |
| GWTG | Get With The Guidelines |
| HBO | hyperbaric oxygen |
| HT | hemorrhagic transformation |
| ICA | internal carotid artery |
| ICH | intracerebral hemorrhage |
| ICU | intensive care unit |
| IPC | intermittent pneumatic devices |
| IV | intravenous |
| IVT | intravenous thrombolytics |
| LMWH | low-molecular-weight heparin |
| LOE | level of evidence |
| LVO | large vessel occlusion |
| MCA | middle cerebral artery |
| MFV | mean flow velocity |
| MI | myocardial infarction |
| MRA | magnetic resonance angiography |
| mRS | modified Rankin Scale |
| MRI | magnetic resonance imaging |
| MSU | mobile stroke unit(s) |
| NBO | normobaric hyperoxia |
| NCCT | noncontrast computed tomography |
| NIHSS | National Institutes of Health Stroke Scale |
| NINDS | National Institute of Neurological Disorders and Stroke |
| NIRS | near-infrared spectroscopy |
| OR | odds ratio |
| PE | pulmonary embolism |
| PES | pharyngeal electrical stimulation |
| PSC | primary stroke center |
| PSD | poststroke depression |
| QI | quality improvement |
| RCT | randomized controlled trial(s) |
| RIC | remote ischemic conditioning |
| RR | risk ratio |
| RWI | relationship(s) with industry |
| SAE | serious adverse event |
| SAPT | single antiplatelet therapy |
| SBP | systolic blood pressure |
| $SpO_2$ | oxygen saturation |
| SSOC | stroke systems of care |
| SSRI | selective serotonin reuptake inhibitor |
| TIA | transient ischemic attack |
| TICI | thrombolysis in cerebral infarction |
| tPA | tissue-type plasminogen activator |
| TSC | thrombectomy-capable stroke center |
| UFH | unfractionated heparin |
| UTI | urinary tract infection |
| VTE | venous thromboembolism |

## 1. INTRODUCTION

Every year in the United States, >600 000 individuals have a first ischemic stroke and approximately 200 000 more have a recurrent stroke.[1] More than 9 million Americans age 20 years and older self-report having had a stroke, with an overall prevalence estimated at 3.3%.[1] The prevalence of stroke in the United States continues to increase with the aging population. It is estimated that by 2030 an additional 3.4 million US adults (3.9% of the adult population) will have had a stroke, representing an increase of >20% from 2012.[2] Strokes occur at disproportionately higher rates among individuals with adverse socioeconomic circumstances or social determinants of health, including economic instability, lower education, residing in stressed neighborhoods, and







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residing in states that make up the US Stroke Belt.[3,4] Ischemic strokes account for >80% of all strokes in the United States and >60% of all strokes globally.

Stroke is also a leading cause of death and disability.[1] Almost half of individuals who survive >6 months after a stroke are dependent in at least 1 activity of daily living.[5] The cumulative brain injury from stroke and recurrent events contributes further to subsequent cognitive decline.[6] Similar to stroke incidence, stroke mortality disproportionately impacts individuals with adverse socioeconomic or social determinants of health.

Evidence pertaining to the evaluation and treatment of patients with AIS continues to emerge, with tremendous potential to improve care and outcomes for stroke patients. This guideline aims to incorporate this updated evidence in order to provide an up-to-date, comprehensive set of recommendations for the acute evaluation and management of patients with AIS.

## 1.1. Methodology and Evidence Review

The recommendations listed in this guideline are, whenever possible, evidence-based and supported by extensive evidence review. A search for literature derived from research principally involving human subjects, published in English since the last AIS guideline in 2018 and the 2019 update, and indexed in MEDLINE, PubMed, Cochrane Library, and other selected databases relevant to this guideline, was conducted between September and December 2024. (Additional high impact studies and articles published through March 2025 were added later, where appropriate.) The Data Supplement contains the final evidence tables summarizing the evidence used by the Guideline Writing Group to formulate recommendations. Additionally, the Guideline Writing Group reviewed documents related to subject matter previously published by the AHA and ASA (Table 1). References selected and published in the present document are representative and not all-inclusive.

Each topic area was assigned a primary, and sometimes secondary writer, as well as a primary, and sometimes secondary, reviewer. These assignments were based on the areas of expertise of the members of the Guideline Writing Group and their lack of any relationships with industry related to the section material. All recommendations were fully reviewed and discussed among the full group to allow for diverse perspectives and considerations for this guideline. Recommendations were then voted upon and a modified Delphi process used to reach consensus. Guideline Writing Group members who had relationships with industry that were relevant to certain recommendations were recused from voting on those particular recommendations. All recommendations in this guideline were agreed upon by between 83% and 100% of the voting Guideline Writing Group members.

## 1.2. Organization of the Guideline Writing Group

The writing group was assembled by the AHA Stroke Council's Scientific Statements Oversight Committee, ensuring representation from a wide range of medical and scientific expertise. The AIS guideline writing group consisted of vascular neurologists, neuro-interventionalists, emergency physicians, neurosurgeons, neurocritical care physicians, a nurse scientist, and 2 patient representatives. The writing group included representatives from the AHA and ASA, American Academy of Neurology, American Association of Neurological Surgeons/Congress of Neurological Surgeons, Neurocritical Care Society, Society for Academic Emergency Medicine, Society of NeuroInterventional Surgery, and Society of Vascular and Interventional Neurology. The group adhered strictly to the conflict of interest policy of the American Heart Association, with members



**Table 1. Associated AHA/ASA Guidelines and Statements**

| Title | Organization | Publication year |
|---|---|---|
| Guidelines | | |
| Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack | AHA/ASA | 2021[9] |
| Guidelines for Adult Stroke Rehabilitation and Recovery | AHA/ASA | 2016 |
| AHA/ASA scientific statements | | |
| Identifying Best Practices for Improving the Evaluation and Management of Stroke in Rural Lower-Resourced Settings | AHA | 2024[10] |
| Large-Core Ischemic Stroke Endovascular Treatment | AHA | 2024[11] |
| Care of the Patient With AIS (Posthyperacute and Prehospital Discharge) | AHA | 2021[12] |
| Care of the Patient With AIS (Prehospital and Acute Phase of Care) | AHA | 2021[13] |
| Recommendations for Regional Stroke Destination Plans in Rural, Suburban, and Urban Communities From the Prehospital Stroke System of Care Consensus Conference | AAN/AHA/ASA/ASN/ NAEMSP/ NASEMSO/SNIS/SVIN | 2021[14] |
| Management of Stroke in Neonates and Children | AHA/ASA | 2019[15] |
| Comprehensive Overview of Nursing and Interdisciplinary Care of the Acute Ischemic Stroke Patient | AHA | 2009[16] |

AAN indicates American Academy of Neurology; AHA, American Heart Association; ASA, American Stroke Association; ASNR, American Society of Neuroradiology; NAEMSP, National Association of EMS Physicians; NASEMSO, National Association of State EMS Officials; SNIS, Society of NeuroInterventional Surgery; and SVIN, Society of Vascular and Interventional Neurology.

recusing themselves from discussions or voting on topics relevant to their industry relationships. Appendix 1 of this document lists Guideline Writing Group members' relevant Relationships With Industry (RWI) and other entities. For the purposes of full transparency, the Guideline Writing Group members' comprehensive disclosure information is available online.

## 1.3. Document Review and Approval

This document was reviewed by the AHA's Stroke Scientific Statements Oversight Committee, AHA's Science Advisory and Coordinating Committee, AHA's Executive Committee, reviewers from the AAN, AANS/CNS, NCS, SAEM, SNIS, and SVIN, as well as by 24 individual content reviewers. Appendix 2 lists reviewers' comprehensive disclosure information.

## 1.4. Scope of the Guideline

This guideline addresses the evaluation and treatment of adult patients with AIS and is intended to update and replace the AHA and ASA "2018 Guideline for the Early Management of AIS" and its 2019 update.[7,8] The guideline provides general recommendations based on the currently available evidence to assist clinicians caring for adult patients with AIS. Where sufficient evidence exists, the guideline additionally includes recommendations for pediatric patients with AIS. In the process of developing this guideline, the Writing Group reviewed previously published AHA and ASA guidelines and scientific statements, listed in Table 1. These are resources for readers and reduce the need for repetition of existing guideline recommendations. For example, primary prevention, secondary prevention, and postacute care of patients with ischemic stroke were considered out of scope given already existing guidelines.

This guideline aims to cover the full course of the emergency evaluation and early management of the patient with AIS (Figure 1). This includes the earliest interaction with the health care system in the prehospital space (section 2), early evaluation and treatment (sections 2, 3, and 4), and in-hospital management of patients with AIS (sections 5 and 6). When making individual patient care decisions, additional considerations include local resources and expertise, specific clinical circumstances, patient preferences, and any evidence published since these guidelines. The guideline also highlights a number of areas where data are limited and future research is needed.



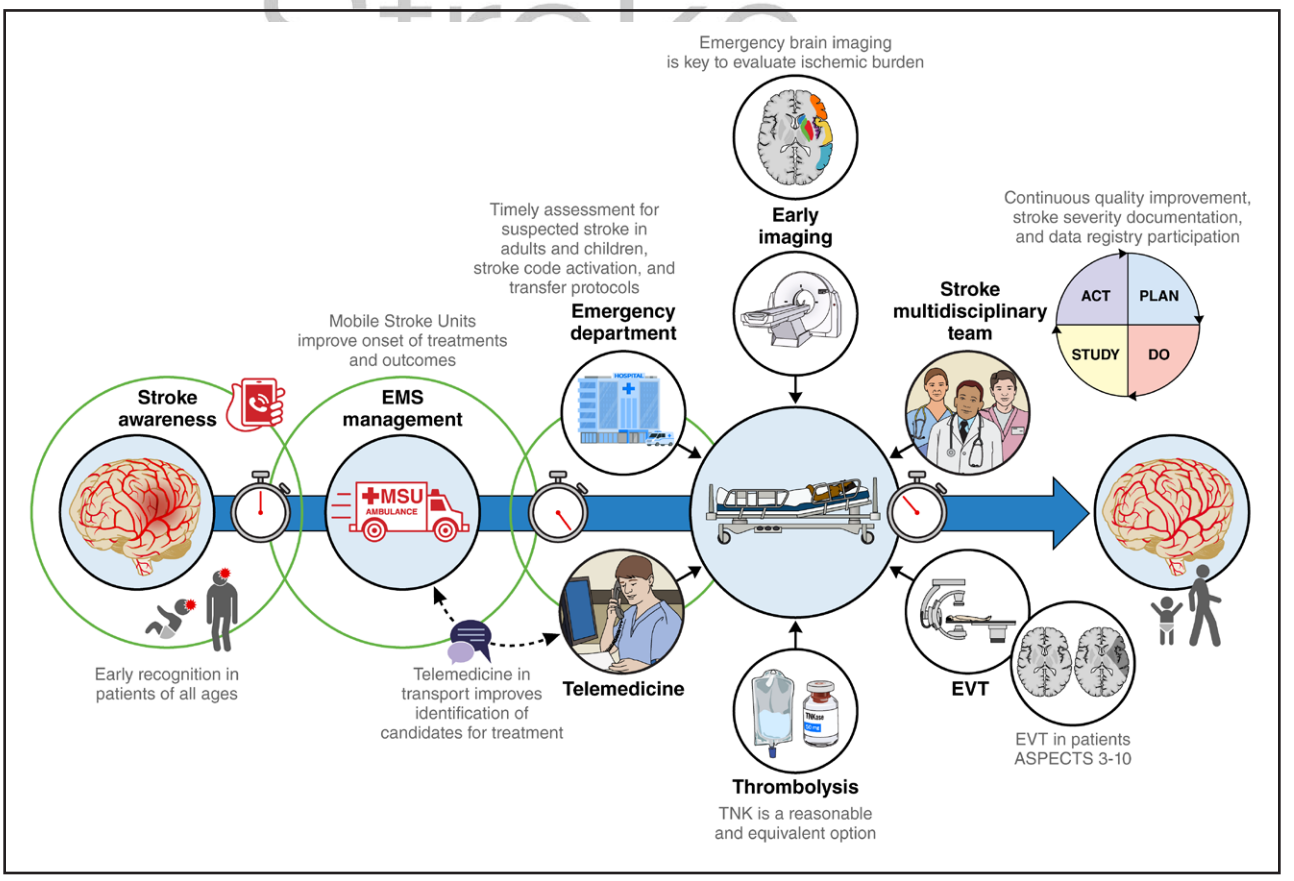


**Figure 1. Journey of a patient with AIS.**
The phases of care and key management steps and treatments are highlighted to ensure the most optimal functional outcome. AIS indicates acute ischemic stroke; EMS, emergency medical services; EVT, endovascular thrombectomy; MSU, mobile stroke unit; and TNK, tenecteplase.


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**Table 2. Applying Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care**

## CLASS (STRENGTH) OF RECOMMENDATION

### Class 1 (STRONG) — Benefit >>> Risk

**Suggested phrases for writing recommendations:**
- Is recommended
- Is indicated/useful/effective/beneficial
- Should be performed/administered/other
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is recommended/indicated in preference to treatment B
  - Treatment A should be chosen over treatment B

### Class 2a (MODERATE) — Benefit >> Risk

**Suggested phrases for writing recommendations:**
- Is reasonable
- Can be useful/effective/beneficial
- Comparative-Effectiveness Phrases†:
  - Treatment/strategy A is probably recommended/indicated in preference to treatment B
  - It is reasonable to choose treatment A over treatment B

### Class 2b (WEAK) — Benefit ≥ Risk

**Suggested phrases for writing recommendations:**
- May/might be reasonable
- May/might be considered
- Usefulness/effectiveness is unknown/unclear/uncertain or not well-established

### Class 3: No Benefit (MODERATE) — Benefit = Risk (Generally, LOE A or B use only)

**Suggested phrases for writing recommendations:**
- Is not recommended
- Is not indicated/useful/effective/beneficial
- Should not be performed/administered/other

### Class 3: HARM (STRONG) — Risk > Benefit

**Suggested phrases for writing recommendations:**
- Potentially harmful
- Causes harm
- Associated with excess morbidity/mortality
- Should not be performed/administered/other

## LEVEL (QUALITY) OF EVIDENCE‡

### Level A
- High-quality evidence‡ from more than 1 RCT
- Meta-analyses of high-quality RCTs
- One or more RCTs corroborated by high-quality registry studies

### Level B-R (Randomized)
- Moderate-quality evidence‡ from 1 or more RCTs
- Meta-analyses of moderate-quality RCTs

### Level B-NR (Nonrandomized)
- Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies
- Meta-analyses of such studies

### Level C-LD (Limited Data)
- Randomized or nonrandomized observational or registry studies with limitations of design or execution
- Meta-analyses of such studies
- Physiological or mechanistic studies in human subjects

### Level C-EO (Expert Opinion)
- Consensus of expert opinion based on clinical experience

COR and LOE are determined independently (any COR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although RCTs are unavailable, there may be a very clear clinical consenus that a particular test or therapy is useful or effective.

* The outcome or result of the intervention should be specified (an improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

† For comparative-effectiveness recommendations (COR 1 and 2a; LOE A and B only), studies that support the use of comparator verbs should involve direct comparisons of the treatments or strategies being evaluated.

‡ The method of assessing quality is evolving, including the application of standardized, widely-used, and preferably validated evidence grading tools; and for systematic reviews, the incorporation of an Evidence Review Committee.

COR indicates Class of Recommendation; EO, expert opinion; LD, limited data; LOE, Level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

### 1.5. Class of Recommendations and Level of Evidence

Recommendations are designated with both a Class of Recommendation (COR) and a Level of Evidence (LOE). The COR indicates the strength of recommendation, encompassing the estimated magnitude and certainty of benefit in proportion to the risk. The LOE rates the quality of scientific evidence supporting the intervention based on the type, quantity, and consistency of data from clinical trials and other sources (see Table 2). Please note, COR and LOE are determined independently (any COR may be paired with any LOE).

## 2. STROKE SYSTEMS OF CARE AND PREHOSPITAL MANAGEMENT

### 2.1. Stroke Awareness (Population Level)

**Recommendations for Stroke Awareness (Population Level) Referenced studies that support recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. For the general public, implementation of educational programs on stroke recognition in patients of all ages and the need to seek emergency care (calling 9-1-1) is recommended and should be implemented by public health and community leaders and medical professionals to reduce gaps in knowledge about stroke warning signs and to improve stroke preparedness.[1–10] |
| 1 | B-NR | 2. For the general public, educational programs on stroke recognition should be designed to reach diverse communities and populations (ie, diversity by age, race and ethnicity, sex and gender, and other social determinants of health such as education, income, and neighborhood) to reduce knowledge gaps in stroke warning signs and improve stroke preparedness across all demographics.[1–4,9–12] |
| 1 | B-NR | 3. For the general public, educational programs on stroke recognition should be sustained over time to improve long-term knowledge of stroke warning signs and stroke preparedness.[4,7,11] |
| 1 | B-NR | 4. In addition to the general public, emergency medical services (EMS) professionals, physicians (including primary care professionals), and other health care personnel should receive targeted stroke educational programs to reduce prehospital delays and maximize eligibility for acute treatment of ischemic stroke (eg, thrombolysis).[13–16] |

#### *Synopsis*

Stroke awareness, which includes the knowledge of key stroke warning signs and stroke symptoms, and stroke preparedness, the knowledge of the correct action to take when stroke symptoms occur, are critical to reducing delays in acute stroke care. Prior studies demonstrate that there are major gaps in stroke awareness and delays in arrival after stroke symptom onset across the population with inequities by race, sex, age, and other sociodemographic characteristics.[10,12,17–19] Improving stroke knowledge and preparedness across the population has the potential to decrease emergency department (ED) arrival times, reduce delays to diagnosis and treatment, and increase the number of eligible patients treated with time-sensitive reperfusion treatments such as intravenous thrombolysis (IVT) and endovascular thrombectomy (EVT). Ultimately, reducing delays to diagnosis and treatment has the potential to reduce morbidity and mortality from AIS. Previously published literature has demonstrated the potential for educational interventions to increase knowledge and stroke preparedness,[1,2,20] and such data are the foundation for the recommendations above.

#### *Recommendation-Specific Supportive Text*

1. Lack of awareness of stroke warning signs and the need to call 9-1-1 in the case of stroke symptoms contributes to delays to hospital arrival and has the potential to reduce patients' eligibility for reperfusion therapies. Both randomized[1,2] and nonrandomized studies[3–9] have demonstrated short-term increases in stroke knowledge and preparedness after implementing educational interventions targeted at children and adults in the general public, including interventions delivered in the school setting,[1,5] with some studies demonstrating changes in objective behaviors such as EMS use.[6,8,21] With the exception of 2 randomized controlled trials (RCTs), the data supporting this recommendation are largely observational, with various limitations; however, the potential benefit greatly outweighs the risk of such interventions.
2. Consistent inequities in delays to hospital arrival, EMS use, and stroke treatment rates by race, age, ethnicity, and other sociodemographic factors have been well documented.[10,12,19] Additionally, interventions that are culturally tailored, targeted toward specific minoritized groups, and that take into account barriers to accessing care have demonstrated that educational interventions can increase both stroke knowledge and preparedness among demographic groups at risk for delays to care.[1–4,7,9] For example, RAPIDO (Rostro caido, Alteración del equilibrio, Pérdida de fuerza, Impedimento visual, Dificultad para hablar, Obtenga ayuda rapido) was developed as an acronym to improve awareness and recognition of stroke symptoms among Spanish speakers.[22] Such data should be taken into consideration for the design of future interventions targeted at changing behaviors of both patients and health care professionals.
3. Despite evidence of improved stroke knowledge and preparedness after educational interventions,[7] some studies measuring retention of knowledge over time have demonstrated that stroke knowledge is not sustained in the long-term after completion of the intervention.[4,11] Although the optimal timing of repeat intervention or boosters is unknown, the potential for a decrease in stroke awareness and preparedness over time should be incorporated into future efforts to design stroke preparedness interventions.







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4. Given the role of EMS in the rapid transport of stroke patients to hospitals with appropriate treatment capabilities and the frequency with which patients may contact health care professionals outside of the ED when stroke symptoms occur, interventions to increase stroke awareness among health care professionals also improve reperfusion treatment rates and efficiency. Previous interventions specifically targeted towards prehospital personnel[13,14] and outpatient health care professionals[15,16] have demonstrated increased rates of EMS use, EMS professional's' recognition of stroke, and hospital prenotification by EMS professionals.

### *Knowledge Gaps and Future Research*

- There are limitations to the work in this area; notably, few interventions have demonstrated efficacy in changing patient behavior (ie, use of EMS)[6,8] or rates of acute reperfusion treatment. This may be due to factors such as the lack of feasibility of studying individual patient behavior after educational interventions (due to challenges with sample sizes and event rates) or to the known challenges of translating health knowledge to behavioral changes. Some previous research has used hospital- or community-level treatment metrics as a way of measuring changes in behavior,[23] showing that an ED-based educational intervention was associated with improved rates of thrombolysis for AIS across the community, although the multimodal intervention that included a community component was not.[23]
- Future research is needed to better understand barriers to recognizing stroke and calling 9-1-1, the optimal design of educational and behavioral interventions when stroke is suspected, how to best educate the lay public regarding the role of bystanders and family members[1,3,5] in recognizing stroke and activating EMS, and strategies for maintaining knowledge over time.[24]

## 2.2. EMS Systems

| Recommendations for EMS Systems<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | B-NR | 1. Health care policy makers should establish regional systems of stroke care to increase access to time-sensitive therapies that include the determination of: a) health care facilities that provide initial emergency care, including administration of IVT, and b) centers capable of performing endovascular stroke treatment with comprehensive periprocedural care to which rapid transport must be arranged when appropriate.[1] |
| 1 | B-NR | 2. EMS leaders, together with local experts, regional or state agencies, and medical authorities, should develop prehospital triage protocols to ensure that patients with suspected stroke are rapidly identified, assessed with a validated tool for stroke screening, and preferentially transported to the most appropriate stroke centers.[2–13] |
| 2a | B-NR | 3. Monitoring and feedback on quality metrics related to prehospital care can be useful to reduce delays from symptom onset to ischemic stroke reperfusion treatment and increase the odds of discharge to home.[14–16] |

### *Synopsis*

Prehospital coordination is crucial for the timely treatment of patients with acute stroke and has a great impact on clinical outcomes. Regional stroke coordinating bodies must ensure that systems are organized in a way that identifies hospital capabilities for stroke care and that the routing protocols to available stroke centers at their level are equitable for the entire population. It is also important to measure, analyze, and offer feedback about prehospital quality of care indicators as part of continuous quality improvement (QI).

### *Recommendation-Specific Supportive Text*

1. Health systems must operate in a coordinated manner to accelerate the delivery of AIS care. The designation of stroke centers and their levels of expertise are based on criteria established by the AHA and ASA (https://www.heart.org/en/professional/quality-improvement/healthcare-certification/stroke-certification) (see section 2.6, "Hospital Stroke Capabilities"). EMS and stroke centers, together with the regional public health agencies and administrations, must develop transport policies and protocols within stroke networks according to distances and available centers at a regional level, in an equitable way for the entire population. As an example, the IMPROVE (Initiative to Maximize Progress in Optimized Vascular Events) Stroke Care program, which aimed to improve a regional system of care within comprehensive stroke networks, including a QI program, was successful at improving the delivery of thrombolytic treatment at both spoke and hub sites in the network and identified opportunities for continuous QI.[1]
2. Prehospital triage protocols should be established at the regional level, with the choice of screening tool made as part of this comprehensive regional prehospital approach. The choice of screening tool is discussed in more detail in section 2.3 on "Prehospital Assessment and Management."
3. Quality metrics have been proposed for prehospital stroke care: dispatch within 90 seconds of 9-1-1 call, prehospital stroke screen documentation, glucose check, determination of last known well time, maintenance of scene times ≤15 minutes, hospital prenotification, including stroke-specific details and IV line placement. Compliance with these metrics has been associated with a reduced time from EMS contact to evaluation and thrombolytic

treatment at the receiving hospital and higher odds of discharge to home.[14–16] With the exception of scene time ≤15 minutes, these metrics may also apply to mobile stroke units (MSUs).

## Knowledge Gaps and Future Research

- More evidence related to the benefit of coordinated regionalized stroke care is needed.
- More evidence related to the benefit of the protocolization of prehospital care with the use of checklists, as well as the unification or linkage of prehospital and hospital records, together with quality measure performance and feedback, would be useful to facilitate quality control and continuous performance improvement.[17]

## 2.3. Prehospital Assessment and Management

**Recommendations for Prehospital Assessment and Management Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| Dispatch | | |
| 2a | B-NR | 1. In callers to 9-1-1, EMS dispatch use of a telephone stroke assessment tool is reasonable and can be beneficial in early identification of stroke, reduced on-scene time, and/or prioritization of transport.[1,2] |
| Ambulance Transport | | |
| 1 | A | 2. In patients with suspected stroke transported by ambulance, use of a brief stroke assessment tool by prehospital personnel is recommended to improve early stroke identification, including large vessel occlusion (LVO) stroke.[3,4] |
| 1 | B-NR | 3. In patients with suspected stroke transported by ambulance, prehospital personnel should provide advance notification to the receiving hospital of an inbound suspected stroke to reduce in-hospital evaluation times, increase thrombolytic use, and decrease mortality.[5,6] |
| 3: No Benefit | B-R | 4. In patients with suspected stroke transported by ambulance, ambulance-initiated remote ischemic conditioning (RIC) with arm blood pressure (BP) cuff inflation does not improve functional outcome and is not recommended.[7] |
| 3: Harm | A | 5. In patients with suspected stroke transported by ambulance, prehospital initiation of stroke treatment with transdermal glyceryl trinitrate (GTN, nitroglycerin) does not improve functional outcome and is potentially harmful.[8–11] |
| 3: No Benefit | B-R | 6. In patients with suspected stroke transported by ambulance, intensive BP control in the field to a target of 130 to 140 mm Hg systolic does not improve functional outcome.[12] |
| 2b | B-NR | 7. In pediatric patients with suspected stroke transported by ambulance, the usefulness of common adult stroke screening tools is uncertain because they perform poorly for identification of stroke. Newer pediatric stroke screening tools demonstrate good interrater reliability; however, their sensitivity, specificity, and predictive value in the prehospital setting remain to be determined, and their usefulness is unknown.[13–16] |

### *Synopsis*

EMS professionals play a crucial role in the early identification and management of suspected stroke. Use of a stroke-specific training module for dispatchers has been shown to improve recognition of stroke.[17] Use of structured telephone stroke assessment tools by EMS dispatchers is recommended to facilitate earlier stroke recognition and reduce on-scene times.[1,2] Once on-site, EMS professionals' use of prehospital stroke scales—such as the Cincinnati Prehospital Stroke Scale (CPSS), Los Angeles Prehospital Stroke Screen (LAPSS), and Rapid Arterial Occlusion Evaluation (RACE)—are effective in improving early stroke detection, including LVOs, although they remain nondiagnostic.[3,4] EMS prenotification of receiving hospitals enhances treatment timelines and outcomes, including increased thrombolysis rates and reduced mortality.[5,6]

Emerging technologies, such as electroencephalography (EEG) and cranial accelerometers, show promise in prehospital stroke detection but require further validation.[18–20] Conversely, certain interventions have shown no benefit. RIC and the prehospital use of GTN were not associated with improved functional outcomes and may pose harm, particularly in cases of intracerebral hemorrhage (ICH).[7–11] Similarly, early BP reduction to 130 to140 mm Hg was not beneficial and could be harmful in ischemic stroke.[12] For pediatric cases, adult stroke scales perform poorly, and while pediatric-specific tools show reliability, their clinical use in the field remains uncertain.[13–16]

### *Recommendation-Specific Supportive Text*

1. A 2024 systematic review of 24 studies assessed EMS dispatcher recognition of stroke. Nineteen of 24 (79%) reported the use of a dispatcher screening tool, including the CPSS (3); Face, Arm, Speech, Time (FAST, n=3); Medical Priority Dispatch System/Software (MPDS, n=8); or a locally developed protocol or other system (n=5). When using an overall dispatch system, the dispatcher sensitivity for stroke identification ranged from 41.0% to 83.0% with a positive predictive value ranging from 30.2% to 82.9%. When using a stroke-specific scale, the sensitivity ranged from 48.0% to 80.0%, and the positive predictive value ranged from 24.0% to 87.7%. For the local structured interview or no interview or not reported group, sensitivity ranged from 17.9% to 58.3%.[2] Data primarily originated from the United States, Europe, and Australia, and the findings were supported by earlier reports.[21–26] A retrospective study analyzing National EMS Information System (NEMSIS) data on 966 745 US patients transported by EMS between 2012 and 2016 assessed the impact of dispatch complaints on prehospital time intervals for patients with suspected stroke. Approximately







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37% of dispatch complaints were identified by EMS as suspected strokes. Compared with nonstroke dispatches, stroke-identified calls had shorter on-scene times, with 57.4% meeting the benchmark of ≤15 minutes versus 48.0% for nonstroke calls.[1] These findings highlight the importance of EMS dispatchers in recognizing stroke symptoms and the need for continuing improvement.

2. Multiple prehospital stroke scales assist in early identification of patients with acute stroke. A 2019 Cochrane review identified 8 scales, with the CPSS and LAPSS extensively assessed in the prehospital setting. The mean sensitivity of the LAPSS was 0.83 (95% CI, 0.75–0.89), and the mean specificity was 0.93 (95% CI, 0.88–0.96). The better-quality CPSS study reported a sensitivity of 0.89 (95% CI, 0.86–0.91) and a specificity 0.69 (95% CI, 0.65–0.73).[27] More recently, prehospital tools have been developed to identify anterior LVO (aLVO) stroke. The 2021 Prehospital Triage of Patients with Suspected Stroke Symptoms (PRESTO) trial evaluated the accuracy of 8 prehospital stroke scales for detecting aLVO stroke: Rapid Arterial Occlusion Evaluation (RACE), Gaze-Face-Arm-Speech-Time (G-FAST), Conveniently-Grasped Field Assessment Stroke Triage (CG-FAST), Los Angeles Motor Scale (LAMS), CPSS, Postural Assessment Scale for Stroke (PASS), Cincinnati Stroke Triage Assessment Tool (C-STAT), and FAST-PLUS. Conducted in the Netherlands, the study included 1039 patients, of whom 120 (12%) had aLVO stroke confirmed by computed tomography angiography (CTA). The area under the receiver operating characteristic curve (AUC) ranged from 0.72 to 0.83.[3] These findings mirror another large study from the Netherlands that identified 7 prehospital stroke scales with accuracies ranging from 0.79 to 0.89. The sensitivity ranged from 38% to 62% and the specificity from 78% to 88% in identifying aLVO stroke.[28] The prehospital use of stroke scales assists EMS professionals in identifying patients requiring urgent intervention; however, they remain nondiagnostic.[4]
3. EMS prenotification of the receiving hospital significantly enhances the evaluation and treatment of patients with AIS. A comprehensive study involving 371 988 patients transported by EMS and enrolled in the Get With The Guidelines–Stroke registry found prenotification led to improved outcomes, including shorter door-to-imaging times (26 versus 31 minutes), reduced door-to-needle (DTN) times (78 versus 80 minutes), and increased rates of IV tissue-type plasminogen activator (tPA) administration within the recommended time frame (82.8% versus 79.2%).[5] Data from the Massachusetts Paul Coverdell Stroke Registry found EMS prenotification to be associated with reduced odds of in-hospital mortality among stroke patients.[6] Despite its benefits, EMS prenotification remains underused, with only two-thirds of eligible patients receiving this service.
4. The Remote Ischemic Conditioning in Patients With Acute Stroke Trial (RESIST) was a randomized, sham-controlled, double-blind, clinical trial conducted in Denmark on 1500 patients with prehospital stroke symptoms ≤4 hours from onset. The intervention tested whether RIC initially delivered in the ambulance using an inflatable cuff on a single upper extremity (pressure ≤200 mm Hg) and continued in-hospital improved functional outcome (modified Rankin Score [mRS] score shift at 90 days) compared with a sham cuff (pressure 20 mm Hg). In total, 902 patients had a target diagnosis of stroke (82% ischemic, 18% hemorrhagic). RIC treatment was not significantly associated with improved outcomes or differences in serious adverse events (SAEs), and this held for secondary endpoints assessing outcomes by stroke subtype and use of reperfusion therapy. Limitations included poor treatment adherence (62.6%) and mild stroke severity at baseline (median National Institutes of Health Stroke Scale [NIHSS] score, 5) with high use of reperfusion therapy (75% of patients). The latter potentially created a ceiling effect to identifying treatment benefit. The trial, however, demonstrated feasibility of prehospital RIC.[7]
5. The MR ASAP and RIGHT-2 trials investigated the prehospital use of transdermal GTN for acute stroke management and its potential to improve functional 90-day outcome. Conducted in the Netherlands, MR ASAP was a multicenter, open-label, blinded-endpoint, phase 3 trial that enrolled 325 ambulance patients with presumed acute stroke. Participants received either 5 mg/day of transdermal GTN or standard care within 3 hours of symptom onset in the prehospital setting. The primary outcome, mRS at 90 days, showed no significant difference between groups (adjusted common odds ratio [OR], 0.97 [95% CI, 0.65–1.47]). However, in patients with ICH, the GTN group had a higher 7-day mortality rate (34% versus 10%), leading to the trial's premature termination due to safety concerns.[10] The UK RIGHT-2 was a randomized, paramedic-delivered, sham-controlled, blinded-endpoint, phase 3 trial that included 1149 patients with presumed acute stroke. Participants received either transdermal GTN or a sham treatment within 4 hours of symptom onset. The primary outcome, a shift in mRS scores at 90 days, revealed no benefit from GTN in either the intention-to-treat, target-disease (confirmed stroke and transient ischemic attack [TIA]), or global analyses.

GTN use was associated with a tendency for worse functional outcomes in the target-disease analysis. This tendency toward harm was particularly seen in patients with ICH, stroke onset ≤1 hour, and severe strokes.[9]

6. A large, open-label, randomized, multicenter, trial with blinded outcome assessment evaluated whether very early prehospital BP control improved functional outcomes compared with usual management among patients with undifferentiated stroke. Patients with suspected stroke with motor deficit and a systolic blood pressure (SBP) ≥150 mm Hg assessed within 2 hours of symptom onset and transported by ambulance were randomized (1:1) to receive IV urapidil (an $\alpha_1$-adrenoreceptor antagonist and 5-$HT_{1A}$ receptor agonist with peak BP effect within 5 minutes) to achieve a target SBP of 130 to 140 mm Hg, or usual care. The intention-to-treat population comprised 2404 patients (50% cerebral ischemia, 43% hemorrhagic stroke, and 7% mimic or uncertain). At hospital arrival, the mean SBP was 159±26 mm Hg (intervention) versus 170±27 (usual care). At 90 days, the mRS did not differ significantly between groups. This finding was robust across multiple analyses. Exploratory analysis found a decreased risk for poor functional outcome in patients with hemorrhagic stroke and an increased risk in patients with cerebral ischemia. The incidence of SAEs was similar between the intervention and usual care groups.[12]
7. Pediatric stroke is uncommon, with an estimated incidence in children between approximately 1.2 and 13 cases per 100 000 children per year in developed countries[29–32] and an important cause of pediatric morbidity and mortality. The currently available stroke screening tools, developed for an adult population, do not accurately distinguish strokes from mimics in the pediatric population.[13,14] Newer stroke screening tools to identify pediatric stroke have been adapted from existing adult scales, with the pediatric modification of the National Institutes of Health Stroke Scale (PedNIHSS) demonstrating good to excellent interrater reliability between child neurologists.[15] In a small study, the Pediatric Rapid Arterial Occlusion Evaluation (PedRACE) demonstrated good interrater reliability between prehospital and ED pediatricians and child neurologists and good correlation with PedNIHSS.[16] The sensitivity, specificity, and negative and positive predictive values for pediatric stroke scales both in-hospital and prehospital remain to be determined and their ability to be scaled to the prehospital environment demonstrated. These will be important steps to further enhance acute stroke care for pediatric patients.

## Knowledge Gaps and Future Research

- There is a need for better tools to identify stroke patients and subtype in the field.
- There is a need for further integration of EMS data into existing electronic medical records and stroke registries to improve patient care and enhance research on prehospital outcomes.
- There is a need for real-time knowledge on moment-to-moment EMS conditions and local/regional stroke resource availability to allow matching of patient needs and system ability.
- There is a need to further understand the trade-offs inherent between time-and-distance decisions in the delivery of stroke patients to hospital-based care.
- Further development and testing of pediatric stroke assessment tools in the prehospital environment is warranted.
- Emerging portable stroke detection devices such as near-infrared spectroscopy (NIRS), ultrasound, EEG, microwave imaging, and volumetric impedance phase shift spectroscopy (VIPS) are under development to enhance prehospital stroke triage. Most devices, however, require trained personnel and have not been extensively tested in prehospital settings[18–20]; therefore, their clinical use remains uncertain.

## 2.4. EMS Destination Management

| Recommendations for EMS Destination Management<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| General principles | | |
| **1** | **B-NR** | 1. In patients with suspected acute stroke, EMS professionals should prioritize transport to the closest appropriate facility (acute stroke-ready hospital [ASRH], primary stroke center [PSC], thrombectomy-capable stroke center [TSC], or comprehensive stroke center [CSC]) to reduce time to treatment compared with transport to a nonstroke capable hospital.[1–5] |
| Areas with local access to thrombectomy-capable stroke center(s) | | |
| **2a** | **B-NR** | 2. In patients identified by EMS professionals as having a suspected LVO stroke, direct transport to a TSC can be beneficial to increase EVT rates and reduce time to treatment compared with initial transport to a non-TSC with secondary hospital-to-hospital transfer.[6–8] |
| Areas without local access to thrombectomy-capable stroke center(s) | | |
| **2b** | **B-NR** | 3. In areas without well-coordinated stroke systems of care (SSOC) and local hospital(s) proficient in thrombolysis delivery and secondary interhospital transfer, it may be reasonable for EMS professionals to consider direct transport of suspected LVO patients to the closest appropriate TSC (if transport will not disqualify the patient from IVT) to increase rates of EVT and reduce time to treatment, compared with initial transport to a local stroke center with secondary hospital-to-hospital transfer for treatment.[9] |





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| Recommendations for EMS Destination Management (Continued) | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **3: No Benefit** | **B-R** | 4. In areas with well-coordinated SSOC and local hospital(s) proficient in thrombolysis delivery and secondary interhospital transfer, direct transport of patients with suspected LVO to a distant (eg, 45–60 min) TSC compared with transport to a local stroke center does not improve 3-month clinical outcomes.[10–14] |
| Interhospital transfer | | |
| **1** | **B-NR** | 5. Hospitals and EMS professionals should establish agreements and protocols to prioritize interhospital transfer of patients with acute stroke needing a higher level of care to reduce door-in–door-out (DIDO) times.[15] |

### Synopsis

For patients identified with suspected stroke in the prehospital setting, multiple variables are incorporated into the choice of specific hospital destination, including transport time and distance, geography, weather, individual patient and stroke characteristics, local EMS resources, air medical access, and local hospital stroke treatment capabilities, efficiency, specialist(s), telemedicine, and imaging access. A high-quality clinical trial has demonstrated that in settings with local hospitals proficient in thrombolytic delivery and interhospital transfer, direct transfer to a distant (approximately 1 hour) TSC is not beneficial. The generalizability of these findings to urban areas, or other rural areas without high-performing PSCs or different geography, is uncertain, and further work is needed. Implementing agreements and protocols between hospitals to reduce DIDO times is reasonable and useful.

### Recommendation-Specific Supportive Text

1. EMS professionals play a critical role in the early identification and appropriate triage of patients with AIS. Rapid transport to the most suitable facility, rather than simply the nearest hospital, is essential for optimizing outcomes. Ideal EMS destination plans are complex, nuanced, and may vary based on changing local circumstances. EMS destination decision input data include patient-specific findings, EMS resources, traffic patterns, and hospital capabilities and performance.[1] In the pre-EVT era in Chicago, implementation of prehospital stroke triage policies to direct patients with suspected stroke to PSCs (versus non-PSCs) was associated with increased rates of EMS prenotification (65.5%–76.5%), increased IV tPA use (3.8%–10.1%), and decreased onset-to-treatment time (17–146 minutes), mirroring previous findings in Toronto.[2,3] In the EVT era, modeling studies comparing transport to CSCs versus PSCs indicate the optimal EMS transport decision is context specific and highly sensitive to small changes in the model inputs (including stroke severity, geographic proximity of hospitals, transport time, triage tool used, and efficiency of destination hospital for DTN, DIDO, and door-to-groin-puncture times).[5,16]
2. Observational studies using pre- and postimplementation designs have demonstrated increased EVT treatment rates after implementation of prehospital algorithms to identify patients for direct transfer to thrombectomy centers. Beginning in September 2018, patients in Chicago with suspected stroke (as determined by the CPSS within 6 hours of symptom onset and identified as suspected LVO using the 3-Item Stroke Scale and finger-to-nose test) were recommended for transport to the closest CSC. A multicenter study evaluating the effect of the policy found the rate of EVT increased from 4.9% to 7.4% ($P<0.001$) among all patients with AIS and among EMS-transported patients increased from 4.8% to 13.6% ($P<0.001$). Nonsignificant improvements were reported in the rate of IV tPA use and onset-to-thrombolysis time.[6] Similarly, in Lucas County, Ohio, EMS professionals used a RACE scale ≥5 to identify potential LVO patients for direct transport to interventional capable stroke centers. Compared with preimplementation stroke-alert protocols, the RACE-alert group had higher rates of IV tPA use (25.7% versus 12.7%) and EVT (20.2% versus 7.7%) and significantly shorter treatment times (IV tPA DTN, 46 versus 75 min; EVT door-to-puncture, 68 versus 128 min).[7] In the central Denmark region, EMS dispatchers and ambulance paramedic used LVO identification screens to identify patients for direct transport to CSCs, bypassing PSCs. Evaluation of the system change identified a significant reduction in median system (prehospital + hospital) delay for EVT (from 234–185 min).[8]
3. Delivery of eligible patients with AIS for rapid reperfusion strategies is the principal objective of SSOC. In areas without local access to TSC and well-coordinated SSOC (specifically rapid local DTN for thrombolysis-eligible patients and DIDO times for transfer of thrombectomy-eligible patients) substantial uncertainty exists on the ideal prehospital destination selection. Neither RACECAT nor TRIAGE-STROKE data inform the answer in this setting.[11,12] Earlier systematic reviews comparing systems were limited and conflicting, while a more recent meta-analysis of 18 studies (n=7017 patients) found a direct transfer model superior to a local PSC drip-and-ship approach for functional independence (53% versus 47%). Meta-regression analysis identified an association between onset-to-needle time and good functional outcome, with longer times being detrimental. Onset-to-needle times were significantly shorter in the direct transfer group, even after the additional transport time, compared with the local PSC group.[9]

4. In nonurban Catalonia, Spain, the multicenter, cluster-randomized, RACECAT trial compared whether EMS transport of 1401 patients with suspected acute LVO stroke resulted in better outcomes if transported directly to a distant TSC compared with the local non-TSC. The primary outcome was shift-analysis of the median mRS score at 90 days and was not different between the 2 groups (3, interquartile range [IQR], 2–5 versus 3 [IQR, 2–5]). Secondary outcomes identified significantly lower odds of receiving IV tPA in patients directly transported to TSCs (47.5% versus 60.4%) and higher odds of receiving thrombectomy (48.8% versus 39.4%). Mortality at 90 days was similar between groups (27.3% versus 27.2%). The trial identified a highly efficient Catalan stroke system at both the thrombectomy-capable center and local stroke center levels. Local stroke centers had median (IQR) DTN times of 33 (25–48) minutes and DIDO times of 78 (63–97) minutes, potentially limiting generalizability to other regions.[11,17] Among RACECAT patients receiving a final diagnosis of ICH, a prespecified secondary analysis identified worse functional outcomes and higher mortality and dependency at 90 days in those transported directly to a distant EVT-capable center compared with the nearest local stroke center.[10] The TRIAGE-STROKE trial evaluated the benefit of direct transport of IVT-eligible patients with suspected LVO to a CSC, bypassing the nearest PSC. This study was terminated after 4 years as planned, after enrollment of 171 patients of a 600-patient sample size, without identifying benefit a benefit of improved functional outcome.[12]
5. In a retrospective US registry-based study that included 108913 patients with acute stroke requiring interhospital transfer from 1925 hospitals, the median DIDO time was 174 minutes (IQR, 116–276 min). Only 27.3% had a DIDO of ≤120 minutes (the recommended target). For the subgroup of patients with AIS eligible for EVT, the median DIDO was 132 minutes (IQR, 97–189 min). The following were significantly associated with a shorter median DIDO time: EMS prenotification (−20.1 min), NIHSS score >12 versus 0 to1 (−66.7 min), and patients with AIS eligible for EVT versus the hemorrhagic stroke subgroup (−16.8 min).[15]

## Knowledge Gaps and Future Research

- Additional research is needed to optimize prehospital identification of patients with stroke who benefit from a higher level of care, under what conditions, in what environment, and within what geographic and transport constraints (distance, traffic). In particular, when multiple stroke centers are available, additional research is needed to inform whether transport to a thrombectomy-capable stroke center is beneficial compared to a non-thrombectomy stroke center for patients without suspected LVO but known to be ineligible for thrombolytic therapy.
- The optimal methods for assessing stroke severity in the field are still understudied.
- The effectiveness of current and novel stroke education and training programs for EMS professionals should be rigorously studied.
- The cost-effectiveness of different EMS destination protocols for stroke care needs further investigation.

## 2.5. Role of Mobile Stroke Units

| Recommendations for Role of Mobile Stroke Units<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | A | 1. In patients with suspected AIS, the use of MSUs over conventional EMS where available is recommended for the transport and management of thrombolytic-eligible patients to ensure the fastest achievable onset-to-treatment time and improve functional outcomes.[1–7] |
| 1 | A | 2. In patients with suspected acute stroke, MSUs must be equipped to diagnose and treat patients with IVT.[1–7] |
| 1 | B-R | 3. In patients with suspected acute stroke, MSU care, including streamlined protocols and use of neurological expertise, either in-person or remote telemedicine consultation, is beneficial for emergent evaluation and treatment of patient symptoms without safety concerns.[2–4,8–10] |
| 2a | B-NR | 4. In endovascular thrombectomy-eligible patients, use of MSUs can be beneficial to identify and triage patients to the appropriate thrombectomy-capable facility with prehospital notification of receiving stroke teams.[2–4,11–15] |

### *Synopsis*

AIS management begins in the prehospital setting. An MSU is a specialized ambulance dispatched after a 9-1-1 call and its interdisciplinary team, comprising paramedics, technicians, nurses, and physicians, including telemedicine consultants, brings direct emergency care to the patient, saving crucial time. MSUs initiate treatment, provide comprehensive prehospital notification, and ensure patients are accurately triaged to the most appropriate receiving hospital. MSU management speeds thrombolytic treatment and improves outcomes for patients eligible for reperfusion therapy. It also potentially enables faster treatment of the most catastrophic type of ischemic stroke, those due to LVO, by expediting the pathway to EVT.

### *Recommendation-Specific Supportive Text*

1. Multiple randomized studies and meta-analyses have shown that, for patients eligible for







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thrombolysis, MSU management results in improvement of functional outcomes at 90 days, reduced onset to treatment times, and increased the proportion of patients receiving IVT within 60 minutes from symptom onset. The B_PROUD (Berlin Pre-hospital Or Usual Delivery of stroke care) trial demonstrated improved functional outcomes for patients treated in MSUs and increased rates and faster administration of thrombolytics. These positive findings were confirmed with the BEST-MSU (Benefits of Stroke Treatment Using a Mobile Stroke Unit) trial, which demonstrated significantly faster thrombolysis and improved clinical outcomes for patients eligible for thrombolytics. Improved outcomes with MSUs were strongly related to higher thrombolytic rates within the first golden hour. No safety concerns (all-cause mortality, proportion of stroke mimics treated with IVT, symptomatic intracerebral hemorrhage [sICH]) were identified for patients managed with an MSU compared with conventional EMS care.[1–7]

2. MSUs are specialized ambulances designed to provide rapid on-site diagnosis and treatment of stroke. They are equipped with advanced imaging capabilities, such as CT scanners, and staffed by highly trained personnel, including neurologists, paramedics, and radiology technicians. Evidence from clinical studies demonstrates that MSUs significantly improve the speed and efficiency of stroke treatment. The B_PROUD and BEST-MSU trials showed that MSUs increased the rates of thrombolysis and reduced the time from stroke onset to treatment, leading to better functional outcomes for patients eligible for thrombolytics. Additionally, the use of MSUs has been associated with higher frequencies of ultra-early thrombolysis within the critical golden hour, which is crucial for minimizing brain damage and improving recovery. By providing immediate access to diagnostic tools and thrombolytic therapy, MSUs ensure that patients receive timely and effective treatment, which is essential given the narrow therapeutic window for thrombolysis in AIS. This approach not only enhances the chances of positive outcomes but also reduces long-term disabilities.[1–7]
3. When implementing MSUs, it is essential to maintain the benefits observed in clinical studies within routine practice. Based on current evidence, this requires streamlined protocols with EMS dispatch, incorporating specialist neurological expertise, either through an in-person stroke expert or via remote consultation and prenotification to receiving hospital stroke teams en route to the receiving center.[2–4,8–10]
4. Two recent randomized trials, B_PROUD and BEST-MSU, confirmed the benefit of MSU management for thrombolysis compared with conventional management by EMS; however, these studies failed to demonstrate improved clinical outcomes for EVT. A recent meta-analysis demonstrated an overall neutral effect of MSU management on alert to puncture times, but a positive effect was seen in studies where a CTA was obtained on board the MSU.[2–4,11–15]

## Knowledge Gaps and Future Research

- Further research is needed to better understand the ideal geographic setting and minimum population density required for the successful implementation of MSUs into SSOC.
- Further studies are required to achieve seamless integration of MSUs in existing EMS and hospital networks, including optimal dispatch pathways.
- More evidence is needed regarding the benefit of MSUs for the management of patients with AIS with LVO.
- More evidence is needed regarding the benefit of MSUs for the management of patients with hemorrhagic stroke.
- More evidence is needed to understand the impact of MSUs on other patients (eg, stroke mimics) evaluated and transported by MSUs.



## 2.6. Hospital Stroke Capabilities

**Recommendation for Hospital Stroke Capabilities**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendation |
|---|---|---|
| 1 | B-NR | 1. In hospitals caring for patients with AIS, certification as a stroke specialty hospital certified by an external health care credentialing agency that uses national evidence-based standard criteria is recommended.[1–7] |

### *Synopsis*

Standardizing hospital stroke capabilities through stroke center certification ensures that patients are treated at hospitals matched to their specific care needs. For example, standardizing hospital stroke capabilities and designating certain hospitals as PSCs versus CSCs helps professionals triage patients based on factors such as the presence of LVO requiring thrombectomy. Standardized hospital stroke capabilities also enables the design of SSOC for specific geographic regions, a strategy to ensure the appropriate distribution of resources and care. Agencies currently providing stroke center certification include The Joint Commission, Det Norske Veritas, Accreditation Commission for Health Care, the Center for Improvement in Healthcare

Quality, and state-based certifiers,[7] in addition to global certification programs such as the World Stroke Organization. Certification of hospitals as stroke centers is a process based on established, evidence-based criteria such as timeliness of initial imaging, timeliness of IVT and thrombectomy, and use of known interventions such as aspirin, anticoagulants, venous thromboembolism (VTE) prevention, and lipid modification therapy as medically indicated during the stroke admission.

### *Recommendation-Specific Supportive Text*

1. Numerous large observational studies, many of which used national stroke registries or other large administrative datasets, have demonstrated that hospitals certified as stroke centers outperform other hospitals in acute stroke care as measured by metrics such as time to imaging, DTN time, and door-to-groin puncture time for patients undergoing EVT.[1,2,4–6] In addition to improved stroke-specific quality metrics, hospitals certified as stroke centers have been shown to have lower short- and long-term mortality rates for patients with stroke.[3] Revised from the 2019 AHA guidelines, this recommendation emphasizes the need for external certifying organizations (as opposed to self-certification programs)[6] and deemphasizes the specific list of certification bodies due to remaining knowledge gaps about differences in performance.[7]

## Knowledge Gaps and Future Directions

- Recent data indicate that there is variability in hospital performance depending on the certifying body[7] and suggests that state-certified stroke centers may have lower rates of IVT and higher rates of mortality, but more data are needed to understand the contributors to such differences between hospitals and to help inform whether these findings warrant recommendations for 1 certifying body over another.
- Further, more research is needed to identify and address socioeconomic barriers to hospital stroke center certification, as previous literature suggests that stroke center status is associated with urban (versus rural) location, higher income service areas, and higher profit margins compared with hospitals that are not certified as stroke centers.[8,9]
- Finally, more knowledge is needed to elucidate the role of stroke center certification in the care of pediatric patients with stroke, as existing data suggest that children with stroke face longer delays to recognition and diagnosis,[10] but time metrics in the acute window for children with suspected stroke can be improved by the implementation of stroke alert protocols.[11] Further, there are some data for the implementation of regional stroke protocols to improve the feasibility of reperfusion therapies in children,[12] suggesting the need to include pediatric stroke care as part of stroke center certification. Currently, however, external certification bodies commonly used by hospitals do not include pediatric-specific standards, despite previous work to develop processes for certification of pediatric stroke centers.[13]

## 2.7. Emergency Evaluation of Patients With Suspected Stroke (Including ED and Stroke Teams)

**Recommendations for Emergency Evaluation of Patients With Suspected Stroke (Including ED and Stroke Teams)**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-NR | 1. Patients of all ages, including pediatric patients, with acute neurological deficits should benefit from an organized protocol for the emergent evaluation of their symptoms in terms of early recognition and treatment.[1–5] |
| 1 | C-EO | 2. In pediatric patients with sudden onset and ongoing focal neurological deficits, including first-time seizure, acute stroke should be suspected to provide timely diagnosis. |
| 1 | B-NR | 3. Patients with suspected stroke should benefit from designation of an acute stroke team, including clinicians, nurses, and laboratory/radiology personnel to ensure careful clinical assessment, including neurological examination.[3,6,7] |
| 1 | A | 4. Patients with suspected stroke should benefit from the development and education of multidisciplinary stroke teams with access to stroke expertise to safely increase the rate of IVT treatment.[8–11] |
| 1 | A | 5. Thrombolytic-eligible patients and EVT-eligible patients should benefit from stroke teams to ensure the fastest achievable onset-to-treatment time and best clinical outcomes.[12–19] |

### *Synopsis*

Given the narrow therapeutic windows for treating AIS, it is imperative to ensure timely evaluation and diagnosis. Hospital systems must establish efficient processes and pathways to manage patients with stroke effectively in both emergency and inpatient settings. This involves the ability to promptly receive, identify, evaluate, and treat patients with suspected stroke. Additionally, hospitals should have access to stroke expertise when necessary for diagnostic or treatment purposes.

Implementing these measures is crucial for improving the overall management and outcomes of patients eligible for thrombolytic therapy or EVT. By streamlining the processes and ensuring rapid response times, hospitals can significantly enhance the chances of positive outcomes for patients with stroke. This comprehensive approach not only facilitates early intervention but also ensures that patients receive the most appropriate and timely care, ultimately leading to better recovery rates and reduced long-term disabilities. These measures are to be integrated within







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comprehensive systems and pathways of care for hyperacute pediatric stroke care.

### *Recommendation-Specific Supportive Text*

1. The evaluation and initial treatment of patients of all ages with suspected stroke should be performed expeditiously. Organized protocols and the availability of a stroke team speed the clinical assessment, the performance of diagnostic studies, and decisions for early management. The clinical assessment (history, general examination, and neurological examination) remains the cornerstone of the evaluation. Stroke scales, such as the NIHSS, provide important information about the severity of stroke and prognostic information and influence decisions about acute treatment.[20–24] Because time is critical, a limited number of essential diagnostic tests are recommended.[25–33] Stroke protocols and pathways should clearly define which tests must be performed before acute treatment decisions and which may be performed after acute stroke therapies.[1–5]
2. In pediatric patients, there is observational evidence that delayed diagnosis of AIS is common and associated with several factors.[34] One of the most important factors is the lack of awareness and suspicion of ischemic stroke in children. Thus, the guideline-writing group advises that AIS be suspected in children with sudden onset of neurological symptoms, to provide timely diagnosis. Ideally, children should also be evaluated jointly by experts in pediatrics and stroke.
3. There is considerable evidence supporting the effectiveness of dedicated stroke teams in the ED for improving clinical outcomes in acute stroke care. According to a comprehensive review by the AHA, the implementation of specialized stroke teams in the ED significantly enhances the speed and accuracy of stroke diagnosis and treatment. This review highlights that stroke teams, which include neurologists, emergency physicians, nurses, and radiology personnel, are crucial for ensuring rapid assessment and intervention, leading to better patient outcomes. Structured protocols and the presence of dedicated stroke teams in the ED lead to faster administration of thrombolytic therapy and improved functional outcomes for patients. These findings are supported by multiple clinical trials and meta-analyses, which have consistently shown that coordinated stroke care in the ED reduces mortality and disability rates among patients with stroke.[3,6,7]
4. There is substantial evidence that the use of thrombolytics is safely and effectively increased when multicomponent programs incorporate acute stroke teams and, when needed, telestroke specialist consultations. In the INcreasing Stroke Treatment through Interactive behavioral Change Tactics (INSTINCT) trial, alteplase use increased from 1.00% before intervention to 2.62% after intervention within the intervention group hospitals without safety concerns. In the PRomoting ACute Thrombolysis in Ischemic StrokE (PRACTISE) trial, after multilevel implementation of an intensive stroke treatment strategy, intervention hospitals treated 13.1% of all patients with acute stroke versus 12.2% at control hospitals (adjusted OR, 1.25 [95% CI, 0.93–1.68]). The AVC II trial yielded similar results for increasing thrombolytic rates between intervention and control groups (adjusted OR, 1.39 [95% CI, 1.01–2.02]). The Thrombolysis in Pediatric Stroke (TIPS) trial found no significant change in thrombolytic rates, suggesting that ongoing programs are needed to sustain initial modifications in behavior. Developing local stroke protocols that effectively use available local and regional resources, while clearly identifying access to neurological expertise, enhances the chances for timely and effective acute treatment.[8–11]
5. IVT is proven to benefit select patients with AIS when administered within 4.5 hours of symptom onset. Data from RCTs and the AHA Get With the Guidelines (GWTG)-Stroke registry show that the earlier the treatment, the greater the benefit, which diminishes over time. Rapid treatment, evaluated in 15-minute increments, is linked to reduced in-hospital mortality (OR, 0.96 [95% CI, 0.95–0.98]; $P<0.001$), lower rates of sICH (OR, 0.96 [95% CI, 0.95–0.98]; $P<0.001$), increased independent ambulation at discharge (OR, 1.04 [95% CI, 1.03–1.05]; $P<0.001$), and higher rates of discharge to home (OR, 1.03 [95% CI, 1.02–1.04]; $P<0.001$). For EVT, a pooled analysis of 5 RCTs comparing EVT with medical therapy alone, mostly within 6 hours of symptom onset, found that the odds of improved disability outcomes at 90 days (measured by the mRS) decreased with longer times from symptom onset to arterial puncture. Trials with 6- to 16-hour and 6- to 24-hour treatment windows showed similar treatment effects in highly selected patients. To maximize the number of eligible patients receiving thrombolytics and/or thrombectomy and best clinical outcomes, rapid evaluation and treatment are essential.[12–19]

## Knowledge Gaps and Future Research

- Further research is needed regarding the optimal trigger for ED code stroke in patients with acute neurological deficits.
- Further research related to the integration and benefit of artificial intelligence in stroke recognition and treatment is needed.

## 2.8. Telemedicine

| Recommendations for Telemedicine<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| Prehospital telemedicine | | |
| 1 | B-R | 1. For patients with suspected stroke in the prehospital setting, telemedicine in the ambulance should be considered, when feasible, to complement paramedic assessment to identify candidates for reperfusion interventions.[1–4] |
| Teleradiology | | |
| 1 | B-NR | 2. For patients with AIS presenting to EDs without in-house imaging interpretation expertise, teleradiology systems are recommended for timely review of brain imaging, identification of contraindications to thrombolysis, and facilitation of IVT decision-making.[5–7] |
| Telestroke for thrombolytic decision-making and administration | | |
| 1 | B-R | 3. For patients with AIS presenting to EDs without acute neurological expertise, telestroke systems are effective over usual care by the ED team for IVT decision-making and optimal thrombolytic delivery including increased thrombolytic administration and shorter time to delivery.[8–20] |
| 2a | B-NR | 4. For patients with AIS treated at hospitals without local stroke expertise, telestroke is reasonable to reduce short-term mortality.[11,16,20–22] |
| 2a | C-LD | 5. For patients with AIS treated at hospitals without in-house stroke expertise or telestroke capabilities, decision-making support by telephone consultation with a stroke specialist can be beneficial for IVT decision-making and consideration of EVT eligibility.[8–10,23] |
| Telestroke in stroke systems of care | | |
| 1 | C-EO | 6. Health care institutions, government payers, and vendors should support the use of telemedicine/telestroke resources and systems to ensure adequate 24-hour/day and 7-day/week coverage and care of patients with AIS in various settings. |
| 2b | B-NR | 7. For patients with AIS presenting to hospitals with telestroke capability, use of telestroke may be reasonable for triage of patients who may be eligible for appropriate interfacility transfer for emergency EVT versus local care.[12,14,15,22,24–27] |

### *Synopsis*

Telestroke technology has been instrumental in bridging gaps in access for patients in remote locations or who would not have otherwise had access to stroke-related expertise. Telestroke has applications across the continuum of care. In the prehospital setting, the use of telemedicine in the ambulance may be advantageous to identify candidates for reperfusion interventions and, in turn, guide transport destination decisions and facilitate preparations at the receiving hospital.[1–4] In the acute ED setting, teleradiology and telestroke are valuable for enabling timely reviews of brain imaging, facilitating thrombolytic decision-making, and optimizing timeliness of thrombolytic delivery.[5,7,8] Recent nonrandomized studies have also demonstrated the benefit of telestroke for improving patient outcomes, including short-term mortality.[11,20,23] Studies have additionally demonstrated the role of telestroke in SSOC, with potential benefits that include triage and transfer of patients eligible for EVT as well as identification of patients who do not require transfer and may safely receive care locally.[3,14,15,22,24–27]

### *Recommendation-Specific Supportive Text*

1. The use of telemedicine in the ambulance, before hospital arrival, for patients with suspected stroke involves audio-video communication for video-based consultation during patient transportation, with communication between prehospital personnel and stroke specialists for the purpose of guiding transport destination decisions and facilitating preparation at the receiving hospital. A small-cluster randomized clinical trial compared telemedicine in the ambulance with paramedic assessment using a modified stroke scale. Relative to paramedic assessment, telemedicine performed better at identifying patients for reperfusion intervention.[1] Three additional observational studies also demonstrated benefit, including that telemedicine in the prehospital setting was accurate for identification of AIS due to LVO[2] and for improving time-based metrics after hospital arrival, including DTN time for thrombolytic delivery.[3,4]
2. Studies of teleradiology to read brain imaging in acute stroke have successfully assessed feasibility; agreement between telestroke neurologists, radiologists, and neuroradiologists over the presence or absence of radiological contraindications to IV alteplase; and reliability of telestroke radiological evaluations. These studies include a pooled analysis of the Stroke Team Remote Evaluation Using a Digital Observation Camera (STRokE DOC) and STRokE DOC Initial Mayo Clinic Experience (AZ TIME) trials as well as the STRokE DOC in Arizona trial, which were prospective, outcome-blinded, RCTs comparing telemedicine and teleradiology with telephone-only consultations. In these studies, CT scan interpretations by hub vascular neurologists showed very high agreement (95.4%) with central reads by a blinded adjudicating committee with respect to identification of radiological contraindications to thrombolysis and overall reports (ie, presence of a normal scan, ICH, subarachnoid hemorrhage, subdural hematoma, tumor, or hyperdense artery).[5,8] Observational data have also demonstrated good agreement between CTs read by telestroke neurologists and neuroradiologists for identification of early ischemic changes and clinically relevant CT interpretation (<2% of CTs read with clinically relevant discrepancies).[7]







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3. The STRokEDOC RCTs supported the hypothesis that, compared with telephone-only consultation, telemedicine consultations resulted in more accurate thrombolytic eligibility decision-making for patients with suspected stroke in the ED.[5,7,8] A large quasi-experimental difference-in-differences analysis also demonstrated that, relative to control hospitals, patients presenting to telestroke hospitals had higher reperfusion rates.[11] Several additional nonrandomized studies and 1 systematic review and meta-analysis have demonstrated improved IVT delivery with telestroke, including similar or improved time to thrombolytic delivery and fewer complications among telestroke sites.[16–18,20] Other observational studies and a systematic review and meta-analysis have demonstrated similar performance between telestroke spoke and hub hospitals with respect to thrombolytic delivery, times to treatment, and complication rates.[12,13,15,19] Another systematic review and meta-analysis comparing a drip-and-stay telestroke model with a hub-based drip-and-ship model also found similar functional outcomes, rates of sICH, and 90-day mortality.[14]
4. One large quasi-experimental difference-in-differences analysis demonstrated that, relative to control hospitals, patients presenting to telestroke hospitals had lower 30-day mortality,[11] with similar findings of decreased in-hospital mortality demonstrated in 2 large observational studies.[20,21] In addition, 2 systematic reviews and meta-analyses have examined outcomes among patients treated with thrombolysis in a telestroke model, finding that patients treated via telestroke had similar outcomes to those treated in stroke centers or hub hospitals. One review of 1863 patients from 7 studies examined patients treated with thrombolysis via telestroke versus in-person stroke neurologist consultation and found similar rates of sICH, functional independence, and mortality.[12] A second review of 4164 patients from 10 studies compared patients treated via a drip-and-stay telestroke model versus hub-based and drip-and-ship models of care and found no significant difference in rates of sICH, functional outcomes, or 90-day mortality between the drip-and-stay model and compared to hub-based or drip-and-ship models.[14]
5. For patients with acute stroke syndromes treated at hospitals with radiology or teleradiology but without in-house stroke expertise or telestroke capabilities, telephone consultations may be useful. Advantages include feasibility, established precedence, simplicity, availability, portability, short consultation time, and facile implementation.[23] The STRokEDOC randomized trials, which examined telestroke versus telephone consultation, demonstrated similar secondary outcomes between groups, including rate of thrombolytic use.[5,7,8]
6. Given the evidence of benefit for telestroke in improving clinical decision-making and patient outcomes for patients with ischemic stroke presenting to the ED and hospitals without on-site neurological expertise, the use of telestroke resources and systems should continue to be supported by health care institutions, governments, payers, and vendors to ensure more equitable access to stroke care regardless of patient geography or site of initial presentation.
7. Telestroke networks may enable the triage of selected patients with ischemic stroke transferred from remote hospitals for EVT consideration at capable centers. An observational study compared clinical outcomes after EVT between patients with anterior circulation stroke transferred after teleconsultation and those directly admitted to a TSC. Compared with the 103 directly presenting patients, the 48 transferred patients had higher rates of thrombolytic receipt, lower rates of sICH and mortality, and similar rates of reperfusion and favorable functional outcomes, despite prolonged time to EVT initiation.[24] A number of observational studies, mostly from individual telestroke networks, have also described the application of telestroke for transfer avoidance, largely without deleterious impact on patient outcomes.[15,25,26] However, 1 observational study from a single health system did find that drip-and-stay patients had increased risk adjusted in-hospital mortality, longer length of stay, and decreased long-term survival.[22]

## Knowledge Gaps and Future Research

- The role of telestroke in SSOC warrants further study and development. Recent studies have identified the feasibility and safety of telestroke for reducing interhospital transfers and treating patients locally, including through the use of telestroke for inpatient services.[25,26] Particularly in the current context of crowded EDs and hospitals and already strained interhospital transfer systems, the potential for telestroke to enable more patients to be safely treated locally is appealing. However, a large, national, observational study found that implementation of telestroke did not impact stroke patient transfer patterns.[27] Further research confirming the safety and other patient-centered benefits of using telestroke to avoid unnecessary interhospital transfer is warranted to inform the role of telestroke in the organization of SSOC.

## 2.9. Organization and Integration of Components

**Recommendations for Organization and Integration of Components**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-EO | 1. Hospitals should participate in an accountable SSOC that consists of an integrated network of certified hospitals (ie, ASRH, PSC, TSC, CSC) and prehospital EMS systems designed so patients in need of acute stroke care receive appropriate and timely evaluation, diagnosis, treatment, and interhospital transfer (when appropriate) that optimizes their long-term outcomes. |
| 1 | C-EO | 2. Hospitals caring for patients with acute stroke that do not provide 24/7 thrombectomy treatment (eg, ASRH, PSC hospitals) should develop interhospital transfer protocols and procedures to ensure fast, safe, and efficient transfer of patients who are potentially eligible for EVT. |
| 1 | B-NR | 3. PSC hospitals caring for patients with acute stroke that do not provide 24/7 thrombectomy treatment and therefore rely on interhospital patient transfers should have the capability to rapidly perform and interpret intracranial vascular imaging (CTA or magnetic resonance angiography [MRA]) to identify patients with LVO eligible for EVT.[1–6] |
| 1 | B-NR | 4. Hospitals caring for patients with acute stroke should develop and adopt care protocols that reflect current clinical guidelines as established by national and international professional organizations or state or federal agencies and laws.[7–10] |
| 1 | B-R | 5. Hospitals caring for patients with acute stroke that provide EVT (ie, TSC, CSC hospitals) should develop a system to comprehensively track key time metrics and other care processes relevant to thrombectomy (eg, door-to-puncture time, successful reperfusion), as well as long-term patient outcomes.[1,11–13] |
| 1 | C-EO | 6. Hospitals caring for patients with acute stroke that provide EVT (ie, TSC, CSC hospitals) should credential neurointerventionalists using established and agreed upon training and certification standards. |
| 2a | B-NR | 7. ASRH caring for patients with acute stroke that rely on interhospital patient transfers can consider having the capability to rapidly perform and interpret intracranial vascular imaging (CTA or MRA) to identify patients with LVO eligible for EVT.[3–6] |
| 2b | B-NR | 8. Depending on the characteristics of the local and regional systems of care, individual SSOC may consider developing mobile intervention teams to improve timely delivery of EVT.[14–16] |

### *Synopsis*

At a local or regional level, the delivery of evidence-based reperfusion therapies (ie, thrombolysis and EVT) in a timely, efficient, and equitable manner requires establishment of a coordinated SSOC.[1] The system should include an integrated network of EMS agencies, and hub and spoke hospitals with appropriate levels of stroke certification (ie, ASRH, CSC, TSC, PSC) that collaborate together to provide access to all essential components of acute stroke care. Each system should include ≥1 hub (or referral) centers that provide thrombectomy treatment (ie, CSC, TSC, PSC) as well as other advanced neurosurgical care (ie, CSC). Care protocols for the safe, efficient, and expedient delivery of reperfusion therapy should be established by all hospitals, regardless of where they sit within an SSOC. Spoke hospitals should develop an interhospital transfer protocol that ensures the expedient transfer of patients eligible for EVT or other advanced stroke care.[2] Transfer decisions should be informed by the results of advanced neurological imaging that is appropriate to the hospital's expected level of resources and position within the SSOC. Every SSOC should be definable, recognizable, and accountable to the local or regional populations that it serves.[17]

### *Recommendation-Specific Supportive Text*

1. Accurately identifying and treating patients with acute stroke who are eligible for reperfusion therapies in an effective and equitable manner requires the development of an SSOC that provides a comprehensive, well-coordinated, and efficient health care delivery system, bridging the prehospital, in-hospital, and posthospital environments. An accountable SSOC places emphasis on the importance of hospitals' and health systems' involvement in defining a given SSOC, understanding their role in it, and taking ownership of its functions, capacities, and care provided to the communities that it serves.[17] Consensus-based guidelines are available that identify the optimal structures, functions, and goals for SSOC.[1,2] Model- or simulation-based research studies do exist that seek to identify the optimal organizational or functional components of stroke systems[18–22]; however, the generalizability of their findings to SSOC in other countries or under other health care systems is uncertain. Uncertainty therefore remains in terms of how an SSOC can be best designed, optimized, and monitored.
2. SSOC should be designed around a hub and spoke system in which hub hospitals (eg, CSC, TSC) act as referral centers for the delivery of reperfusion therapies and other advanced neurosurgical care. Such systems require that spoke hospitals (eg, ASRH, PSC) develop and implement interhospital transfer protocols that quickly identify and transfer patients to the closest CSC that can provide the required level of specialty care.[2] Previous studies have shown that the number of interhospital transfers for acute stroke care is increasing over time[23–25] but that prolonged interhospital transfer times (eg, >120 minutes) are common in patients with acute stroke,[25,26] and transfer delays are associated with poorer patient outcomes in those treated with endovascular therapy.[27] Thus, protocols should be developed that emphasize system efficiency and speed; however, we note that research studies undertaken to identify the ideal organizational structures and processes for interhospital transfers are lacking.
3. The efficient interhospital transfer from PSCs of patients with acute stroke who can benefit from







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EVT requires the accurate and expedient identification of LVO using intracranial vascular imaging.[1,2] Because only a minority of patients with acute stroke are eligible for EVT (upper estimates range, 10%–15%),[28] and transfers potentially move patients farther from their support networks and increase the burden on referral centers, it is essential to accurately identify patients with LVO and who are likely to receive EVT once transferred. CTA- or MRA-based intracranial vascular imaging is an efficient and accurate approach for identifying this subgroup of patients.[3] Information from CTA-/MRA-based imaging studies combined with efficient decision-making and interhospital transfer processes can minimize the time from stroke onset to EVT treatment, resulting in fewer false-positive transfers.[3] A large majority of community-based EDs in the United States report having access to CTA.[29] Single-center studies have demonstrated the value of applying CTA imaging to all AIS admissions who arrive within 24 hours.[4] Implementing a broad CTA imaging strategy increased the detection of LVO lesions and the use of EVT treatment, which was also delivered more rapidly.[4] However, the ideal imaging capability at spoke hospitals that maximizes diagnostic accuracy and maintains an efficient interhospital transfer while proving to be feasible, cost-effective, and sustainable for spoke hospitals is still uncertain. The ideal approach will, to a large extent, be dependent on the particular organizational features of the SSOC to which the PSC belongs.[2,3]

4. The coordinated delivery of high-quality clinical care to patients with acute stroke requires a well-organized, multidisciplinary care team. The use of care protocols or pathways that contain a detailed set of instructions based on current best evidence-based practices is a logical step to ensure that optimal care is provided to every patient. Written care protocols have been identified as a key element for establishing PSCs.[7,8] Numerous observational QI programs designed to improve access and timeliness of thrombolysis treatment have included care protocols as part of their interventions.[9,10,30,31] More recently, several multicomponent QI intervention studies designed to improve care across a broader range of quality indications have included care protocols.[32–34] Although these projects demonstrated improvements in care quality and/or outcomes, they were not designed to identify the independent effects of care protocols.
5. With a number needed to treat (NNT) as low as 3, EVT for AIS is 1 of the most efficacious treatments available in all of medicine.[35] However, as with IVT treatment, clinical benefit of thrombectomy is directly related to time from stroke onset; therefore, performing thrombectomy as expeditiously as possible is of the utmost importance. Performance metrics designed to monitor the quality, timeliness, and outcomes related to thrombectomy care have been developed,[13,37] and have been incorporated into stroke center certification processes.[38] Consensus statements emphasize the importance of tracking EVT time points and patient outcomes[1] and conducting ongoing QI activities, including peer review for monitoring thrombectomy care.[13] Case examples exist of successful QI-based programs related to thrombectomy care,[12,39–41] including evidence from randomized trials.[11] These studies can serve as templates for individual hospitals and health care systems to improve and monitor the quality of thrombectomy care and associated patient outcomes.
6. Training and certification standards are important tools to help ensure quality of training and maintenance of skills through continuing education. At present, several national certifications for neurointerventional training programs and individual practitioners are in broad use, including those from the ACGME (Accreditations Council for Graduate Medical Education), UCNS (United Council of Neurological Subspecialists) and CAST (Committee on Advanced Subspecialty Training). Certification pathways for these organizations are also available to neuro-interventionalists who trained prior to fellowship certifications or trained in non-accredited fellowships, but who perform neuro-interventional procedures as a substantial component of their clinical practice. These pathways are known as "practice-based" tracks. A consensus document describing institutional requirements for neurointerventional training programs was published in 2017.[42]
7. The critical need to improve identification of LVO stroke in rural and lower-resource centers has recently been highlighted.[43] Obviously, the need for accurate and expedient identification of LVO at ASRHs is no less important than at PSC hospitals. Recent studies have highlighted the rapid growth of CTA and other forms of advanced neuroimaging in patients with acute stroke,[44,45] as well as increases in the use and capabilities for advanced imaging in US-based EDs.[29,46] However, these studies also illustrate the lower imaging capabilities of smaller and more rural hospitals.[29,45,46] Although studies have described alternate strategies for CTA implementation,[4,47] the optimal imaging approach for ASRHs remains undefined. The tradeoffs of expanding vascular imaging capabilities at lower resourced hospitals in terms of the feasibility, efficiency, and cost-effectiveness is more uncertain; hence, recommendations have to be based on

realistic assessments of the potential gains relative to cost and practical concerns. Beyond direct improvements in neuroimaging capabilities (involving the rapid acquisition, interpretation, and transfer of vascular images) at ASRHs, improvements are also needed in provider training to increase the detection of LVO cases in the field so that CTA resources can be more efficiently targeted in those patients suspected of having LVO.[43]

8. The majority of endovascular treatments are delivered at specialty stroke centers to patients who either arrive directly (mothership model) or are admitted after interhospital transfer (drip-and-ship model). The number and distribution of hospitals in the United States that deliver EVT have occurred with little oversight; thus, current regional systems are not optimized,[48] leading to inefficiencies and geographic disparities in access.[49] Alternative models of care that improve geographic coverage while maintaining system efficiency are needed. The mobile intervention team approach is one in which the endovascular team travels to the spoke hospital to deliver EVT. Transportation modes that have been evaluated include the use of helicopters (Bavaria, Germany),[14] the combination of subway trains and vehicles (New York City, USA),[15,50]or vehicles only (Heidelburg, Germany[16]; Hokkaido Prefecture, Japan[51]). Compared with alternative approaches, all mobile intervention team models demonstrate faster EVT treatment and, in some studies, better patient outcomes.[14,52] However, the implementation of such systems is complicated and would depend on the characteristics of local and regional systems of care, such as the size and population density of the proposed coverage area, the geographic distribution of existing EVT care centers, the willingness of hospitals/health systems to collaborate, and reimbursement mechanisms.

## Knowledge Gaps and Future Research

- Development and implementation of model- or simulation-based research methods that seek to define the optimal organizational and functional components of SSOC for a given region or defined population are required.
- Studies undertaken to define the ideal organizational structure and processes of interhospital transfers and the influence of interhospital transfer delays are needed.
- More research is needed on the optimal imaging approach, particularly with respect to candidates for interhospital transfer (eg, simultaneous versus sequential CT, CTA, and CT perfusion [CTP] imaging).
- More quantitative assessments of the ideal imaging capabilities at spoke hospitals (ie, PSC, ASRH) involved in SSOC would be beneficial to understand the feasibility, cost-effectiveness, and sustainability of wider implementation of intracranial vascular imaging capabilities.
- More surveys and qualitative studies of imaging capabilities at spoke hospitals (ie, PSC, ASRH) involved in SSOC would be beneficial.
- Further studies to identify the independent effects of care protocols on quality of care and patient outcomes would be useful.
- Studies to measure the effectiveness of QI efforts for improving and monitoring thrombectomy treatment metrics and patient outcomes are needed.

## 2.10. Stroke Registries, Quality Improvement, and Risk Adjustment

**Recommendations for Stroke Registries, Quality Improvement, and Risk Adjustment**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. Hospitals treating patients with acute stroke should engage in a multicomponent QI process that involves the continuous monitoring, review, and feedback of stroke quality indicators, benchmarks, and evidence-based practices, in order to increase quality of care, improve patient outcomes, and reduce health care disparities.[1–8] |
| 1 | B-NR | 2. Hospitals treating patients with acute stroke should participate in stroke data registries to increase the adherence to quality indicators and guideline recommendations and improve patient outcomes.[1,3,7,9–17] |
| 1 | B-NR | 3. Hospitals treating patients with acute stroke should measure and document baseline stroke severity (eg, NIHSS score) in all acute stroke patients so that risk adjustment models used to compare hospital performance can be sufficiently accurate and reliable.[18–29] |

### *Synopsis*

QI interventions promote adherence to evidence-based performance measures, quality standards, and better patient care, and are associated with improved patient outcomes, including reduced mortality in patients with AIS. Effective individual strategies consist of identification of clinical leaders and QI care teams, staff training and educational workshops, identification of barriers and gaps, development of clinical pathways and action plans, and continuous monitoring and feedback.[1–3] As a foundation for conducting QI on a continuous basis, a standardized stroke registry (or data repository) is the ideal tool for monitoring, analyzing, and providing feedback to stakeholders. Registry data provide opportunities to explore the quality of care according to current quality indicators and recommendations, identify disparities and needs in health care, implement benchmarking, and support clinical research.[30–32] Stroke severity, ideally







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measured by the NIHSS, is a significant predictor of stroke outcomes and should be used in risk adjustment models to compare hospital performance. However, to avoid the introduction of selection bias, it is important that NIHSS scores are recorded accurately and consistently at each center for all patients admitted with AIS.

### *Recommendation-Specific Supportive Text*

1. Data from 3 cluster RCTs have shown that multicomponent QI interventions are effective in improving adherence to evidence-based performance measures[1–3] and faster thrombolysis treatment[2] in patients with AIS. Individual strategies and components used in these trials include educational workshops, staff training, identification of clinical leaders, development of QI care teams, identification of barriers and gaps, development of clinical pathways, care protocols, or action plans, and continuous monitoring and feedback of care performance.[1–3] Results from nonrandomized studies using a matched hospital design[4] or pre- and post-comparative designs[5,6] have also highlighted the effectiveness of multicomponent QI interventions to improve the quality of care[4–6] and patient outcomes after ischemic stroke.[6] Two large registry-based studies that used multiple individual QI strategies to target the timeliness of IVT treatment both demonstrated rapid declines in DTN times and improved patient outcomes.[6,8]
2. Nonrandomized observational studies analyzing trends over time in centers participating in stroke registries and pre- and post-intervention studies have shown that participation in a stroke data registry as 1 part of a QI process has been associated with improved adherence to stroke care quality measures[9,11,12] increased rate and earlier administration of reperfusion therapy,[8,10,15,16,33] more patients discharged at home,[10,33] lower mortality,[7,10,11,14] and fewer clinical vascular events during follow-up.[1] Several studies have shown that participation in a stroke registry improves both the quality of care and patient outcomes; an analysis of the Reasons for Geographic and Racial Differences in Stroke (REGARDS) population-based cohort found that 207 patients with incident stroke who were admitted to a hospital that participated in a stroke registry received better quality care than 339 patients admitted to a nonparticipating hospital.[13] A comparison study of 732 hospitals that were matched according to whether they participated in the GWTG-Stroke registry or not found that patients treated at registry hospitals had greater reductions in mortality at 30 days and 1 year and higher rates of discharge to home compared with patients treated at nonparticipating hospitals.[7] Another comparison study of 50 579 patients, including 56% treated in centers participating in the Coverdell Acute Stroke Registry, found that patients cared for at nonparticipating centers had a higher risk of death after the first week of admission compared with patients cared for at participating hospitals.[17] Access to the current definitions of the stroke measures tracked by the Joint Commission can be found on its website,[34] while the list of 2023 quality measures for the AHA-GWTG program can be found on its website.[35]
3. Stroke outcomes at the individual patient level are strongly influenced by baseline stroke severity, as measured by the NIHSS.[18–20,29] Including the NIHSS in multivariable prediction models of stroke outcomes results in meaningful increases in model performance.[21,22] When comparing hospital performance based on stroke outcomes, risk adjustment models should include a measure of stroke severity.[21,23] However, accurate profiling or rank ordering of hospitals requires that NIHSS data are recorded accurately and consistently at each center. Although documentation of NIHSS data in registries such as the GWTG-Stroke has improved in recent years, historically, NIHSS data have had high rates of missingness combined with selection bias,[24] which can complicate risk adjustment procedures.[25] An administrative code for the NIHSS score (ICD-10 R29.7xx) was introduced in 2016 to allow for the broader implementation of stroke risk adjustment across hospitals regardless of their participation in a stroke registry.[26] However, as with the data from stroke registries, this code suffers from incomplete documentation (ie, missingness) and evidence of selection bias.[22,27,28]

## Knowledge Gaps and Future Research

- Expansion of registries to capture more data from the prehospital setting and related to interhospital transfer processes would be of value to enable future research in those domains.
- More than 25 national registries have been identified around the world[36]; examples of regional or national level registry data include GWDG (EUA), RES-Q (Europe), GWTG-Stroke (US), AusCR (Australia), and SSNAP (UK). Further research is required to understand how health systems and regional stroke programs can best facilitate the use and management of data from regional or national stroke registries that allow comparisons across centers and regions. An international stroke registry consortium may be a viable future endeavor.
- Further research is also required to understand how best to sustain QI interventions across SSOC, to demonstrate if and how such QI interventions affect

patient outcomes, and to understand the role of organizational- and systems-level contexts in supporting QI efforts.
- Although a study has shown high interrater reliability of the PedNIHSS by trained pediatric neurologists, future research is required to determine its use for risk adjustment model evaluations.[37]

## 3. EMERGENCY EVALUATION AND TREATMENT

### 3.1. Stroke Scales

| Recommendation for Stroke Scales<br>Referenced studies that support the recommendation are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendation** |
| **1** | **B-NR** | 1. In patients with suspected AIS, the use of a stroke severity rating scale, preferably the NIHSS, is recommended for measuring clinical deficits at baseline and after reperfusion therapies.[1,2] |

#### *Synopsis*

The NIHSS is a well-established standardized scale that can be accurately performed by a broad spectrum of health care professionals and reliably quantifies the degree of neurological deficit, facilitates communication, helps identify patients eligible for thrombolysis or EVT, allows an objective measurement of changing clinical status, and identifies those patients at higher risk for complications such as ICH.[1–5]

#### *Recommendation-Specific Supportive Text*

1. Stroke severity at baseline as measured by the NIHSS has been found to be one of the strongest predictors of mortality and rate of independence at 30 days and 3 months.[1,2] Baseline NIHSS score and Δ NIHSS score at 24 hours are independent predictors of 3-month good functional outcome in patients with postthrombolysis sICH.[3] Further, absolute 24-hour NIHSS score, treated as a continuous variable and adjusted for baseline score, is the best predictor of 90-day functional outcomes.[4] The NIHSS score within 1 week after EVT fulfills the requirements for a surrogate endpoint for longer-term outcomes.[5] Thus, the NIHSS is the primary tool for initial stroke assessment, treatment decisions, and predicting clinical course.

### Knowledge Gaps and Future Research

- Key gaps in knowledge include the limitations of the NIHSS in evaluation of posterior circulation strokes, its overall interrater reliability,[6–8] its left brain bias, and cultural appropriateness of the imaging depictions in its current widely used format. The modified NIHSS was previously proposed to improve reliability and reduce complexity.[7] However, it has not gained widespread clinical use likely due to only modest improvements compared with the original NIHSS.[6] A study by Stockbridge et al recently attempted to address the left brain bias and cultural limitations, providing new picture stimuli to assist health care professionals caring for patients with stroke.[9] Although the new images seem to offer broader cultural applicability, further studies are needed to inform the clinical use of the modified NIHSS and evaluate its ability to overcome the left brain bias in neurological assessment by the original NIHSS.
- In limited studies, the PedNIHSS has shown high interrater reliability among pediatric neurologists assessing stroke in children. However, future studies to validate these early results are necessary.[10]

### 3.2. Initial, Vascular, and Multimodal Imaging Approaches

| Recommendations for Initial, Vascular, and Multimodal Imaging Approaches<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| IVT evaluation | | |
| **1** | **A** | 1. In patients with suspected AIS, emergent brain imaging with NCCT or MRI is recommended on initial evaluation to assess ischemic burden (eg, ASPECTS) and exclude intracranial hemorrhage before initiating reperfusion interventions (see Figure 2). |
| **1** | **B-NR** | 2. In hospital systems that care for patients with suspected AIS, protocols based on process improvement initiatives should be established so that emergent brain imaging can be performed as rapidly as possible (eg, within 25 minutes) to facilitate timely reperfusion interventions.[1,2] |
| **1** | **B-NR** | 3. In patients with suspected AIS and LVO, emergent vascular imaging with contrast-enhanced CTA and/or CTP should not be delayed to obtain serum creatinine concentration.[3,4] |
| **2a** | **C-LD** | 4. In pediatric patients with suspected AIS, emergent brain and vascular imaging with MRI/MRA of the cervical and intracranial vessels is reasonable to identify patients with large vessel occlusion and to differentiate arterial ischemic stroke from hemorrhagic stroke or stroke mimics.[5–8] |
| **2a** | **C-LD** | 5. In pediatric patients with suspected AIS, emergent brain and vascular imaging with CT/CTA of the cervical and intracranial vessels is reasonable if MRI/MRA imaging is not available immediately (within 25 minutes) to identify patients with large vessel occlusion.[5–9] |
| **2a** | **B-R** | 6. In patients with suspected AIS who awaken from symptoms or have unknown time of onset >4.5 hours from last known well, but are otherwise eligible for thrombolysis, MRI DWI-FLAIR mismatch selection can be useful to determine eligibility for extended window IVT.[10,11] |







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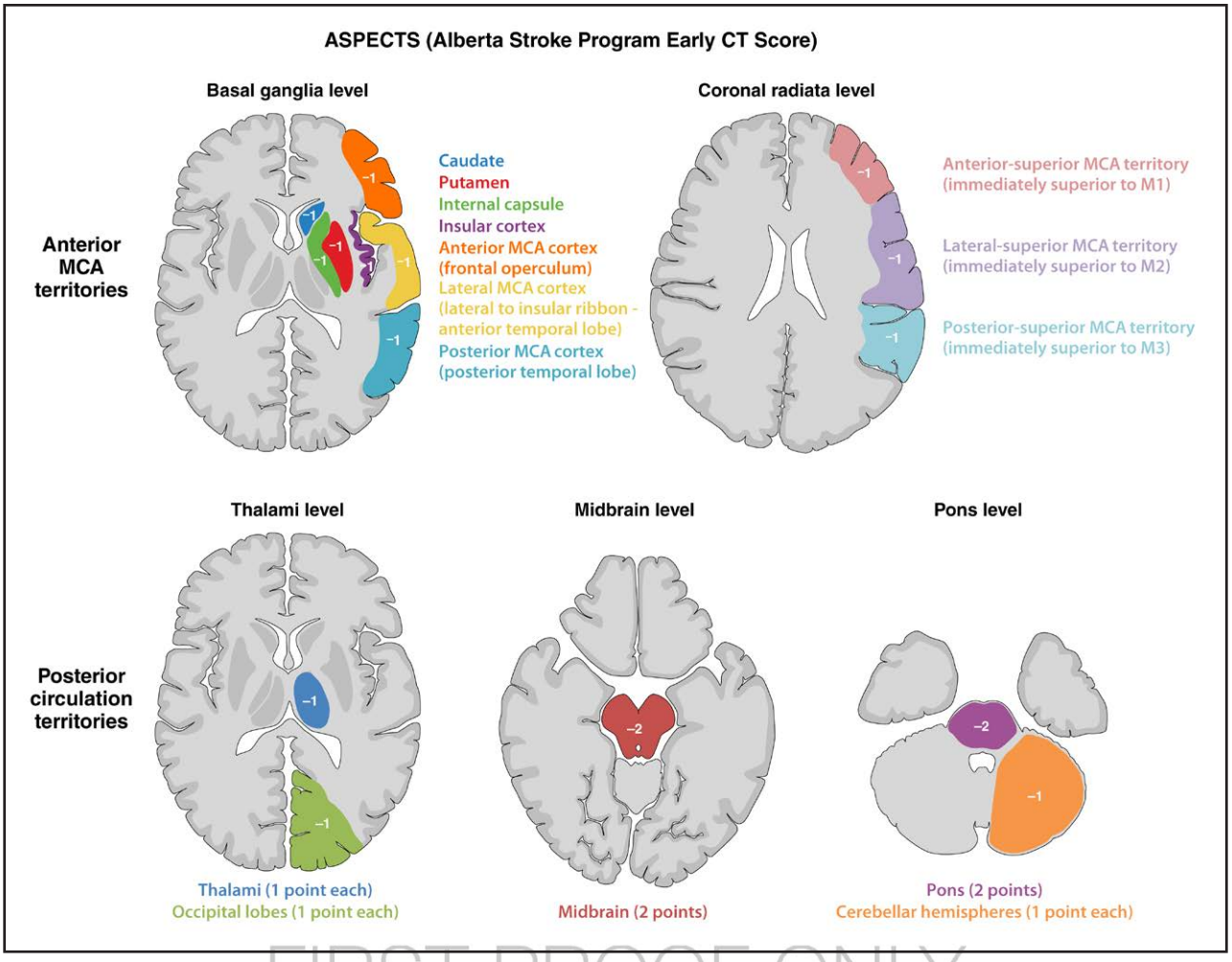


**Figure 2. ASPECTS: Alberta Stroke Program Early CT Score.**
CT indicates computed tomography; and MCA, middle cerebral artery.



| Recommendations for Initial, Vascular, and Multimodal Imaging Approaches (Continued) | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **2a** | **B-R** | 7. In patients with suspected AIS who awaken with symptoms or have unknown time of onset 4.5 to 24 hours from last known well, CTP or MR DWI-PWI (perfusion-weighted imaging) selection with automated postprocessing software analysis can be useful to determine eligibility for extended window IVT.[12,13] |
| Endovascular thrombectomy evaluation | | |
| **1** | **A** | 8. In patients with suspected AIS and LVO presenting within 24 hours of last known well, emergent brain and vascular imaging (CT/CTA or MRI/MRA) of the cervical and intracranial vessels should be performed as rapidly as possible for EVT selection and treatment planning. |
| **2a** | **A** | 9. In patients with suspected AIS and LVO presenting within 6 to 24 hours of last known well, adjunctive CTP, MRI (DWI-FLAIR mismatch), or MR DWI-PWI with automated postprocessing software analysis can be useful in the evaluation for EVT, if immediately available.[14] |

| Recommendations for Initial, Vascular, and Multimodal Imaging Approaches (Continued) | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| **2b** | **B-R** | 10. In patients with suspected AIS and LVO based on prehospital assessment with a validated stroke severity scale (eg, RACE >4) and eligible for EVT, direct triage to the angiography suite (DTAS) for flat-panel head CT versus conventional imaging workflow followed by catheter-based angiography may be considered to reduce time to intervention and improve functional outcomes.[15–17] |
| **2b** | **B-NR** | 11. In emergently transferred patients with suspected AIS due to LVO (based on imaging or clinical assessment) and eligible for EVT, DTAS may be considered without repeat brain imaging (unless there is clinical change or transfer delay) on arrival to the thrombectomy center.[16,18–20] |

## *Synopsis*

Brain imaging is essential to exclude hemorrhage in adult and pediatric patients eligible for AIS reperfusion therapies. Although CT-based protocols are more efficient and generalizable, MRI-based protocols may be appropriate

in high-resource settings and in pediatric populations if similar time to imaging can be achieved as with CT. When required for EVT selection, vascular neuroimaging of the cervical and intracranial vessels to identify LVO should be performed rapidly and not be delayed by obtaining kidney function testing, given the time dependence of functional outcomes on reperfusion. Two imaging paradigms for patient selection for IVT in the 4.5- to 24-hour window and EVT in the 6- to 24-hour window may be considered: DWI-FLAIR mismatch and CT or MR PWI-based ratio of ischemic penumbra to core infarct volume. A novel approach of DTAS has recently shown promise in patients with suspected LVO requiring EVT but requires further confirmatory study. Other elements of the current guidelines for management of adults with AIS, such as imaging diagnostic tests and general emergency care, should be incorporated and adapted within the institutional pediatric AIS pathways.

### *Recommendation-Specific Supportive Text*

1. In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and a negative NCCT or an NCCT showing early ischemic changes.[21,22] NCCT imaging of patients with acute stroke is effective for the rapid detection of acute ICH. NCCT was the only neuroimaging modality used in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA (Recombinant Tissue-Type Plasminogen Activator) trials and in ECASS (European Cooperative Acute Stroke Study) III and is therefore sufficient neuroimaging for decisions about IVT to be made in most patients.[23] MRI was as accurate as NCCT in detecting hyperacute intraparenchymal hemorrhage in patients presenting with stroke symptoms within 6 hours of onset when gradient echo sequences were used.[1,24,25]
2. Brain imaging studies are recommended to primarily exclude ICH but also to identify LVOs and assess ischemic tissue burden, as part of the initial evaluation of patients with AIS who are potentially eligible for EVT. The benefit of IVT or EVT is time dependent, with earlier treatment times leading to benefits of greater proportion.[26,27] With respect to endovascular treatment, a pooled analysis of 5 randomized trials comparing EVT with medical therapy alone in which the majority of the patients were treated within 6 hours found that the odds of improved disability outcomes at 90 days (as measured by the mRS score distribution) decreased with longer time from symptom onset to arterial puncture.[28] Studies of the 6- to 16-hour and 6- to 24-hour treatment window trials, which used advanced imaging to identify a relatively uniform patient group, showed limited variability of treatment effect with time in these highly selected patients.[29,30] However, the absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure that the greatest proportion of eligible patients presenting in the 6- to 24-hour window have access to and optimally benefit from EVT, evaluation and treatment should be performed as rapidly as possible. Although several large-core thrombectomy trials included patients presenting as long as 24 hours from last known well, some trials were limited to presentations within 6 to 12 hours, indicating large-core thrombectomy patients can also be early infarct progressors warranting intervention as quickly as possible.[31–33] Reducing the time interval from ED presentation to initial brain imaging reduces the time to reperfusion treatment initiation. Studies have shown that median or mean door-to-imaging times of ≤25 minutes can be achieved in various different hospital settings. Hospitals using MRI as the initial imaging modality should strive to achieve similar door-to-imaging times (eg, <25 minutes) as with CT-based protocols.[9,34–36]
3. In 1 study-level meta-analysis of 14 studies reporting on acute kidney injury (AKI) in patients with AIS who underwent CTA/CTP, the authors found no difference in AKI rates between groups undergoing CTA/CTP versus NCCT after adjusting for baseline renal function. The overall rate of AKI and hemodialysis in CTA/CTP patients was 3% and 0.07%, respectively. Nonrandomized evidence suggests that CTA/CTP are not associated with statistically significant increases in risk of AKI in patients with stroke, even among those with known chronic kidney disease.[3,4]
4. There are limited data from observational studies that MRI/MRA imaging should be the modality of choice for evaluation of children with suspected stroke in the hyperacute setting to identify patients eligible for IVT or EVT. Although MRI may lead to slightly longer delays to diagnosis,[5] it is more reliable for differentiating AIS from stroke mimics and does not rely on ionizing radiation, 2 common concerns among pediatric patients.
5. To keep the delay to diagnosis at a minimum in the evaluation of children with suspected stroke, the use of CT and CTA is reasonable if MRI is not available immediately (within 25 minutes) or if there are contraindications for MRI, to identify patients eligible for reperfusion interventions.[9] To mitigate radiation risk, CT/CTA must follow pediatric-specific dose reduction strategies.[37]
6. In patients presenting with wake-up stroke or unclear time of onset >4.5 hours from last known well, mismatch selection can be useful for selecting patients who may benefit from IVT in these extended time windows (Table 3). The

**Table 3. Imaging Criteria Used in the Extended Window Thrombolysis Trials**

| Trial name | Imaging criteria |
|---|---|
| WAKE-UP | DWI/FLAIR mismatch: presence of an abnormal signal on DWI and no visible signal change on FLAIR in the region of the acute stroke |
| THAWS | DWI/FLAIR mismatch: presence of an abnormal signal on DWI and no marked signal change on FLAIR in the region of the acute stroke |
| EPITHET | PWI/DWI mismatch: PWI/DWI volume ratio >1.2 and PWI–DWI volume ≥10 mL (PWI volume defined as Tmax >2 s) |
| ECASS-4 | PWI/DWI mismatch: PWI/DWI volume ratio of ≥1.2 and PWI ≥20 mL |
| EXTEND | CTP or DWI/PWI mismatch: ischemic penumbra to core volume ratio >1.2, penumbra – core volume >10 mL, and core volume <70 mL (core defined as <30% of normal regions on CTP or DWI volume; penumbra defined as Tmax >6 s on CTP or PWI) |
| TIMELESS | CTP or DWI/PWI mismatch: ischemic penumbra to core volume ratio >1.8, penumbra volume >15 mL, and core volume <70 mL (core defined as <30% of normal regions on CTP or DWI volume; penumbra defined as Tmax >6 s on CTP or PWI using RAPID automated postprocessing) |
| TRACE-3 | CTP or DWI/PWI mismatch: ischemic penumbra to core volume ratio >1.8, penumbra volume >15 mL, and core volume <70 mL (core defined as <30% of normal regions on CTP or DWI volume; penumbra defined as Tmax >6 s on CTP or PWI using iStroke software) |

CTP indicates computed tomographic perfusion; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; and PWI, perfusion-weighted imaging.

WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) used MRI mismatch between abnormal signal on DWI and no marked visible signal changes on FLAIR and excluded DWI lesions larger than one-third of the MCA territory.[10] Subsequently, the Thrombolysis With Alteplase at 0.6 mg/kg for Stroke With Unknown Time of Onset (THAWS) trial was terminated early after the WAKE-UP trial results but also used DWI-FLAIR mismatch selection.[11] Several RCTs studied the efficacy of IVT in the extended >4.5-hour time window using perfusion-based selection with MR DWI-PWI (EPITHET,[38] ECASS-4)[39] and/or predominantly CTP (EXTEND,[12] TRACE-III,[13] TIMELESS)[40] to estimate ischemic core versus salvageable ischemic penumbra volumes as defined by automated postprocessing software analysis. EPITHET was an early phase 2 trial selected patients with MR perfusion (PWI [Tmax >2 sec] to DWI mismatch ratio >1.2, mismatch volume >10 mL, DWI volume <100 mL, PWI volume [Tmax >8 sec] <100 mL). ECASS-4 selected patients in the >4.5- to 9-hour window from last known well with MR perfusion (PWI-DWI mismatch ratio >1.2, mismatch volume >20 mL, and DWI volume <100 mL). EXTEND selected patients who also presented in the >4.5- to 9-hour window but allowed either MR DWI-PWI or CTP imaging selection (hypoperfusion [Tmax >6 sec] to ischemic core [DWI or regional cerebral blood flow (rCBF) <30%] mismatch ratio >1.2, mismatch volume >10 mL, and ischemic core <70 mL). Finally, TRACE-III randomized 516 patients in China to IV tenecteplase versus standard medical treatment, presenting in a more extended 4.5- to 24 hour window with large vessel internal carotid artery (ICA)/M1-M2 MCA occlusions (<2% underwent rescue EVT) and salvageable ischemic tissue on MR DWI-PWI or CTP imaging (hypoperfusion [Tmax >6 sec] to ischemic core [DWI or rCBF <30%] mismatch ratio >1.8, mismatch volume >15 mL, and ischemic core <70 mL) as per automated post-processing software analysis. Please refer to section 4.6.3. "Extended Time Windows for Intravenous Thrombolysis" for treatment-related recommendations.

7. Neurovascular imaging with CT/MRA is a critical component in the emergent imaging protocol and triage of patients with AIS with suspected LVO. CTA/MRA imaging of the intracranial vasculature was required to document LVOs before randomization in the multiple RCTs that demonstrated the efficacy of EVT in both the early and late interventional time windows (MR CLEAN,[41] THRACE,[42] ESCAPE,[43] EXTEND IA,[44] SWIFT PRIME,[45] REVASCAT,[46] DAWN,[29] DEFUSE3).[30] In addition, CTA/MRA imaging of the cervical vasculature was extensively used in these trials for interventional planning (eg, vascular access, aortic arch/great vessel anatomy, guide catheter and thrombectomy device selection), recognition of tandem pathology (carotid atherosclerotic stenoses, occlusions, and dissections), and the potential for adjunctive interventions (antiplatelet/anticoagulation medical therapy versus angioplasty/stenting). In the HERMES meta-analysis, nearly 10% of patients (122/1254) harbored tandem occlusions, and emergent revascularization with EVT demonstrated a significant benefit over medical management in this subgroup (cOR, 2.95 [95% CI, 1.38–6.32]); please see section 4.8.2, "Endovascular Thrombectomy").
8. Advanced tissue imaging with CTP, MR DWI-FLAIR, or MR DWI-PWI was used as an adjunctive tissue selection strategy in most early window, late window, and large-core thrombectomy RCTs. However, because MR CLEAN and THRACE used only NCCT and LVO detection before randomization, adjunctive imaging with CTP, MR DWI, or DWI-PWI-based selection criteria of ischemic core and/or penumbral volumes (using automated postprocessing software analysis) is not required in the early (<6 hours) interventional time windows

to prevent excluding patients who may still benefit from EVT. Both the DAWN and DEFUSE-3 trials employed adjunctive tissue imaging to select optimum candidates for EVT in the extended 6- to 24-hour interventional time windows with either a clinical-core infarct mismatch (combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP rCBF <30% or MR-DWI) or a perfusion-based target mismatch profile (hypoperfusion [Tmax >6 sec] to core infarct [DWI or rCBF <30%] mismatch ratio >1.8, mismatch volume >15 mL, and core infarct <70 mL) using automated postprocessing software analysis, respectively, but with no loss in treatment effect compared with the early interventional time window trials (DAWN[29]/DEFUSE3[30]). Although the results of multiple large-core EVT trials suggest advanced tissue imaging modalities with these strict selection criteria may also exclude patients who could benefit from EVT, it is important to note the increased sensitivity of CTP, MR DWI-FLAIR, or MR DWI-PWI over CT ASPECTS in identifying patients with posterior circulation or large-core infarct burdens who may still be eligible and included for EVT, especially in later time windows (ATTENTION[47]/BAOCHE).[48] In fact, the majority of the large-core thrombectomy RCTs used some form of adjunctive tissue imaging selection in addition to ASPECTS as part of their imaging inclusion criteria (RESCUE LIMIT,[32] SELECT2,[49] ANGEL ASPECT,[50] LASTE[31]). RESCUE LIMIT and LASTE recruited >80% of their patients with MR-DWI ASPECTS and required DWI-FLAIR mismatch for any patient in the 6- to 24-hour time window. Both ANGEL ASPECT and SELECT2 allowed alternative imaging inclusion based on CTP (rCBF <30%) or MR-DWI estimation of core infarct volumes if >70 mL and ≤100 mL (range, 29–86 mL) or >50 mL (range, 57–118 mL) as per automated postprocessing software analysis, respectively. Finally, if the time to perform adjunctive imaging with CTP or MR DWI-PWI can be minimized, the value of advanced tissue imaging with both automated software analysis and detection applications can provide advantages in stroke interventional workflow and QI, including early LVO/core infarct size recognition and team activation to reduce EVT treatment times, prognosis for family consenting/counseling, intraprocedural and postprocedural management (hemodynamics, antiplatelet/anticoagulation, hyperosmolar therapy versus craniectomy planning), and thrombectomy efficacy/safety assessment based on core versus final infarct comparisons.[14]

9. One single-center RCT and several nonrandomized studies provide data supporting DTAS without additional imaging or triage in the ED. The ANGIOCAT study was a single-center, prospective, RCT of 174 patients identified before hospital arrival with high suspicion for LVO within 6 hours of symptom onset who either underwent conventional evaluation in the ED with CT and CTA of the head or DTAS with flat-panel CT followed by catheter-based angiography (DTAS group). Compared with conventional workflow, the DTAS group experienced faster workflow (door-to-groin puncture,18 versus 42 minutes; $P<0.001$; door to reperfusion, 57 versus 84 minutes; $P<0.001$) and higher rates of good outcomes (ordinal mRS: cOR, 2.2 [95% CI, 1.2–4.1]; $P=0.009$).[15,16]
10. Several studies provide data supporting DTAS without additional imaging or triage in the ED. In a nonrandomized, retrospective, multicenter study of 1140 transfer patients with LVO, DTAS was associated with faster times from arrival to groin puncture (34 versus 60 minutes) and better functional and safety outcomes, overall and in both early and late windows, compared with patients who underwent repeat imaging after transfer to the thrombectomy center.[16,18–20]

## Knowledge Gaps and Future Research

- Although 1 study reported that the modified ASPECTS in MRI for pediatric patients correlates with the risk of hemorrhagic transformation (HT) and clinical outcomes at 12 months, the general use of the ASPECTS scale or its modification for MRI in pediatric patients for patient selection and treatment needs to be systematically studied.[51]
- Extended window thrombolysis using head CT alone (without advanced imaging) may be attractive in low-resource settings. Nonrandomized studies suggested this approach was not associated with increased hemorrhage risks.[52,53] The TWIST trial aimed to determine whether thrombolytic treatment with IV tenecteplase given within 4.5 hours of awakening improves functional outcome in patients with ischemic wake-up stroke selected using NCCT.[54] Patients were randomized to tenecteplase 0.25 mg/kg versus no tenecteplase. Treatment with tenecteplase was not associated with better functional outcome, according to mRS score at 90 days (aOR, 1.18 [95% CI, 0.88–1.58]; $P=0.27$). However, limitations of the trial include that it was underpowered, with a planned treatment effect of 11.5% subsequently adjusted to 10% during the trial's conduct. Further, the plan of 600 enrollments was not reached due to poor enrollment during COVID. Overall, NCCT alone cannot be recommended at this time for thrombolytic treatment decisions from 4.5 to 24 hours, but adequately powered trials are needed.
- The performance of flat-panel CT imaging in the angiography suite has not been compared with conventional NCCT and therefore requires formal study.







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## 3.3. Other Diagnostic Tests

| Recommendations for Other Diagnostic Tests Referenced studies that support recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | C-LD | 1. In patients with suspected acute stroke, baseline electrocardiographic assessment is recommended but should not delay initiation of IVT or EVT.[1–4] |
| 1 | B-NR | 2. In patients with suspected acute stroke, baseline troponin is recommended but should not delay initiation of IVT or EVT.[5–9] |

### *Synopsis*

For patients presenting with suspected acute stroke, it is important to consider the performance of relevant tests in the ED that either contribute to the diagnosis of acute stroke or aid in the identification of stroke mechanism. Relevant diagnostic tests include point-of-care glucose testing, covered in additional detail in section 4.5 ("Blood Glucose"), baseline electrocardiogram (ECG),[1–4] and testing of serum troponin.[5–9] Although available literature suggests that tests such as ECGs and troponins may aid in prognosis and identification of mechanism, understanding the recommended timeline of diagnostic tests in relation to acute interventions such as IVT and EVT is critical given the time-sensitive nature of these reperfusion therapies in patients with AIS. Current limited and nonrandomized data suggest that acquisition of ECG and troponins should not delay initiation of reperfusion therapies in patients with AIS.

### *Recommendation-Specific Supportive Text*

1. Data from single-center, observational studies suggest that performing an ECG during the initial work-up for patients with suspected AIS is potentially beneficial as the findings may help to identify abnormal heart rhythms or cardiac ischemia, aiding in the identification of stroke mechanism and assessment of illness severity. For example, data from a nonrandomized, single-center study indicate that specific ECG changes such as nonsinus rhythm, inverted T-waves, ST segment changes, and atrioventricular nodal blocks are associated with higher 1-year mortality rates among patients with AIS.[2] Previous studies have demonstrated specific ECG findings (eg, strain pattern, altered T-waves, atrial fibrillation [AF], ST segment changes) are associated with worse 3-month outcomes, including both functional outcomes (dependency) and mortality.[1,4] Other observational data demonstrated an association between left ventricular hypertrophy on ECG and stroke severity, in-hospital mortality, and functional status at the time of hospital discharge.[3] Although data supporting baseline ECGs are limited to observational studies, the risk of harm associated with ECG performance is low, with benefits outweighing the risk.
2. Revised from the 2019 AIS guideline to incorporate recently published evidence, this recommendation focuses on the use of baseline troponins drawn during the initial work-up for patients with AIS. Nonrandomized studies, including 2 systematic reviews, indicate that elevated troponin levels can help to predict cardioembolic stroke mechanism[9] as well as elevated risk of mortality after stroke.[6–8] In addition, some data indicate that elevated troponins help to predict mortality[8] as opposed to flat or decreasing serial troponins, and other data suggest that troponin levels measured after 4.5 hours of symptom onset are more sensitive for detection of acute myocardial infarction (MI) among stroke patients.[5]

## Knowledge Gaps and Future Research

- Although serial troponins are recommended for the detection of acute MI in patients with suspected acute coronary syndromes, the use and optimal timing of serial troponins in patients with suspected AIS likely depends on factors such as concern for concomitant coronary heart disease or cardioembolic stroke mechanism as well as the characteristics of available assays (ie, availability of high-sensitivity troponins) and requires further study.

# 4. GENERAL SUPPORTIVE EARLY MANAGEMENT

Strategies for general supportive early management of childhood stroke rely on both adult stroke-specific and general pediatric data. There is limited knowledge on the specific effects of supportive care measures after AIS in children, which warrants future research.

## 4.1. Airway, Breathing, and Oxygenation

| Recommendations for Airway, Breathing, and Oxygenation Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | C-LD | 1. In patients with acute stroke and decreased consciousness or bulbar dysfunction, airway support and ventilatory assistance are recommended as needed to provide airway maintenance, protection and adequate ventilation and oxygenation.[1–3] |
| 1 | C-LD | 2. In patients with AIS with hypoxia, supplemental oxygen should be provided to maintain oxygen saturation ($SpO_2$) >94%.[4,5] |
| 2b | B-R | 3. In patients with AIS within 6 hours from onset, NIHSS score 10 to 20, CT ASPECTS of ≥6, and anterior circulation LVO (M1 or carotid terminus) with planned EVT (with or without IVT) normobaric hyperoxia (NBO) before EVT may be reasonable to improve functional outcomes at 90 days.[6–9] |

| Recommendations for Airway, Breathing, and Oxygenation (Continued) | | |
|---|---|---|
| COR | LOE | Recommendations |
| 2b | B-NR | 4. In patients with AIS due to arterial air embolism, hyperbaric oxygen (HBO) may be reasonable to improve clinical outcome.[10] |
| 3: No benefit | B-R | 5. In patients with AIS without hypoxia who are ineligible for EVT, supplemental oxygen is not recommended to improve functional outcomes.[11–16] |
| 3: No benefit | B-R | 6. In patients with AIS, not associated with air embolism, HBO is not recommended to improve functional outcomes.[17] |

### Synopsis

Maintenance of the airway with adequate oxygenation and ventilation is essential in patients with acute stroke.[1–3] Depending on stroke location, alterations in consciousness, swallowing function, and/or breathing (via respiratory center involvement) may occur, increasing the risk of hypoxia, pulmonary complications (eg, aspiration, pneumonia, pulmonary edema), and respiratory failure. Acute and chronic prolonged hypoxia has known detrimental effects.[18,19] Therefore, it is intuitive that oxygen supplementation in hypoxic patients with acute stroke would prevent hypoxia-related complications, although data specific to the stroke population are limited. In contrast, supplemental oxygen for nonhypoxic patients with acute stroke has not been shown to consistently be associated with improvement in clinical outcome in multiple RCTs, with the exception of the subgroup of patients with AIS with LVO undergoing EVT, where there are promising data that NBO may be associated with improved functional outcomes. HBO is the inhalation of pure oxygen (95%–100%) in a pressurized environment to augment oxygen levels in the blood and tissue and has various indications, including wound healing, carbon monoxide poisoning, and decompression sickness.[20] A meta-analysis of nonrandomized trials in cerebral air embolism has shown that earlier time to HBO is associated with increased probability of favorable clinical outcome. However, routine use of HBO has not been shown to consistently improve clinical outcomes in patients with acute stroke without air embolism.

### Recommendation-Specific Supportive Text

1. Airway support and ventilatory assistance in acute stroke should be determined by the patient's: 1) ability to maintain or protect the airway, 2) ability to provide adequate ventilation and oxygenation, and 3) their anticipated clinical course and likelihood of deterioration.[1,2,21] Hypoxia is common in patients with stroke, affecting up to 63% of patients at some time after admission, and is associated with increased risk of death and difficulty with airway protection.[22,23] Failure to adequately provide airway support and ventilatory assistance may result in complications with resultant increased mortality and disability.[3]
2. A retrospective cohort study of patients with AIS (n=1479) showed that good oxygenation (time-weighted ratio of oxygen saturation/inspiratory oxygen fraction [$SpO_2/FiO_2$] ratio) in the first few hours was associated with lower mortality in a dose-dependent manner.[4] This study also showed that $SpO_2$ <93% had a higher mortality compared with $SpO_2$ 93% to 95% (12.5% versus 6.9%), although this difference was not statistically significant. A post-hoc analysis of the International Head Positioning in acute Stroke Trial (HeadPoST) found an inverse J-shaped association between lowest $SpO_2$ and death/dependency, with a nadir for optimal outcome at 96% to 97%. When analyzed as a binary variable, patients with hypoxia ($SpO_2$ <93%) did not have a significantly higher odds of death or dependency (55.6% versus 40.0%; aOR, 1.19 [95% CI, 0.95–1.48]), but there was a significant association of $SpO_2$ and SAEs, with a decrease in SAEs as $SpO_2$ increased (aOR, 1.34 [95% CI, 1.07–1.38]).
3. The negative results from earlier studies of NBO in patients with AIS may be due to lack of recanalization, and several small single-center, randomized clinical trials explored testing in the setting of EVT. The first randomized 180 subjects undergo EVT to either 50% oxygen by Venturi mask or 3 L oxygen by nasal cannula (approximately 32%) for 6 hours after EVT. This study determined NBO to be safe and possibly effective.[6] The second study randomized 86 subjects to either 100% oxygen via face mask (10 L/min x 4 hours, starting in the ED) or room air. This study determined NBO to be safe and identified a reduction in infarct volume growth from 24 to 48 hours. Secondary measures of clinical outcome demonstrated improvement in the NBO group.[7] A third single-center dose-escalation trial in China randomized 100 patients with AIS undergoing EVT into 4 arms (25 patients in each arm) of control, NBO-2 hours, NBO-4 hours, and NBO-6 hours of oxygen (100% oxygen at a flow rate of 10 L/min face mask).[8] The primary endpoint was cerebral infarct volume after 72 hours from randomization. The infarct volumes were 39.4 ± 34.3 mL, 30.6 ± 30.1 mL, 19.7 ± 15.4 mL, and 22.6 ± 22.4 mL, respectively ($P$=0.013). The NBO-4 hours and NBO-6 hours groups both showed significant differences (adjusted $P$ values, 0.011 and 0.027, respectively) compared with the control group, but there was no difference between the NBO-4 hours and the NBO-6 hours groups. Secondary endpoints such as change in NIHSS score were also significant between the NBO-4 hours and NBO-6 hours groups compared with the control group. The Normobaric Hyperoxia Combined With







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Reperfusion for AIS (OPENS-2) trial, a single-blind, sham-controlled trial in 26 centers in China, randomized 282 patients with AIS with LVO who underwent EVT to NBO (100% oxygen at a flow rate of 10 L/min through a nonrebreather mask for 4 h or an $FiO_2$ of 1.0 if intubated) versus sham NBO treatment (100% oxygen at a flow rate of 1 L/min or an $FiO_2$ of 0.3). The primary outcome (blinded assessment) was the comparison of the ordinal scores on the mRS at 90 days. The median mRS score for the NBO group was 2 (IQR, 1–4) and was 3 (IQR, 1–4) in the sham NBO group (adjusted cOR, 1.65 [95% CI, 1.09–2.50]; *P*=0.018). The evidence for NBO with EVT is promising, but these results need to be replicated in other large-scale multicenter studies in more diverse populations to validate these findings.

4. A meta-analysis of 10 nonrandomized studies (n=263) of patients with iatrogenic cerebral arterial gas embolism in a defined period of time showed that the probability of favorable outcome decreased from 65% when HBO is started immediately to 30% when HBO is delayed for 15 hours. These results demonstrate that earlier treatment with HBO in cerebral air embolism is associated with better outcomes.[10]
5. A meta-analysis of 15 studies (n=9255) of patients with stroke (ischemic and hemorrhagic) showed that supplemental oxygen was not associated with early neurological improvement or improved functional outcomes at 3 to 6 months in patients with acute stroke.[11] The largest RCT in that meta-analysis (n=8003) included patients with acute stroke (ischemic and hemorrhagic) within 24 hours of admission and demonstrated that supplemental oxygen (continuous or nocturnal only) for 3 days was not associated with improved functional outcomes at 90 days.[12] Other smaller RCTs have shown similar results, including a quasi RCT (n=550) of patients with acute stroke (ischemic and hemorrhagic) that demonstrated supplemental oxygen for 24 hours was not associated with improved 1-year survival or 7-month neurological impairment and disability.[13] An RCT (n=289) of patients with acute stroke (ischemic and hemorrhagic) within 24 hours of admission showed that supplemental oxygen for 72 hours was not associated with improved functional outcome at 6 months.[14] Supplemental oxygenation does not appear to be beneficial, but there is growing concern that hyperoxia may even be harmful. In a meta-analysis of 16 037 mixed-population patients (most patients were a mix of acutely and medically ill, but 6398 patients with stroke patients were included), liberal oxygen supplementation (median $FiO_2$ of 0.52, range, 0.28–1.00; IQR, 0.39–0.85) was compared with conservative supplementation (median $FiO_2$ 0.21, range, 0.21–0.50; IQR, 0.21–0.25).[15] In 8 of the trials, oxygen was delivered by invasive mechanical ventilation. The baseline median $SpO_2$ in the liberal oxygen arm was 96.4% (range, 94.0%–99.0%); when this group was exposed to liberal oxygenation, an increase in mortality risk was observed. In ventilated patients with stroke (ischemic and hemorrhagic) admitted to the intensive care unit (ICU), arterial hyperoxia was independently associated with in-hospital mortality (adjusted OR, 1.2 [95% CI, 1.0–1.5]).[16]
6. A meta-analysis of 8 RCTs in patients with AIS (n=493) found no difference between HBO versus control in terms of the NIHSS score, Barthel index, tumor necrosis factor-alpha, soluble intercellular adhesion molecule, soluble vascular cell adhesion molecule, soluble E-selectin, and C-reactive protein.[17] An analysis of 2 articles (n=42 in the HBO group and n=42 in the control group) showed that the HBO group had significantly better improvement in mRS score compared with the control group. However, a meta-analysis of the Barthel index (n=80 in the HBO group and n=70 in the control group) and NIHSS score (n=130 in the HBO group and n=134 in the control group) showed no significant differences. Given these mixed results, the current evidence does not support the routine use of HBO for improving clinical outcomes in acute stroke.

## Knowledge Gaps and Future Research

Trials evaluating the benefit of oxygen supplementation in select subgroups of patients with AIS are ongoing (specifically trials related to supplemental oxygen in thrombolysis or endovascular therapy). There is potential concern for deleterious effects of hyperoxia, which may theoretically be harmful due to physiological effects of excessive oxygen (ie, free radical production). Potential areas of research in the future include the following:

- Trials exploring the role of supplemental oxygen in patients with AIS undergoing revascularization therapy (thrombolysis or endovascular therapy), including currently recruiting trials (NCT06224426, NCT05039697, NCT05965687).
- Studies examining controlled oxygenation in stroke populations, specifically exploring whether hyperoxia

has deleterious effects and to determine if there should be a recommendation for an upper limit or cap to oxygen supplementation (ie, 94%–96%).
- Studies exploring the role of HBO in preconditioning for stroke.
- Further large-scale studies of NBO in diverse populations are needed to confirm efficacy and optimize protocols.[8]

## 4.2. Head Positioning

**Recommendations for Head Positioning**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 3: No Benefit | B-R | 1. In patients with AIS overall, there is no benefit of routine 0-degree head positioning compared with 30 degrees for 24 hours, to improve functional outcome.[1,2] |
| 3: No Benefit | B-R | 2. In patients with AIS with probable large artery atherosclerosis cause for whom no reperfusion intervention is available, there is no benefit of routine Trendelenburg positioning (−20 degrees) compared with 0- to 30-degree head positioning to improve functional outcome.[3] |

### *Synopsis*

Zero-degree or lower-head position may play an important role in penumbral blood flow augmentation and subsequent clinical stability during the early management of patients with AIS. There have been 3 RCTs that proposed head positioning as a treatment for acute stroke. The Head Position in Acute Stroke Trial (HeadPoST) enrolled a diverse cohort with both hemorrhagic and ischemic stroke without neuroimaging confirmation of small or LVO with neutral study endpoints.[1] The phase IIb study that preceded HeadPoST enrolled anterior circulation patients with AIS and focused solely on changes in mean flow velocity (MFV), confirming significantly increased MFV at 0 degrees.[2] The Hospitalized Stroke Patients 90-day Outcomes trial (HOPES-2) exclusively enrolled patients with probable large artery atherosclerosis with AIS who were ineligible for any other form of treatment. Patients were positioned at −20 degrees (Trendelenburg position) and compared with standard head positioning (0–30 degrees). No significant difference in functional outcome was found.[3] All these trials have shown the safety and feasibility of 0-degree or head-down positioning, without significantly different complication rates. Overall, the temporary use of 0-degree head positioning may have clinical use in patients with discrete types of AIS, to improve cerebral perfusion.

### *Recommendation-Specific Supportive Text*

1. HeadPoST was a large international, cluster-randomized, crossover open label trial that randomized patients with any stroke type to a flat-head (0 degrees) or elevated head (≥30 degrees) position maintained for 24 hours after randomization.[1] The distribution of mRS scores at 90 days did not differ between the groups. Patients in the flat-head position group were less often able to tolerate the assigned head position for 24 hours, but rates of pneumonia did not differ between the 2 groups. This pragmatic trial has been criticized because of various limitations.[4] HeadPoST enrolled mainly patients with minor strokes (median NIHSS score 4) who would be less likely to benefit from increased perfusion compared with patients with more severe stroke and/or large artery stenosis or occlusion. Additionally, the initiation of the intervention was very delayed (median, 14 hours), potentially missing the window in which head positioning could have been beneficial. A small prospective, multicenter, international, cluster randomized, phase IIb controlled trial[2] that compared a lying-flat position with a 30-degree position for 24 hours after randomization (within 12 hours of stroke symptom onset) in patients with anterior circulation AIS, showed improvement in the MFV in the ipsilateral MCA. There was no significant difference in the functional outcome at 90 days.
2. A prospective, randomized, open-label, blinded-endpoint, multicenter, phase 2 trial enrolled patients with probable large artery atherosclerosis cause and baseline mRS score of 0 to 1 and assessed the feasibility, safety, and efficacy of prolonged (2 weeks) head-down (−20 degrees, Trendelenburg) positioning compared with 0- to 30-degree head positioning. The primary outcome (mRS score, 0–2) at 90 days was not improved in the head-down position (OR, 2.05 [95% CI, 0.87–4.82]; *P*=0.09). However, the secondary outcomes favored the head-down position: change from baseline NIHSS score to day 12 (OR, −0.15 [95% CI, −0.25 to −0.05]; *P*=0.004), mRS score 0 to 1 at 90 days (OR, 2.66 [95% CI, 1.10–6.44]; *P*=0.03), and 90-day ordinal-shift analysis (OR, 2.7 [95% CI, 1.17–5.72]; *P*=0.01). There was no difference in complication rates and mortality between the groups.

## Knowledge Gaps and Future Research

- There may be a benefit of zero-degree head of bed position in patients with AIS and large vessel occlusion before endovascular reperfusion therapy, but this needs further study.
- There may be a benefit of temporary zero-degree head positioning in patients with AIS with fluctuating neurological symptoms presumed to be secondary to impaired cerebral perfusion, but this requires further investigation.







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## 4.3. Blood Pressure Management

| Recommendations for Blood Pressure Management Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| General recommendations (including without reperfusion therapy) | | |
| 1 | C-LD | 1. In patients with AIS, hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.[1–3] |
| 1 | C-EO | 2. In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (eg, concomitant acute coronary event, acute heart failure, aortic dissection, post-thrombolysis sICH, or preeclampsia/eclampsia) to reduce the risk of complications. |
| 2b | C-EO | 3. In patients with BP ≥220/120 mm Hg who did not receive IVT or EVT and have no comorbid conditions requiring urgent antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. |
| 3: No Benefit | A | 4. In patients with BP <220/120 mm Hg who did not receive IVT or EVT and do not have a comorbid condition requiring urgent antihypertensive treatment, initiating or reinitiating treatment of hypertension within the first 48 to 72 hours after an AIS is not effective to prevent death or dependency.[4] |
| Before reperfusion treatment | | |
| 1 | B-NR | 5. Patients with AIS who have elevated BP and are otherwise eligible for treatment with IVT should have their SBP lowered to <185 mm Hg and diastolic blood pressure (DBP) <110 mm Hg before IVT therapy is initiated to reduce hemorrhagic complications.[5–9] |
| 2a | B-NR | 6. In patients for whom EVT is planned and who have not received IVT therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure to avoid complications and improve patient outcomes.[10] |
| After IVT | | |
| 1 | B-R | 7. BP should be maintained at <180/105 mm Hg for at least the first 24 hours after IVT treatment.[11–13] |
| 3: No Benefit | B-R | 8. In patients with mild to moderate severity AIS who have been treated with IVT, intensive SBP reduction (target of <140 mm Hg compared with <180 mm Hg) is not recommended because it is not associated with an improvement in functional outcome.[11] |
| After endovascular thrombectomy | | |
| 2a | B-NR | 9. In patients who undergo EVT, it is reasonable to maintain BP at a level ≤180/105 mm Hg during and for 24 hours after the procedure.[14–17] |
| 3: Harm | A | 10. In patients with AIS with LVO of the anterior circulation who have been successfully recanalized by endovascular therapy (mTICI 2b, 2c, or 3) and without other indication for blood pressure management target, intensive SBP reduction target of <140 mm Hg for the first 72 hours is harmful and not recommended.[18–21] |

### *Synopsis*

In adult patients with AIS, there is a general, mechanistic understanding that extremely high BP concurrent with acute stroke reperfusion may be detrimental, particularly in terms of hemorrhagic complications. The majority of evidence supporting pre-reperfusion BP reduction has either been observational or based on thrombolysis or thrombectomy RCT protocols. Randomized trials evaluating pre-thrombolysis or pre-thrombectomy BP targets are yet unavailable.

Optimal BP targets after IVT and thrombectomy continue to be actively studied because of the known and hypothesized associations with either sICH from hyperperfusion or worsened cerebral ischemia from hypoperfusion, as well as with outcomes including death and dependency. The recommendation for BP targets after IVT and thrombectomy remains largely unchanged from previous guidelines, with further evidence that more intensive BP reduction provides either no benefit in functional outcome (thrombolysis) or harm (thrombectomy).

### *Recommendation-Specific Supportive Text*

1. Observational studies are conflicted, with associations found between worse outcomes and lower BP.[1–3,22] No studies have addressed the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing the use of IV colloids and crystalloids, the odds of death or dependence were similar. Clinically important benefits or harms could not be excluded. There are no data to guide volume and duration of parenteral fluid delivery.[23] No studies have compared different isotonic fluids.
2. Patients with AIS can present with severe acute comorbidities, such as acute heart failure and aortic dissection, which require emergency BP reduction to prevent worsening of these conditions or SAE. Excessive BP lowering, however, can lead to exacerbation of cerebral ischemia[24] in the setting of impaired cerebral autoregulation. Individualized management balancing cerebral and other systemic organ perfusion is recommended with an initial BP reduction of 15%.
3. Severe hypertension (most commonly >220/120 mm Hg) was a contraindication to previous BP-lowering trials.[4,25–29] Despite the lack of controlled studies testing different approaches to BP management in patients with AIS and severe hypertension in the absence of a medical indication such as aortic dissection, BP reduction is still generally recommended. Individualized management balancing cerebral and other systemic organ perfusion is recommended, with an initial BP reduction of 15%.
4. A meta-analysis of numerous clinical trials found that BP lowering[4] initiated within the first 48 to 72 hours after AIS does not improve functional outcomes or mortality. Therefore, in patients with BP <220/120 mm Hg who did not receive reperfusion therapies and do not have a comorbid condition requiring urgent antihypertensive treatment, active BP lowering within the first 48 to 72 hours after

an AIS is not effective to prevent death or dependency. Furthermore, spontaneous lowering of BP is known to occur approximately in 75% of such patients within the first few days after AIS.[30]

5. The RCTs of IV alteplase required the SBP to be <185 mm Hg and DBP <110 mm Hg before treatment.[5,6] Observational studies and meta-analyses suggest that the risk of hemorrhage after administration of alteplase is greater in patients with higher BPs and in patients with more BP variability.[7,31] The AcT trial of tenecteplase versus alteplase excluded patients with hypertension refractory to aggressive hyperacute antihypertensive treatment such that target BP <180/105 mm Hg cannot be achieved or maintained.[32] The TRUTH RCT evaluated BP lowering followed by thrombolysis versus BP nonlowering among patients otherwise eligible for IVT[8] The trial found insufficient evidence of a difference in 90-day mRS with either strategy. Thus, without a clear benefit of 1 versus another strategy, it is reasonable to adhere to BP recommendations of the IVT clinical trial protocols.
6. Of the RCTs that demonstrated clinical benefit of EVT, 5 had eligibility exclusions for BP >185/110 mm Hg (RandomizEd trial of reVascularizAtion with Solitaire FR® device versus best mediCal therapy in the treatment of Acute stroke due to anTerior circulation large vessel occlusion presenting within 8 hours of symptom onset [REVASCAT], Solitaire With the Intention For Thrombectomy as PRIMary Endovascular Treatment [SWIFT PRIME], Extending the Time for Thrombolysis in Emergency Neurological Deficits – Intra-Arterial [EXTEND-IA], THRombectomie des Artères CErebrales [THRACE], Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands [MR CLEAN], DWI or CTP Assessment with Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention [DAWN], Endovascular Treatment for AIS in Asia [ANGEL-ASPECT], and Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke [TESLA]). Observational studies have shown an association between higher prethrombectomy BP and worse outcomes; however, RCT data for optimal BP management approaches before thrombectomy are not available. Because several major RCTs of thrombectomy had preprocedural BP managed <185/110 mm Hg, it is reasonable to use this level as a guideline until additional data become available.
7. In an RCT of thrombolysis-eligible patients presenting with an SBP ≥150 mm Hg, targeting SBP 130 to140 mm Hg versus SBP <180 mm Hg produced no difference in mRS score at 90 days despite fewer patients with ICH in the more intensive target range.[11] Thus, maintaining SBP between 140 and 180 mm Hg postthrombolysis is recommended.
8. A post-hoc analysis of a high-quality RCT demonstrated that in patients with mild to moderate severity AIS after IV alteplase, intensive SBP reduction to a target of <140 mm Hg results in a lower risk of ICH but no benefit in functional outcome compared with a target of <180 mm Hg.[11]
9. Although meta-analyses that include retrospective and observational cohort studies suggest that higher SBP after successful EVT is associated with higher odds of secondary ICH and lower odds of functional improvement,[14] or no difference in functional outcome with intensive SBP reduction (<140 mm Hg),[15] higher quality levels of evidence differ. Two high-quality RCTs demonstrate that intensive SBP reduction to a target of <130 mm Hg is not beneficial to reduce rates of sICH,[16] and a target of <160 mm Hg is unlikely to improve functional outcome after EVT.[17]
10. Two high-quality RCTs, meta-analysis of RCTs, and prespecified subgroup analysis of an RCT demonstrated that intensive SBP reduction to a target of <140 mm Hg in the first 24 hours after EVT[19–21] and without other indication for BP management target, such as tandem occlusion with chronic high-grade stenosis, leads to lower functional independence and higher mortality, and a target of <120 mm Hg for the first 72 hours[18] leads to more early neurological deterioration and major disability at 3 months.

## Knowledge Gaps and Future Research

- The exact BP targets in the hyperacute setting and before thrombolysis or thrombectomy to improve functional outcomes among patients with ischemic stroke are unclear. RCTs are needed that evaluate not only BP lowering but also BP augmentation, particularly among those with LVO.
- In a post-hoc evaluation of RCT data used as an observational cohort, it was shown that smaller SBP variability over the first 24 hours postalteplase is associated with a favorable shift of the mRS score; however, the effectiveness of targeting BP variability is not well-established.[33]
- Trials assessing individualized BP targets based on cerebral perfusion or other biomarkers should also be considered to assess whether BP lowering or augmentation is appropriate in specific subgroups (eg, poor reperfusion post-EVT requiring higher targets).
- There is a dearth of data on BP management in pediatric patients with AIS; optimal BP targets have not been studied in children.







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## 4.4. Temperature Management

| Recommendations for Temperature Management Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | B-R | 1. In patients with AIS who have hyperthermia, targeting normothermia, including using nurse-initiated protocols for managing fever, is recommended for improving functional outcomes and reducing death.[1–3] |
| 1 | C-EO | 2. In patients with AIS and hyperthermia, sources of hyperthermia, such as infection, should be identified and treated to avoid complications. |
| 3: No Benefit | B-R | 3. In patients with AIS and normothermia, treatment with induced hypothermia or prophylactic fever prevention is not recommended for the purpose of improving outcomes.[4–7] |

### *Synopsis*

In patients with AIS with hyperthermia, achieving normothermia, including using nurse-driven protocols to monitor for and treat temperatures >37.5°C improves clinical outcomes and reduces mortality.[1–3] For those with fever, rapidly identifying and treating the cause can improve outcomes. RCTs have demonstrated that induced hypothermia does not improve outcomes and may increase adverse events.

### *Recommendation-Specific Supportive Text*

1. In several RCTs and large observational studies collectively including several thousand patients, high body temperatures in the early in-hospital phase of stroke care have been associated with worse functional outcomes and increased mortality, compared with normothermia.[1–3] Nurse-driven protocols to monitor and treat fever are supported by RCT evidence that demonstrate improved short- and long-term outcomes, including mortality.[5]
2. Although central hyperthermia can occur, it is a relatively uncommon source of hyperthermia in patients with AIS compared with concurrent infection.[8] Patients with AIS and concurrent infection have worse outcomes compared with those without infection.[9,10] The source of infection should be rapidly identified and treated to avoid further complications and worsening of outcomes of patients with AIS.
3. To date, studies of hypothermia in normothermic patients with AIS, including a large phase III trial of prophylactic hypothermia,[3] have shown no benefit in functional outcomes, including among patients with large infarcts undergoing decompressive hemicraniectomy.[8] Some studies suggest that induction of hypothermia increases the risk of adverse events.[4,6] Various cooling methods, including intravascular, surface, and pharmacological, have been studied without clear evidence of benefit of any modality. The limitations of these studies include adverse events with prolonged hypothermia, limited observational study sample size, and exclusion of pediatric patients.

### Knowledge Gaps and Future Directions

- Various cooling methods in various populations with acute stroke have been studied without clear benefit. Further resource allocation to studying temperature management in AIS is not currently warranted.
- The benefits of ultrafast and selective intraarterial brain cooling remain unknown. Potential benefits of these cooling techniques may be specific to stroke subpopulations and require further study.

## 4.5. Blood Glucose Management

| Recommendations for Blood Glucose Management Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | C-LD | 1. In patients with AIS, hypoglycemia (blood glucose <60 mg/dL) should be treated to avoid complications.[1,2] |
| 2a | C-LD | 2. In patients with AIS, it is reasonable to treat persistent hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL with close monitoring to prevent worse functional outcomes.[1,2] |
| 3: No Benefit | A | 3. In hospitalized patients with AIS with hyperglycemia, treatment with IV insulin to achieve blood glucose levels in the range of 80 to 130 mg/dL is not recommended to improve 3-month functional outcomes.[3–5] |

### *Synopsis*

Although observational data suggest that hyperglycemia is associated with increased sICH and unfavorable functional outcomes, a large RCT and meta-analyses demonstrate that in patients with AIS, intensive glucose control to the range of 80 to 130 mg/dL does not improve clinical outcomes and increases the risk of severe hypoglycemia.

### *Recommendation-Specific Supportive Text*

1. Hypoglycemia can not only mimic acute stroke but there is a J-shaped relationship between blood glucose in the acute phase of stroke and mortality and unfavorable functional outcomes.[1,2] As such, significant hypoglycemia (<60 mg/dL) should be corrected to achieve normoglycemia in patients with AIS.
2. Observational clinical data have demonstrated worse clinical outcomes for patients with persistent in-hospital hyperglycemia, including glucose levels >120 mg/dL or 126 mg/dL, suggesting that treatment of very high glucose levels >180 mg/dL is reasonable while monitoring to prevent hypoglycemia.[1,2]
3. The Stroke, Hyperglycemia Insulin Network Effort (SHINE) randomized trial evaluated the benefit of achieving blood glucose between 80 and 130 mg/dL

versus 80 and 180 mg/dL for up to 72 hours after AIS.[3] The trial ended early for futility in a preplanned interim analysis after enrollment of 1151 participants as there was no benefit of intensive blood glucose control on functional outcome at 3 months. Although not clinically significant, severe hypoglycemia (glucose <40 mg/dL) occurred only in the intensive blood glucose treatment group. As such, intensive blood glucose treatment with a target of 80 to 130 mg/dL is not recommended for patients with AIS as there is risk without benefit. Those treated with thrombolysis or EVT may have differential outcomes with intensive blood glucose treatment, but this is currently unknown and warrants future studies.[6]

## Future Research and Knowledge Gaps

- It is unknown if patients receiving thrombolysis or EVT have differential outcomes or differential risk benefit ratios with intensive glucose control.[6,7]
- It is unknown if glucagon-like peptide-1 receptor agonists improve stroke outcomes and control poststroke hyperglycemia.[8]
- The ideal timing of treating hyperglycemia relative to thrombolysis and thrombectomy is unknown.

## 4.6. IV Thrombolytics

### *4.6.1. Thrombolysis Decision-Making*

| Recommendations For Thrombolysis Decision-Making Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| General principles | | |
| 1 | A | 1. In adult patients with AIS with disabling deficits, regardless of NIHSS score), and eligible for IVT, faster treatment improves functional outcomes.[1] |
| 1 | B-NR | 2. In adult patients with AIS who are eligible for IVT within 4.5 hours of symptom onset, treatment should be initiated as quickly as possible, assuring safe administration and avoiding potential delays associated with additional multimodal neuroimaging, such as CTA/MRA, and CT/MR perfusion imaging.[2,3] |
| 1 | B-NR | 3. In patients with AIS undergoing IVT, health care professionals should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema, which may cause partial airway obstruction, to reduce poor clinical outcomes.[4–20] |
| 1 | C-EO | 4. In patients with AIS eligible for IVT, health care professionals should discuss its potential risks and benefits with competent patients and/or available patient representatives, when feasible, to ensure shared decision-making. |
| 1 | B-NR | 5. In patients with suspected ischemic stroke, treating health care professionals should determine blood glucose levels before IVT initiation to assess and urgently treat severe hypoglycemia and hyperglycemia, which may mimic acute stroke presentations.[4–20] |
| 1 | C-LD | 6. In patients with suspected ischemic stroke with severe hypoglycemia or hyperglycemia, if symptoms of disabling stroke persist despite correction to normoglycemia, administration of IVT is recommended to improve functional outcomes. |
| 1 | A | 7. In patients with AIS who are otherwise eligible for IVT with early ischemic change of mild to moderate extent (other than frank hypodensity attributable to the clinical presentation) on initial brain imaging, IVT is recommended to improve functional outcome.[21,22] |
| 3: No Benefit | B-R | 8. In eligible adult patients with AIS presenting with mild non-disabling stroke deficits (eg, isolated sensory syndrome in many cases) within 4.5 hours of symptom onset or last known well, IVT is not recommended as it has not shown superiority in improving functional outcomes compared to double antiplatelet treatment.[23–29] |
| Bleeding risk | | |
| 1 | B-NR | 9. In suspected patients with AIS who are taking single or DAPT and are otherwise eligible for IVT, IVT is recommended to improve functional outcomes despite an increase in risk of sICH compared with no antiplatelet therapy.[30] |
| 2a | B-NR | 10. In patients with AIS within 4.5 hours of last known well and eligible for IVT, it is reasonable that IVT not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal result.[31,32] |
| 1 | B-NR | 11. In patients with AIS who are eligible for IVT within 4.5 hours of symptom onset with unknown burden of cerebral microbleeds (CMB), it is recommended that IVT be administered without first obtaining MRI to exclude CMBs.[33–37] |
| 2a | B-NR | 12. In patients with AIS within 4.5 hours of last known well and who are eligible for IVT, administration of IVT is reasonable to achieve better functional outcomes if a small number (eg, 1–10) of CMBs was demonstrated on MRI.[33–37] |
| 2b | B-NR | 13. In patients with AIS within 4.5 hours of last known well and who are eligible for IVT, if they previously had a high burden (eg, >10) of CMBs demonstrated on MRI, usefulness of IVT is uncertain as it may be associated with an increased risk of sICH.[33,34,37] |
| Pediatric patients | | |
| 2b | C-LD | 14. In pediatric patients aged 28 days to 18 years with confirmed AIS presenting within 4.5 hours of symptom onset and disabling deficits, IVT with alteplase may be considered as it is safe, but efficacy is uncertain.[38–42] |

### *Synopsis*

General principles for treatment of IVT include prompt evaluation to assess disabling deficits followed by rapid treatment in eligible patients, given the consistent finding that treatment effect is highly time dependent; shared decision-making when feasible with patients or their representatives; assessment of blood glucose before IVT initiation; and readily available standardized clinical protocols to manage complications such as sICH and orolingual edema. Patients remain eligible for IVT if disabling deficits persist despite correction of hypo- or hyperglycemia,





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the presence of mild to moderate early ischemic changes, and pre-treatment with single or DAPT. However, thrombolysis is not recommended for hyperacute patients presenting with mild, non-disabling deficits. Treatment should not be delayed assessing for CMB and treatment is reasonable if up to 10 CMBs are previously known. The use of thrombolysis in those with high burden of CMBs and in pediatric populations is uncertain.

### *Recommendation-Specific Supportive Text*

1. Prompt clinical assessment by trained professionals is essential to determine whether presenting neurological deficits are disabling in nature. Defining deficits that are disabling for an individual patient is challenged by subjective considerations; a deficit that is disabling for 1 individual may not be for another. Use of the NIHSS score alone does not suffice. For example, lower extremity weakness such that a person cannot walk may lead to an NIHSS score of 2 but is considered disabling. To consider the nature of the specific deficits for an individual patient, the PRISMS trial investigators created an operational definition for "clearly disabling" deficits to guide selection of patients for the trial, as shown in Table 4.[43] Upon completion of the trial, an analysis of the AHA-GWTG registry of patients presenting with NIHSS scores 0 to 5, while considering NIHSS item scores, suggested that the syndromes of patients who were not enrolled in PRISMS tended to match the symptoms and severity of those treated with IVT in the concurrent broad clinical practice.[44] Given that patients with non-disabling deficits in PRISMS did not demonstrate benefit from IVT, this definition may serve as a useful guide when evaluating individual patients for treatment with IVT.
   Once deficits have been determined to be disabling, delaying IVT is potentially harmful, given the powerful impact of time from onset of symptoms to treatment on clinical outcomes. Although faster treatment may lead to higher rates of treatment of stroke mimics, delays should not be incurred to perform additional diagnostic testing unless the possible source of mimic, or the clinical context, leads to concern for increased hemorrhagic risk from treatment. The risk of HT after IVT in stroke mimics, such as conversion disorder, complicated migraine, or seizure, is very low (0.5%).[45]
2. NCCT was the only neuroimaging modality used in the NINDS rt-PA trial and in ECASS III and is therefore sufficient neuroimaging for decisions about IVT in most patients.[2,3] Multimodal CT and MRI, including diffusion and perfusion imaging, are not necessary when the diagnosis of ischemic stroke is very likely, and their performance may delay time-sensitive administration of IVT. In a minority of cases, particularly when there is substantial diagnostic uncertainty, advanced imaging may be beneficial. At centers with proficient workflows for advanced imaging, it is feasible to obtain bundled initial NCCT and advanced CTA and CTP without delay in IVT or providing IVT in the CT scanner after normal CT results and before advanced imaging acquisition.
3. See Table 5 for options for management of symptomatic intracranial bleeding occurring within 24 hours after administration of IVT for treatment of AIS and Table 6 for options for management of orolingual angioedema associated with IVT administration for AIS.
4. Because of proven benefit and the need to expedite treatment, when a patient cannot provide consent (eg, aphasia, confusion) and a legally authorized representative is not immediately available to provide proxy consent, it is justified to proceed with IVT in an otherwise eligible adult patient with AIS and disabling deficits.
5. Severe hypo- and hyperglycemia is typically defined as <50 and >400 mg/dL, respectively. Correction of glucose to normal levels with appropriate medications is recommended and clinical deficits should be assessed after correction of glucose to evaluate thrombolytic eligibility.
6. In patients with persisting stroke-like disabling deficits after correction of glucose derangement, IVT is recommended to improve functional outcomes from suspected stroke. The very small risk of treatment of a stroke mimic is likely outweighed by the major potential benefit of IVT. Furthermore, ancillary evidence of a concurrent stroke, such as a hyperdense artery to signify occlusion or early ischemic changes, should reinforce the decision to treat with IVT despite initial glucose derangements.
7. Early ischemic changes of mild to moderate extent on CT scan did not modify the treatment effect of IVT in the NINDS tPA trial and therefore should not be considered a contraindication.[21,22] A large extent of hypodensity, such as ASPECTS 0 to 2, was rare (n=16) in the NINDS tPA Study. Extensive early ischemic changes or frank hypodensity (ie, severe hypoattenuation as seen with subacute stroke) should lead to revisitation of the timing of symptom onset to ensure eligibility in the 4.5-hour window.
8. A multicenter RCT evaluated IV alteplase versus aspirin in patients with mild AIS and nondisabling deficits. The study showed no significant difference in the adjusted percentage with favorable functional outcome at 90 days (78% versus 81%).[25] Another observational, retrospective study of 319 patients with stroke presenting with nondisabling deficits within 4.5 hours revealed that although alteplase was safe, there were no associations with better functional outcome.[46] Subsequent trials also have not demonstrated benefit of IVT in mild stroke populations but either did not define mild severity

**Table 4. Guidance for Determining Deficits to be Clearly Disabling at Presentation[43]**

| **Among patients with NIHSS scores 0–5 at presentation, if the observed deficits persist, would they still be able to do basic activities of daily living and/or return to work (if applicable)?** | |
|---|---|
| Basic activities of daily living include bathing/dressing, ambulating, toileting, hygiene, and eating (BATHE mnemonic). | |
| To fully evaluate the level of deficits, the ability to ambulate and swallow independently should be assessed. | |
| The clinician should make this determination in consultation with the patient and available family. | |
| **As a guideline, while always considering individual circumstances:** | |
| **The following deficits would typically be considered clearly disabling:** | **The following deficits may not be clearly disabling in an individual patient:** |
| Complete hemianopsia (≥2 on the NIHSS "vision" question) | Isolated mild aphasia (but still able to communicate meaningfully) |
| Severe aphasia (≥2 on the NIHSS "best language" question) | Isolated facial droop |
| Severe hemi-attention or extinction to >1 modality (≥2 on the NIHSS "extinction and inattention" question) | Mild cortical hand weakness (especially nondominant, NIHSS score, 0) |
| Any weakness limiting sustained effort against gravity (≥2 on the NIHSS "motor" questions) | Mild hemimotor loss |
| | Hemisensory loss |
| | Mild hemisensorimotor loss |
| | Mild hemiataxia (but can still ambulate) |

NIHSS indicates National Institutes of Health Stroke Scale.

with individual considerations (ARAMIS) or explicitly beyond local clinical judgment (TEMPO-2).[23–27]

Earlier studies have confirmed the efficacy and safety of DAPT in patients presenting with minor stroke or high-risk TIA within 24 hours when compared with aspirin alone.[28,29] In 2023, a multicenter randomized trial aimed to determine if early administration of DAPT demonstrated similar efficacy as IV alteplase in 90-day functional outcomes in patients presenting with minor, nondisabling strokes within 4.5 hours. DAPT was shown to be noninferior to IV alteplase, with more early neurological deterioration and bleeding events occurring in the alteplase group. In 2024, 2 meta-analyses found no significant difference in functional outcomes between DAPT and alteplase in patients with minor ischemic strokes, with lower sICH rates in the DAPT group.

9. In patients with AIS taking single and DAPT, IVT is associated with a small absolute increased risk (0.9% and 1.2%, respectively) of sICH that is likely outweighed by the anticipated absolute treatment benefit (8%) of IVT.[30]
10. Early initiation of thrombolytic therapy is pivotal for maximizing neurological recovery in AIS. Multiple clinical trials data and large registries have shown that each minute of delay in administering IVT leads to an incremental loss of salvageable brain tissue

**Table 5. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase or Tenecteplase for Treatment of AIS in Adults**

| **Stop alteplase infusion or tenecteplase (if still being pushed)** |
|---|
| Emergent CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match |
| Emergent nonenhanced head CT if a clinical concern exists |
| Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min to maintain fibrinogen level of ≥150 mg/dL; as a rule of thumb 10 U of cryoprecipitate increase fibrinogen level by nearly 50 mg/dL) |
| Tranexamic acid 1000 mg IV infused over 10 min OR e-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) |
| Potential for benefit in all patients, but particularly when blood products are contraindicated by patient/family or if cryoprecipitate is not available in a timely manner |
| Hematology and neurosurgery consultations as necessary |
| Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control |

Adapted with permission from Sloan et al,[4] Mahaffey et al,[5] Goldstein et al,[6] French et al,[7] Yaghi et al,[8–10] Stone et al,[11] and Frontera et al.[12]

AIS indicates acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CBC, complete blood count; COR, class of recommendation; CPP, cerebral perfusion pressure; CT, computed tomography; ICP, intracranial pressure; INR, international normalized ratio; IV, intravenous; LOE, level of evidence; MAP, mean arterial pressure; and PT, prothrombin time.

**Table 6. Management of Orolingual Angioedema Associated With IV Thrombolytic Administration for AIS in Adults[53,54]**

| **Maintain Airway** |
|---|
| Endotracheal intubation may not be necessary if edema is limited to the anterior tongue and lips. |
| Edema involving the larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses a higher risk of requiring intubation. |
| Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after IV thrombolytic use. Cricothyroidotomy is rarely needed and also problematic after IV thrombolytic use. |
| Discontinue IV thrombolytic infusion (if alteplase) and hold ACE inhibitors. |
| Administer IV methylprednisolone 125 mg. |
| Administer IV diphenhydramine 50 mg. |
| Administer ranitidine 50 mg IV or famotidine 20 mg IV. |
| If there is further increase in angioedema, administer 0.1% epinephrine (1 mg/mL concentration) 0.3 mL subcutaneously or by nebulizer 0.5 mg/dL. |
| Icatibant, a selective bradykinin B2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed a total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema. |
| Provide supportive care. |

Adapted with permission from Sloan et al,[4] Mahaffey et al,[5] Goldstein et al,[6] French et al,[7] Yaghi et al,[8–10] Stone et al,[11] and Frontera et al.[12]

ACE indicates angiotensin-converting enzyme; AIS, acute ischemic stroke; COR, class of recommendation; IV, intravenous; and LOE, level of evidence.

and can worsen long-term disability.[31] In individuals without a known coagulopathy or other suspicion for significant hematologic abnormalities, waiting for laboratory confirmation (eg, platelet counts, coagulation parameters) has not demonstrated improved safety or outcomes and can instead forfeit the benefits of timely reperfusion. Therefore, when the likelihood of abnormal test results is low based on clinical history or previous laboratory checks, initiating IVT therapy without delay is consistent with goal-directed stroke care protocols to limit treatment lags. This approach is supported by multiple observational studies indicating that prompt IVT can be delivered safely, as well as by previous guideline statements and QI initiatives emphasizing efficient DTN metrics in stroke centers.[32]

11. Approximately 5% to 20% of patients with AIS receiving IVT have CMBs.[33–35] A recent meta-analysis included 6765 patients receiving IVT and suggested that the presence of CMBs was associated with increased risk of sICH and poorer outcomes.[36] Another report suggested the risk of sICH and poor outcomes with IVT was greatest in patients with >10 CMBs, but the pretest probability of >10 CMBs is low (0.6%–2.7%).[47,48] As such, MRI should only be obtained to screen for CMBs if IVT would only be delayed by a maximum of 10 minutes,[33] which is not plausible in routine clinical practice. Instead, IVT is recommended in patients with an unknown burden of CMBs without first obtaining MRI.
12. Neuroimaging advances, particularly T2*-weighted MRI or susceptibility-weighted imaging, have facilitated the detection of CMBs. Observational and subgroup analyses suggest that having a limited number of microbleeds (1–10) does not substantially heighten the risk of symptomatic hemorrhage beyond baseline expectations. In a secondary analysis of the WAKE-UP trial in which all enrolled patients had MRI before receiving IVT or placebo, 21.4% of patients had at least 1 CMB on baseline imaging and only 3.5% had ≥5 CMBs. The presence of CMBs was associated with a nonsignificant increased risk of sICH (11.2% versus 4.2%; OR, 2.32 [95% CI, 0.99–5.43]; *P*=0.052) but had no effect on functional outcome at 90 days. There was no evidence of reduced treatment effect of IV alteplase in patients with ≥1 CMBs.[30] Although the presence of any microbleeds indicates a degree of small-vessel pathology, several studies note that individuals in this range often still derive meaningful functional improvement from timely thrombolysis. Potential concerns about ICH must be balanced against the established efficacy of clot dissolution in reducing stroke-related disability. Emerging evidence also suggests that the distribution of these microbleeds (eg, deep versus lobar) could modulate risk, but the overall consensus remains that relatively low microbleed burden does not preclude a positive net clinical benefit from IVT therapy. This perspective aligns with broader data supporting the importance of early reperfusion in acute stroke and underscores the value of individualized imaging review to guide treatment decisions.
13. CMBs are common in patients receiving IV alteplase, occurring in 15% to 27%.[34] Patients with extensive microbleeds on pretreatment MRI pose a challenging scenario in acute stroke care. Numerous microbleeds often suggest advanced small-vessel disease or cerebral amyloid angiopathy, conditions that can elevate vulnerability to hemorrhagic complications. Although definitive randomized trials in this subgroup are limited, registry data and retrospective analyses have documented higher rates of sICH with a heavy microbleed burden,[33,37] raising concerns about the net safety profile of thrombolysis. Conversely, clinicians must weigh these risks against the potential for significant neurological recovery, especially if a treatable LVO is present. Because the threshold of 10 microbleeds is frequently used in observational studies to classify high burden, careful individualized judgment is generally advised. The availability of advanced MRI sequences (eg, gradient echo and susceptibility weighted images) and risk prediction models can further inform shared decision-making, which may include discussions about potentially uncertain benefit relative to hemorrhagic risk. Future multicenter trials are expected to refine these risk estimations for better-informed treatment choices.[33]
14. The randomized pediatric TIPS trial, which attempted to investigate functional outcomes after IVT, was stopped due to lack of recruitment. The retrospective analysis of the 26 included patients at least confirms the safety of IV alteplase if administered at a dose of 0.9 mL/kg within 0 to 4.5 hours after symptom onset in pediatric patients aged 28 days to 18 years with a PedNIHSS score ≥4.[38,39,49,50]

## Knowledge Gaps and Future Research

- More research is needed on how to reduce subjectivity in the evaluation of individual patients with NIHSS scores 0 to 5 for disabling versus nondisabling deficits. A significant knowledge gap exists in the lack of a standardized definition for minor, nondisabling stroke deficits, which hinders consistent diagnosis, treatment, and research outcomes across studies. Future research should focus on developing and validating a universally accepted definition to facilitate better understanding of these strokes, their natural history, and optimal management strategies.[37]
- Recent data underscore a nuanced view of thrombolysis in patients with CMBs, with tenecteplase showing

promise in recent trials but requiring more evidence, particularly in populations with a higher burden of CMBs. The burden and location of CMBs (especially strictly lobar) are critical in evaluating hemorrhagic risk and could, in the future, be factored into individualized treatment protocols. Meta-analyses of the association of baseline CMBs on the risk of sICH after IVT generally report that the presence of CMBs increases the risk of ICH and the chances of poor outcomes, but it is unclear whether these negative effects fully negate the benefit of IVT. It is also unknown whether the location and number of CMBs may differentially influence outcomes. Finally, most of these studies include IV alteplase with no large studies on IV tenecteplase and its effects. These questions deserve further investigation.[33]

- The optimal intensity of patient monitoring after IVT for AIS remains uncertain. Current standard protocols involve frequent assessments to promptly identify complications such as sICH. However, these high-intensity monitoring regimens are resource-intensive and may not be necessary for all patients, particularly those with mild neurological deficits. Preliminary findings from the Optimal Post Tpa-Iv Monitoring in Ischemic Stroke (OPTIMIST) trial[51] suggest that low-intensity monitoring may be safe in selected patients, but the small sample size and single-center design limit the generalizability of these results. The ongoing OPTIMIST MAIN trial (https://clinicaltrials.gov/study/NCT03734640) aims to provide more robust evidence by evaluating the safety and effectiveness of a reduced monitoring protocol in a larger, international cohort. Until these results are available, the comparative efficacy of low- versus high-intensity monitoring regimens remains an important knowledge gap in postthrombolysis stroke care.
- There are initial data that IV tenecteplase (TNK) may be safe in childhood arterial ischemic stroke. However, this evidence is limited to 11 children who received TNK and did not experience ICH.[52] Larger, prospective studies are needed to further define the safety, optimal dosage, and efficacy in pediatric stroke and to determine whether children with arterial occlusion but low NIHSS may benefit from thrombolytics.

### 4.6.2. Choice of Thrombolytic Agent

| Recommendations for Choice of Thrombolytic Agent Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | A | 1. In adult patients with AIS presenting within 4.5 hours of symptom onset or last known well and eligible for IVT, tenecteplase at a dose of 0.25 mg/kg body weight (max 25 mg) or alteplase at a dose of 0.9 mg/kg body weight is recommended to improve functional outcomes.[1–5] |
| 3: No Benefit | A | 2. In adult patients with AIS presenting within 4.5 hours of symptom onset or last known well and eligible for IVT, tenecteplase at a dose of 0.4 mg/kg body weight is not recommended.[6–9] |

#### *Synopsis*

Since the 2019 AIS guidelines, there have been multiple large phase 3 RCTs testing tenecteplase 0.25 mg/kg body weight (max 25 mg) given as a bolus versus alteplase 0.9 mg/kg body weight (max of 90 mg) with 10% administered as a bolus and the remainder by infusion during a 60-minute period in patients with AIS presenting within 4.5 hours of stroke symptom onset or last known well.[1–5] These RCTs have included >6000 patients from across the world, with broad eligibility criteria attesting to generalizability. Each of these trials individually has shown noninferiority of tenecteplase versus alteplase for prespecified primary outcomes (mRS score 0–1 or the entire scale at 90 days) with similar safety outcomes. No significant differences have been noted in secondary analyses or in per protocol analyses. Given the obvious ease of administration of tenecteplase (single bolus over 5–10 seconds) versus alteplase (bolus followed by a 1-hour infusion), these studies suggest that tenecteplase at a dose of 0.25 mg/kg body weight (max 25 mg) can replace alteplase as the thrombolytic agent of choice in patients with AIS presenting within 4.5 hours of stroke symptom onset. Of note, all previous phase II and phase III RCTs suggest that tenecteplase (0.25 mg/kg body weight) is either similar or better than alteplase in these patients with similar safety. Phase 2 and phase 3 trials using tenecteplase at a dose of 0.40 mg/kg body weight (when compared with 0.25 mg/kg tenecteplase or 0.9 mg/kg body weight alteplase) have not shown any additional benefit and have shown the potential for harm with the higher dose of tenecteplase.[6–9]

#### *Recommendation-Specific Supportive Text*

1. Randomized trials evaluating IVT administered within 4.5 hours from last known well in patients presenting with disabling AIS have consistently demonstrated favorable efficacy and safety outcomes. Tenecteplase at a dose of 0.25 mg/kg body weight has been evaluated extensively in recent large trials, showing noninferiority to alteplase at a dose of 0.9 mg/kg body weight in terms of functional outcomes. Emerging data have further strengthened confidence in the use of tenecteplase across diverse patient populations, confirming both safety and effectiveness. Clinical judgment remains essential when selecting patients for IVT therapy, considering factors such as comorbidities, timing, and the availability of neuroimaging to exclude hemorrhage.[1–5]

   Tenecteplase may offer practical advantages over alteplase, including a single bolus injection and fewer dosing complexities. This aligns with the principle of prompt, effective reperfusion as a cornerstone of acute stroke care. Several studies have compared single-bolus tenecteplase to the







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standard alteplase infusion for AIS, suggesting that a bolus-based regimen may simplify administration, thus potentially reducing the potential for dosing errors and treatment delays. Tenecteplase's 1-time bolus approach may streamline workflows in settings where timely therapy is crucial, potentially shortening DTN and DIDO times.[10] Real-world data and patient level pooled meta-analyses may help clarify whether any clinical differences exist beyond ease of use. For now, institutions considering tenecteplase should ensure readiness to manage potential adverse events and confirm availability of necessary resources for implementation (Table 7).[1–5]

2. Phase 2 and 3 trials have evaluated tenecteplase dosing in AIS, revealing that a 0.4 mg/kg dose may increase the risk of sICH without improving functional outcomes. For instance, the Norwegian Tenecteplase Stroke Trial (NOR-TEST) 2 trial, which compared tenecteplase 0.4 mg/kg with alteplase 0.9 mg/kg, was prematurely terminated due to worse safety and functional outcomes in the tenecteplase group.[6] Similarly, a previous pilot dose-escalation study reported an increase in sICH in patients receiving 0.4 mg/kg tenecteplase.[11] Another study comparing tenecteplase 0.4 mg/kg with 0.25 mg/kg body weight found no additional advantages with the higher dose though sICH rates were not significantly increased in the higher dose group (unadjusted risk difference, 3.3% [95% CI, −0.5% to 7.2%]).[9] Current evidence from multiple large trials supports using a 0.25 mg/kg dose of tenecteplase, which has demonstrated a more favorable safety and efficacy profile. Therefore, administering tenecteplase at 0.4 mg/kg is not recommended for patients with AIS presenting within 4.5 hours of symptom onset.[6–9]

## Knowledge Gaps and Future Research

- Comparison of tenecteplase and alteplase across a multitude of patient factors and clinical scenarios: To comprehensively evaluate the efficacy and safety of tenecteplase and alteplase across diverse patient populations and clinical scenarios, conducting patient-level pooled analyses is essential. Such analyses enable a more nuanced understanding of how different subgroups—defined by factors like age, comorbidities, stroke severity, and time to treatment—respond to each thrombolytic agent. By aggregating individual patient data from multiple studies, researchers can identify patterns and interactions that may not be apparent in aggregated data analyses. This approach facilitates the development of tailored treatment protocols and informs clinical decision-making to optimize outcomes for various risk groups. Therefore, future research should prioritize the collection and sharing of individual patient data to support these comprehensive analyses.
- Optimal dosing methodology for tenecteplase: Recent trials testing tenecteplase at a dose of 0.25 mg/kg



**Table 7. Treatment of AIS in Adults*: IVT**

| Alteplase: Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min | | |
|---|---|---|
| **Tenecteplase: Push 0.25 mg/kg (up to maximum 25 mg) based on patient body weight†:** | | |
| **Patient weight (kg)** | **TNK (mg)** | **Volume TNK to be administered (mL)** |
| <60 kg | 15 | 3 |
| 60 kg to <70 kg | 17.5 | 3.5 |
| 70 kg to <80 kg | 20 | 4 |
| 80 kg to <90 kg | 22.5 | 4.5 |
| ≥90 kg | 25 | 5 |
| Admit the patient to an intensive care or stroke unit for monitoring | | |
| If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain an emergency head CT scan. | | |
| Measure BP and perform neurological assessments every 15 min during and after IVT administration for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase treatment | | |
| Increase the frequency of BP measurements if SBP is >180 mm Hg or if DBP is >105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels | | |
| Delay placement of nasogastric tubes, indwelling bladder catheters, or intraarterial pressure catheters if the patient can be safely managed without them | | |
| Obtain a follow-up CT or MRI scan at 24 h after IVT before starting anticoagulants or antiplatelet agents | | |
| *Dosing for pediatric patients has not been determined.<br>† If <50kg and accurate weight is known, dosing per 1-kg band may be used. Do not delay thrombolysis to obtain exact weight – timely treatment is critical. With estimated weights, dosing per 1-kg band is not necessarily safer than 10-kg band dosing. | | |

AIS indicates acute ischemic stroke; BP, blood pressure; CT, computed tomography; DBP, diastolic blood pressure; IV, intravenous; IVT, intravenous thrombolysis; MRI, magnetic resonance imaging; and SBP, systolic blood pressure.

body weight in patients with AIS have employed different weight-based dosing strategies, namely, a unit kg weight, 2-kg weight band increments, or decile (10 kg weight band) increments. The decile weight band increment is also used for administration of tenecteplase in acute coronary syndromes. More research is needed to compare these methods and better understand which of these strategies could simplify dosing calculations and reduce administration errors, thereby improving patient outcomes.

- Tenecteplase dosing in patients with elevated bleeding risk: Managing patients at high risk of bleeding from IVT presents a significant clinical challenge. It is unclear whether administering lower doses of tenecteplase in this subgroup could mitigate bleeding risks while maintaining therapeutic efficacy. Tailored dosing regimens for these high-risk patients have yet to be established, underscoring the need for clinical trials focused on dose adjustments based on individual bleeding risk profiles.
- Bridging with tenecteplase versus alteplase before EVT: Though tenecteplase demonstrated efficacy in clot dissolution before EVT in the EXTEND-IA trial,[12] a pre-specified analysis of the ACT[13] showed no difference in recanalization rates before EVT and no difference in functional outcomes. Furthermore, concerns have been raised regarding its potential to fragment thrombi earlier and more effectively than alteplase, leading to clot migration and distal embolization and potentially complicating EVT procedures and worsening outcomes. Further research is warranted to assess the impact of tenecteplase on thrombus dynamics and EVT outcomes, potentially necessitating a reevaluation of the bridging strategies involved with this thrombolytic agent.
- Although 1 study has shown that tenecteplase appears to be safe in pediatric patients, further studies of its use in pediatric patients are needed including pharmacokinetic and pharmacodynamic studies to determine the appropriate weight-based dosing for young children.[14]

### 4.6.3. Extended Time Windows for Intravenous Thrombolysis

**Recommendations for Extended Time Windows for Intravenous Thrombolysis**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-R | 1. In patients with AIS who (a) have unknown time of onset and are within 4.5 hours from symptom recognition and (b) have an MRI-DWI lesion smaller than one-third of the MCA territory and no marked signal change on FLAIR, IVT administered within 4.5 hours of stroke symptom recognition can be beneficial to improve functional outcomes.[1] |

**Recommendations for Extended Time Windows for Intravenous Thrombolysis (Continued)**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-R | 2. In patients with AIS who have salvageable ischemic penumbra detected on automated perfusion imaging and who (a) awake with stroke symptoms within 9 hours from the midpoint of sleep or (b) are 4.5–9 hours from last known well, IV thrombolysis may be reasonable to improve functional outcomes.[2,3] |
| 2b | B-R | 3. In patients with AIS due to LVO with salvageable ischemic penumbra, presenting within 4.5 to 24 hours from symptom onset or last known well, and who cannot receive EVT, treatment with IVT directed by individuals with expertise in thrombolytic stroke care may be beneficial to improve functional outcomes.[2–5] |

#### Synopsis

Based on the NINDS tPA and ECASS-III trials, treatment with IVT for patients within 4.5 hours of last known well is well-established as standard of care. The WAKE-UP trial has since shown that patients with an unknown time of onset, but within 4.5 hours of symptom recognition and having MRI parameters suggesting biological onset within 4.5 hours benefit from IVT. This treatment effect was consistent in lacunar and nonlacunar stroke subgroups.[6,7] Since the last guideline was published, the EXTEND and TRACE-3 trials used CT perfusion parameters for patient selection and found further signal of benefit in the 4.5- to 9-hour and 4.5- to 24-hour windows, respectively.

#### Recommendation-Specific Supportive Text

1. The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) used MRI mismatch. WAKE-UP required absence of a clearly visible, or marked, hyperintense signal in the same region on FLAIR as DWI. The trial allowed enrollment of patients with MRI showing subtle FLAIR changes (http://wakeuptraining-tool.com); WAKE UP trialists were offered the option to quantify the mean signal intensities of both mirroring regions of the FLAIR to objectively assess marked FLAIR change. A signal intensity ratio <1.2 was recommended for randomizing in the WAKE-UP trial; NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. The primary endpoint of an mRS score of 0 to 1 at 90 days was achieved in 53.3% of the IV alteplase group versus 41.8% of the placebo group ($P$=0.02). The THAWS trial halted early after WAKE-UP[1] and with limited randomization of 131 patients, no clinical outcome benefit in the alteplase group (32/68 [47.1%]) could be demonstrated over the control group (28/58, 48.3% risk ratio [RR], 0.97 [95% CI, 0.68–1.41]; $P$=0.892).[8]







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2. The EXTEND trial randomized 225 patients using perfusion-based selection of patients with salvageable penumbra and achieved its primary outcome of an improvement in mRS score 0 to 1 at 90 days (35.4% versus 29.5%; adjusted risk ratio, 1.44 [95% CI, 1.01–2.06]; *P*=0.04) but with an increased risk of sICH (6.2% versus 0.9%; adjusted risk ratio, 7.22 [95% CI, 0.97–53.5]; *P*=0.05) in the alteplase versus placebo groups, respectively. A meta-analysis of the EPITHET, ECASS-4, and EXTEND trials pooled 414 randomized patients presenting in this >4.5- to 9-hour window with salvageable ischemic penumbra on MR DWI-PWI or CTP imaging and confirmed the benefit of IV alteplase with excellent functional outcomes (mRS score 0–1) at 90 days (adjusted OR, 1.86 [95% CI, 1.15–2.99]; *P*=0.011), despite an increase risk of sICH (adjusted OR, 9.7 [95% CI, 1.23–76.55]; *P*=0.031). An updated meta-analysis of 8 extended window thrombolysis phase 2 (EPITHET, ROSE-TNK, and EXIT-BT) and phase 3 trials (EPITHET, WAKE-UP, EXTEND, ECASS-4, THAWS, and TRACE-III) trials found that IVT was associated with greater odds of excellent (mRS 0–1 at 90 days) outcome (OR, 1.43 [95% CI, 1.17–1.75]) despite an increase in symptomatic hemorrhage (OR, 4.25 [95% CI, 1.67–10.84]).[9]
3. The majority (77%) of EXTEND participants harbored LVOs that would now be treated with EVT, limiting the generalizability of the findings.[3,5]The TRACE-III trial tested IVT in patients with LVO in China, where the majority of patients did not receive EVT, and showed the benefit of extended window IVT for this population.[10] Although TRACE-3 achieved its primary outcome (mRS score 0–1 at 90 days) in favor of the tenecteplase group (33.0% versus 24.2%; risk ratio, 1.37 [95% CI, 1.04–1.81]; *P*=0.03), this effect was in a population not offered timely EVT. In the TIMELESS trial in the same extended 4.5- to 24-hour window and using equivalent MR DWI-PWI or CTP imaging selection criteria but in which rapid EVT was administered, tenecteplase was not beneficial in improving functional outcomes (ordinal mRS: adjusted cOR, 1.13 [95% CI, 0.82–1.57]; *P*=0.45). The CHABILIS-T II trial similarly randomized 224 Chinese patients using CT perfusion-based selection in the 4.5- to 24-hour window to either tenecteplase or placebo; however, unlike TRACE-III, 54.9% underwent EVT. There was significant improvement in recanalization (aOR, 2.5 [95% CI, 1.4–4.4]; *P*=0.002) but no difference in sICH or functional outcomes at 90 days.[10,11]These findings may justify IVT for those with LVO who cannot receive or will receive delayed EVT.[2,10,11]

## Knowledge Gaps and Future Research

- Further data are needed on whether patients within 4.5 hours of awakening from stroke and selected exclusively by CT scan (instead of MRI, which is not widely available especially in low-income and middle-income countries) may benefit from IVT. The TWIST trial intended to address this question by requiring only NCCT that showed hypoattenuation in less than one-third of the MCA territory. Although TWIST showed a favorable direction of effect, it appeared underpowered.[12] This approach, if proven beneficial, would be particularly helpful for low-resource settings.
- The role of IVT in selected patients who do not harbor LVOs with >4.5 hours of symptom duration and salvageable ischemic penumbra requires further investigation.

### *4.6.4. Other IV Fibrinolytics and Sonothrombolysis*

**Recommendations for Other IV Fibrinolytics and Sonothrombolysis Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| Other IV fibrinolytics | | |
| 2b | B-R | 1. In eligible patients with AIS presenting within 4.5 hours from last known normal and not undergoing EVT, IV reteplase, instead of alteplase, may be considered to increase the odds of excellent functional outcome at 90 days.[1,2] |
| 2b | B-R | 2. In eligible patients with AIS within 4.5 hours from last known normal and not undergoing EVT, IV mutant prourokinase, instead of alteplase, may be considered due to lower odds of bleeding and noninferiority for odds of excellent functional outcome at 90 days.[3,4] |
| 3: No Benefit | A | 3. In eligible patients with AIS presenting within 3 to 9 hours from last known normal, IV desmoteplase is not recommended for improving functional independence at 90 days.[5–8] |
| 3: No Benefit | B-R | 4. In eligible patients with AIS within 4.5 hours from last known normal, IV mutant prourokinase in conjunction with low-dose alteplase is not recommended to improve functional outcomes.[9,10] |
| 3: No Benefit | B-R | 5. In eligible patients with AIS within 6 hours from last known normal, IV urokinase is not beneficial for decreasing the odds of death or dependency.[8] |
| 3: Harm | A | 6. In eligible patients with AIS within 6 hours from last known normal, IV streptokinase should not be administered because it does not result in improved rate of functional independence at 90 days and is associated with increased early mortality.[8] |
| Sonothrombolysis | | |
| 3: No Benefit | A | 7. In patients with AIS, sonothrombolysis as an adjunctive therapy to IVT compared with IVT alone is not recommended as it did not increase the odds of early neurological improvement nor improve functional outcome at 90 days.[11,12] |

### *Synopsis*

In addition to alteplase and tenecteplase for acute treatment of patients with AIS, previous trials have studied desmoteplase, urokinase, prourokinase, and streptokinase. The trials did not demonstrate any benefit over

placebo in improving functional outcomes. However, IV reteplase was compared with alteplase in a study performed in China and showed superiority of reteplase over alteplase in achieving excellent functional outcome.

Sonothrombolysis is a noninvasive ultrasound-based therapy that uses pulse waves to lyse intracranial thrombi. An individual patient data meta-analysis showed that this adjunctive treatment was associated with increased odds of full recanalization in patients with intracranial LVOs but with no effect on clinical outcomes.[13] Similarly, 2 randomized trials of sonothrombolysis did not show any clinical outcome benefit from sonothrombolysis as an adjunctive treatment to IVT.

### *Recommendation-Specific Supportive Text*

1. Reteplase was compared with alteplase in 2 RCTs.[1,2] Both were performed in China and enrolled patients 18 to 80 years of age not selected for EVT. The first one was a Phase 2 trial of 180 patients using 2 doses of reteplase 12 mg + 12 mg and 18 mg + 18 mg (given 30 minutes apart) and showed that both doses of reteplase had similar efficacy and safety profiles as alteplase.[2] The second was an RCT comparing reteplase 18 mg + 18 mg versus standard dose alteplase.[1] This trial showed that reteplase was superior to alteplase in achieving excellent functional outcome at 90 days defined as mRS 0–1 (risk ratio, 1.13 [95% CI, 1.05–1.21]; $P$=0.002) with no significant difference in sICH between the 2. The 2 trials have several limitations, including exclusion of patients over 80 years and those who underwent thrombectomy, underrepresentation of women (29% of trial population), and not including patients outside China. Therefore, the generalizability of these findings remains uncertain.
2. Two RCTs conducted in China compared the safety and efficacy of IV mutant prourokinase to IV alteplase in patients with AIS within 4.5 hours from last known normal. The Prourokinase in the Treatment of AIS Within 4.5 hours of Stroke Onset (PROST) trial was a phase III RCT from China of 663 patients allocated to prourokinase (35 mg intravenous dose) versus alteplase (standard dose) in a 1:1 fashion that showed no significant difference in the primary outcome (mRS score 0–1 at 90 days) (65.2% versus 64.3%) or sICH (1.5% versus 1.8%) across the 2 groups (prourokinase versus alteplase) but a lower risk of systemic bleeding within 90 days with prourokinase (25.8% versus 42.2%; $P$<0.001).[3] The PROST-2 trial was an open label noninferiority trial of 1552 patients allocated to prourokinase versus alteplase in a 1:1 fashion. Noninferiority was found in the primary outcome (mRS score at 90 days, 0–1) (72.0% versus 68.7%; $P$<0.0001) but a lower risk of sICH (0.3% versus 1.0%; $P$=0.021) and major bleeding at 7 days (0.5% versus 2.1%; $P$=0.0072) with prourokinase.[4]
3. Randomized placebo-controlled trials have not shown benefit from the administration of IV desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra, large intracranial artery occlusion, or severe stenosis.[6–8,14,15] For instance, a pooled analysis of the DIAS-3, DIAS-4, and DIAS-J trials showed no significant difference in the odds of functional independence defined as mRS 0 to 2 at 90 days with desmoteplase versus placebo (OR, 1.33 [95% CI, 0.95–1.85]; $P$=0.096). Treatment with desmoteplase was safe and was associated with increased odds of vessel recanalization (OR, 1.59 [95% CI, 1.08–2.35]; $P$=0.019).[6]
4. Randomized trials have not shown benefit from the administration of IV mutant prourokinase alone or in conjunction with low-dose alteplase administered within 4.5 hours from last known normal in improving functional outcome at 90 days.[3,16] An open label phase II RCT from 4 centers in the Netherlands randomized patients to receive low- dose alteplase (5 mg) plus 40 mg of prourokinase infusion compared with standard dose alteplase. The trial showed no significant difference between the 2 groups in the primary outcome of any intracranial hemorrhage (adjusted OR, 98 [95% CI, 0.46–2.12]) as well as shift toward improved mRS score at 30 days (adjusted cOR, 1.16 [95% CI, 0.74–1.84]).[16]
5. IV urokinase has been studied in patients with AIS, with the studies being predominantly in China. A Cochrane review that included data from 1 trial of 465 patients demonstrated that IV urokinase versus placebo administered within 6 hours from last known normal did not result in increased risk of sICH (OR, 1.28 [95% CI, 0.47–3.48]) nor was functional dependency decreased at 90 days (mRS score 3–6; OR, 0.99 [95% CI, 0.67–1.47]).[8] while there was decreased odds of mRS score of 2 to 6 with intravenous Urokinase (OR, 0.57 [95% CI, 0.38–0.85]), urokinase was associated with increased odds of fatal ICH within 7 to 10 days (OR, 4.43 [95% CI, 1.08–18.18]).[8] Studies of IV urokinase in patients with AIS have predominantly been done in China, which limits generalizability.
6. Randomized trials have not shown benefit from the administration of IV streptokinase compared with placebo when administered within 6 hours from last known normal in improving functional outcome at 6 months, but some demonstrated increased mortality with streptokinase.[17–20] A Cochrane review demonstrated an increased rate of early death in patients treated with streptokinase versus control (OR, 1.90 [95% CI, 1.37–2.63]) and sICH within 7 to 10 days (OR, 5.20 [95% CI, 3.25–8.32]).[8] Treatment with IV streptokinase did not result in lower odds of functional dependency at last follow-up (OR, 0.94 [95% CI, 0.72–1.24]).[8]







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7. Two RCTs of sonothrombolysis as adjuvant therapy for IVT have shown no clinical benefit. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis (n=93 patients) or sham (n=90 patients). Neurological improvement at 24 hours and functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of sICH.[12] CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in AIS) randomized 676 patients with AIS (NIHSS score ≥10) who received IV alteplase within 3 or 4.5 hours of symptom onset and randomly allocated to operator independent sonothrombolysis (n=335) or sham ultrasound (n=341).[11] Compared with the control arm, the neurological improvement, death, and SAEs in the intervention arm were not statistically different. At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV fibrinolysis.

## Knowledge Gaps and Future Research

- There is limited generalizability on potential benefits of IV reteplase and IV mutant prourokinase. RCTs are needed to determine whether the potential benefits of these thrombolytic agents are generalizable to populations outside China and children.

### 4.6.5. Other Specific Circumstances

| Recommendations for Other Specific Circumstances Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 2a | B-NR | 1. In eligible adult patients with AIS with known sickle cell disease, IVT can be beneficial to improve functional outcome without increased sICH, life-threatening systemic hemorrhage, or other thrombolytic complications.[1] |
| 2b | C-LD | 2. In adults with acute nonarteritic central retinal artery occlusion (CRAO) causing disabling visual loss, and who are otherwise eligible for IVT, the usefulness of treatment with IVT within 4.5 hours of time last known well is uncertain.[2–6] |

### *Synopsis*

Observational data suggest that several specific populations of patients with uncertain thrombolysis risk benefit ratios may be treated without additional safety concerns. A GWTG observational study of patients with sickle cell disease compared with those without demonstrated no difference in safety or outcomes after IV alteplase.[1] A small RCT of 16 patients with CRAO compared 8 patients who received IV alteplase to 8 who did not (placebo group). At 1 week, no improvement in visual acuity was reported in the placebo group, and 25% of the patients receiving alteplase had improved visual acuity. However, the improvement was not sustained at 6 months, and 1 patient (12.5%) who received alteplase[2] developed an ICH.

Several larger meta-analyses of nonrandomized data suggest improved visual recovery in those treated with IV alteplase.[3,4]

### *Recommendation Specific Supportive Text*

1. A case-control analysis using the population from the AHA GWTG-Stroke registry, including 832 adult cases with sickle cell disease and 3328 age-, sex-, and race-matched controls without sickle cell disease with similar severity of neurological deficits at presentation, showed that sickle cell disease was not associated with worsened complications or discharge outcome after treatment with IV alteplase.[1]
2. There is extensive observational literature which examined outcomes in patients with acute nonarteritic CRAO with and without treatment with IVT. One clinical trial[2] randomized patients with acute nonarteritic CRAO to either placebo or IVT within 24 hours of time last known well. This trial did not demonstrate a difference with respect to visual acuity between the 2 groups; however, lower than anticipated enrollment limited the trial's ability to adequately test its primary hypothesis. A participant level meta-analysis[3] (including data from this single clinical trial as well as observational studies enrolling both IVT-treated and untreated patients) included 68 patients presenting with 4.5 hours of time last known well who treated with IVT. Of patients treated with IVT within 4.5 hours of time last known well, 37.3% achieved a final visual acuity of ≥20/100 compared with a historical control cohort of whom only 17.7% achieved a final visual acuity of ≥20/100 ($P<0.001$). As the majority of studies included in this meta-analysis were retrospective and uncontrolled studies, the quality of evidence contained within is deemed to be modest. For IVT to be considered in CRAO, there are several recommended prerequisites. First, an ophthalmological assessment is warranted. This includes evaluation for a relative afferent pupillary defect and a fundus examination (including a dilated fundus examination or visualization of the fundus with a non-mydriatic fundus camera) to determine whether there is evidence of a vitreous hemorrhage, retinal detachment, or other primary ophthalmological pathology. Second, an assay of the erythrocyte sedimentation rate to aid with exclusion of giant cell arteritis (along with a focused history and general examination). Third, a thorough benefit/risk discussion with the patient is warranted with an acknowledgment that, at present, the literature on IVT for CRAO is limited and it is an area of active study. In general, an exact definition of "disabling visual loss" is not always useful but should be made with

reference to the impact of the precise visual deficit on an individual patient. A final decision on IVT should involve a shared decision-making framework with reference to a patient's baseline visual function, goals for quality of life, and philosophy of care.

## Future Research and Knowledge Gaps

- Sickle cell disease is associated with increased risk of AIS and ICH. The risk and benefit of IVT in children (<18 years of age) with sickle cell disease and AIS is unknown and remains an opportunity for future research.
- The role of IVT in CRAO remains to be tested in a well-powered prospective RCT. Currently, there are 3 clinical trials in progress in Europe. The THEIA trial (THrombolysis [Alteplase] in Patients With acutE Central retInal Artery Occlusion; NCT03197194) randomized patients with acute CRAO within 4.5 hours of time last known well to either IV alteplase or placebo, and enrollment has completed. The TenCRAOS trial (TENecteplase in Central Retinal Artery Occlusion Study; NCT04526951) randomizes patients with acute CRAO within 4.5 hours of time last known well to either IV tenecteplase or placebo and is at an advanced stage of enrollment (at the time of writing). The REVISION trial (Early Reperfusion Therapy With Intravenous Alteplase for Recovery of VISION in Acute Central Retinal Artery Occlusion; NCT04965038) is similar in design, permits use of either alteplase or tenecteplase as the IVT agent, and is actively enrolling patients. Completion of these trials may permit the generation of a pooled estimate of a treatment effect of IVT in a mostly European population, although the use of IVT in more diverse populations remains to be studied. It is also not known which clinical, funduscopic, or radiographic biomarkers predict a positive response to IVT.
- The literature on branch retinal artery occlusion is extremely limited. Future studies are needed to determine whether IVT may be warranted in this condition, although such studies may be challenging owing to its rarity.
- Given that patients exposed to anticoagulation were excluded from the pivotal trials that support the use of IVT in acute stroke, it is not known whether there is a subset of unselected patients (ie, those in whom the treating team does not have access to emergency factor Xa activity or thrombin assays) with recent (<48 hours) direct oral anticoagulant (DOAC) exposure in whom the risks of IVT are outweighed by the benefits. Several recent studies reported on outcomes among patients with recent DOAC exposure who received IVT. First, a nationwide cohort study[7] found that, among patients selected for IVT in routine clinical practice, exposure to a DOAC within the 7 days preceding stroke onset was not associated with an elevated risk of sICH. Of 22 977 patients with recent DOAC exposure who presented with ischemic stroke within 3.5 hours of time last known well (a time frame chosen to signify patients for whom it would be practical to administer IVT within 4.5 hours of time last known well) only approximately 2207 were selected for IVT (of whom only 25 were known to have taken a DOAC within 48 hours of time last known well). Second, Meinel et al[8] performed a retrospective, observational cohort study examining patients exposed to DOACs within 48 hours of symptom onset. A series of smaller retrospective cohorts derived from a collection of participating hospitals made up the DOAC-exposed group. The control group included IVT-receiving patients from these same centers and from a prospectively collected stroke registry. In this study, the investigators found that patients from the DOAC-exposed group exhibited a lower risk of sICH than patients in the unexposed group. Third, a single-institution, retrospective, observational, cohort study[9] found that the risk of sICH did not change after an institutional protocol was revised to permit IVT among DOAC-exposed patients. Fourth, a study based on the Austrian Stroke Registry did not demonstrate differences in sICH risk and functional outcomes among DOAC-exposed patients receiving IVT and non-DOAC-exposed patients receiving IVT.[10] High-quality, prospective studies with careful attention to signals of safety are warranted to examine this question.
- There are scant high-quality data on numerous concomitant conditions that patients with AIS may harbor and which may alter benefit-risk calculations. Therefore, individualized decision-making between patient or legally appointed representative and the treating physicians, often with input from relevant consultants, is recommended. Further, given the lack of high-quality data to guide decision-making, expert opinions and limited data form the basis of the general gradient of risk (Table 8; bluer shades indicating relative safety and redder shades indicating relative harm).

## 4.7. Endovascular Thrombectomy

### *4.7.1. Concomitant With IVT*

**Recommendations for Concomitant With IVT**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with AIS who are eligible for both IVT and EVT, IVT is safe and recommended to improve overall reperfusion efficacy and clinical outcomes.[1,2] |
| 1 | A | 2. In patients with AIS who are eligible for both IVT and EVT, IVT should be administered as rapidly as possible, without observation, to assess clinical response or delay in initiating EVT, to improve treatment times and clinical outcomes.[3] |

### *Synopsis*

Based on several recently completed RCTs, a strategy to forgo (or "skip") IVT to facilitate EVT is not recommended. The benefits of IVT include improved reperfusion rates with EVT, without any increased risk of symptomatic hemorrhage.







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**Table 8. Other Situations Wherein Thrombolysis is Deemed to Be Considered**

| Conditions in Which Benefits of Intravenous Thrombolysis Generally are Greater Than Risks of Bleeding | |
|---|---|
| Extracranial cervical dissections | IV thrombolysis in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 h and probably recommended. |
| Extra-axial intracranial neoplasms | The risk of harm of IV thrombolysis in patients with AIS and extra-axial intracranial neoplasm is likely low. Benefit likely outweighs risk in this population and IV thrombolysis should be considered. |
| Angiographic procedural stroke | IV thrombolysis in patients with AIS during or immediately post-angiography should be considered as benefit likely outweighs risk in this population. |
| Unruptured intracranial aneurysm | The risk of harm of IV thrombolysis in patients with AIS and unruptured intracranial aneurysm is likely low. Benefit likely outweighs risk in this population and treatment with IV thrombolysis should be considered. |
| History of GI/ GU bleeding | IV thrombolysis in AIS patients with previous remote history of GI or GU bleeding that is stable may be candidates for IV thrombolysis. Consideration of benefit and risk on an individual basis in conjunction with GI or GU consultation is appropriate. |
| History of MI | IV thrombolysis in AIS patients with remote history of MI probably has greater benefit than risk. |
| Recreational drug use | IV thrombolysis in AIS patients with known recreational drug use probably has greater benefit than risk in most patients and should be considered. |
| Uncertainty of stroke diagnosis/ stroke mimics | When uncertain if a patient is presenting with symptoms due to stroke vs a stroke mimic, unless there are absolute contraindications, the risk of harm with IV thrombolysis is low. The benefit of IV thrombolysis likely outweighs risk in these patients. |
| Moya-Moya | IV thrombolysis in AIS patients with Moya-Moya disease does not appear to have an increased risk of ICH and likely provides benefit that outweighs risk. |

(*Continued*)

**Table 8. Continued**

| Conditions That are Relative Contraindications | |
|---|---|
| Pre-existing disability | The benefits vs risks of offering IV thrombolysis in patients with pre-existing disability and/or frailty remain uncertain. Treatment should be determined on an individual basis. |
| DOAC exposure | In patients with disabling symptoms and recent DOAC exposure (<48 hours) who are within the window for alteplase/tenecteplase, the safety of IV thrombolysis is unknown. Emerging but limited observational data suggest IV thrombolysis may be considered after a thorough benefit vs risk analysis on an individual basis. Benefit vs risk assessments should include considering the timing of the last DOAC administration, renal function, stroke severity, and availability of endovascular thrombectomy as well as availability of DOAC reversal agents and DOAC-specific anti-factor Xa/thrombin time assays acknowledging the potential for delay in thrombolysis and potential increased thrombotic risk. All aspects of DOAC management (timing, reversal agent use, assay results), should be recorded carefully to facilitate ongoing safety analyses. Definitive clinical trials are needed to establish the safety of IV thrombolysis in DOAC patients. |
| Ischemic stroke w/ in 3 months | Use of IV thrombolysis in patients presenting with AIS who have had a prior ischemic stroke within 3 months may be at increased risk of intracranial hemorrhage. Potential increased risk as a result of the timing and size of the stroke should be weighed against the benefits of offering IV thrombolysis in an individualized manner in such patients. |
| Prior ICH | IV thrombolysis administration in patients who have a history of ICH may increase the risk of symptomatic hemorrhage. Patients with known amyloid angiopathy may be considered as having higher risk than patients with ICH due to modifiable conditions (e.g. HTN, coagulopathy). IV thrombolysis may have greater treatment benefit than risk in these latter patients. Treatment should be determined on an individual basis. |
| Recent major non-CNS trauma (between 14 days and 3 months) | Patients with recent major trauma between 14 days and 3 months of their AIS may be at increased risk of harm and serious systemic hemorrhage requiring transfusion from IV thrombolysis. Individual consideration of risk vs benefit, involved areas, and consultation with surgical experts are appropriate. |
| Recent major non-CNS surgery w/in 10 days | Patients with recent major surgery within 10 days of AIS may be at increased risk of harm from IV thrombolysis. Individual consideration of risk vs benefit, surgical area, and consultation with surgical experts are appropriate. |
| Recent GI/GU bleeding w/in 21 days | Patients with recent GI or GU bleeding within 21 days of their AIS may be at increased risk of harm from IV thrombolysis. Individual consideration of risk vs benefit and consultation with GI or GU experts to determine if the GI/GU bleeding has been treated and risk modified/reduced is recommended. |
| Intracranial arterial dissection | The safety of IV thrombolysis in patients with AIS due to intracranial arterial dissection is unknown. |

(*Continued*)





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**Table 8. Continued**

| | |
|---|---|
| Intracranial vascular malformations | The safety of IV thrombolysis for patients presenting with AIS who are known to harbor an unruptured and untreated intracranial vascular malformation is unknown. |
| Recent STEMI w/ in 3 months | Patients with recent STEMI may be at risk for increased harm from IVT. For patients with history of STEMI within 3 months, individual consideration of risk and benefit should be determined in conjunction with an emergent cardiology consultation. For patients with very recent STEMI (previous several days), the risk of hemopericardium should be considered relative to potential benefit. For patients presenting with concurrent AIS and acute STEMI, treatment with IV thrombolysis should be at a dose appropriate for cerebral ischemia and in conjunction with emergent cardiology consultation. Consideration of timing, type and severity of STEMI to determine the risk vs benefit is warranted. |
| Acute pericarditis | IV thrombolysis for patients with major AIS likely to produce severe disability and acute pericarditis, may be reasonable in individual cases. Emergent cardiologic consultation is warranted. |
| Left atrial or ventricular thrombus | IV thrombolysis for patients with known left atrial or ventricular thrombus presenting with major AIS likely to produce severe disability may be reasonable in individual cases. Emergent cardiologic consultation is warranted. |
| Systemic active malignancy | The safety of IV thrombolysis in patients with systemic active malignancy is unknown. Emergent consultation with oncology to assess risk/benefit is warranted. Consideration of type, stage, and active complications of cancer to determine the risk vs benefit is warranted. |
| Pregnancy and post-partum period | IV thrombolysis may be considered in pregnancy and post-partum period when the benefits of treating moderate or severe stroke outweighs the anticipated risk of uterine bleeding. Emergent obstetrical consultation is warranted. |
| Dural puncture w/ in 7 days | IV thrombolysis for patients with AIS post-dural puncture may be considered in individual cases, even in instances when they may have undergone a lumbar dural puncture in the preceding 7 days. |
| Arterial puncture w/in 7 days | The safety of IV thrombolysis in patients with AIS who have had an arterial puncture of a noncompressible blood vessel (e.g,, subclavian artery line) in the 7 days preceding the stroke symptoms is unknown. |
| Moderate to severe traumatic brain injury ≥14 days to 3 months | IV thrombolysis may be considered in AIS patients with recent moderate to severe traumatic brain injury (between 14 days and 3 months). Careful consideration should be made based on the type and severity of traumatic injury and in consultation with neurosurgical and neurocritical care team members. |
| Neurosurgery ≥14 days to 3 months | For patients with AIS and a history of intracranial/spinal surgery between 14 days and 3 months, IV thrombolysis may be considered on an individual basis. Consultation with neurosurgical team members is recommended. |

(*Continued*)

**Table 8. Continued**

| Conditions that are Considered Absolute Contraindications | |
|---|---|
| CT with extensive hypodensity | IV thrombolysis should not be administered to patients whose brain imaging exhibits regions of clear hypodensity that appear to be responsible for the clinical symptoms of stroke. Clear hypodensity is when the degree of hypodensity is greater than the density of contralateral unaffected white matter. |
| CT with hemorrhage | IV thrombolysis should not be administered to patients whose CT brain imaging reveals an acute intracranial hemorrhage. |
| Moderate to severe traumatic brain injury <14 days | IV thrombolysis is likely contraindicated in AIS patients with recent moderate to severe traumatic brain injury (within 14 days) that incurred >30 minutes of unconsciousness and Glasgow Coma Scale of <13 OR evidence of hemorrhage, contusion, or skull fracture on neuroimaging. |
| Neurosurgery <14 days | For patients with AIS and a history of intracranial/spinal surgery within 14 days, IV thrombolysis is potentially harmful and should not be administered. |
| Acute spinal cord injury within 3 months | IV thrombolysis is likely contraindicated in AIS patients with spinal cord injury within 3 months. |
| Intra-axial neoplasm | For patients with AIS who harbor an intra-axial intracranial neoplasm, treatment with IV thrombolysis is potentially harmful and should not be administered. |
| Infective endocarditis | For patients with AIS and symptoms consistent with infective endocarditis, treatment with IV thrombolysis should not be administered. |
| Severe coagulopathy or thrombocytopenia | The safety and efficacy of IV thrombolysis for AIS in patients with platelets <100,000/mm$^3$, INR>1.7, aPTT>40s, or PT>15s is unknown though may substantially increase risk of harm and should not be administered.<br>In patients without recent use of warfarin or heparin, treatment with IV thrombolysis can be initiated before availability of coagulation test results but should be discontinued if INR >1.7, PT, or PTT is abnormal by local laboratory standards. |
| Aortic arch dissection | For patients with AIS and known or suspected aortic arch dissection, treatment with IV thrombolysis is potentially harmful and should not be administered |
| Amyloid-related imaging abnormalities (ARIA) | The risk of thrombolysis related ICH in patients on amyloid immunotherapy or with ARIA is unknown and IV thrombolysis should be avoided in such patients. |

AIS indicates acute ischemic stroke; aPTT, activated partial thromboplastin time; CNS, central nervous system; CT, computed tomography; DOAC, direct oral anticoagulant; GI, gastrointestinal; GU, genitourinary; HTN, hypertension; ICH, intracerebral hemorrhage; INR, international normalized ratio; IRB, institutional review board; IV, intravenous; MI, myocardial infarction; PT, prothrombin time; and PTT, partial thromboplastin time. **Light Teal**: Indicates scenarios with relatively low concerns but not linked to actionable recommendations. **Peach**: Indicates moderate caution where additional consideration may be warranted. **Pinkish Red**: Indicates higher relative harm requiring careful examination but remains unsupported by clinical evidence.



Furthermore, in keeping with a goal to achieve rapid reperfusion of the ischemic penumbra, delay in EVT after thrombolysis to assess for clinical improvement is not recommended.

### *Recommendation-Specific Supportive Text*

1. Although 2 recent Chinese RCTs demonstrated EVT alone was noninferior to IV and EVT for the primary outcome of functional independence at 90 days,[1,2] there was no increased risk of sICH with IVT in any of these trials. Conversely, 4 other trials failed to confirm superiority or noninferiority for EVT alone, either due to increased reperfusion efficacy and/or improved clinical outcomes at 90 days with combined IV and EVT therapy.[4–7] A meta-analysis of

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these 6 RCTs[8] found the benefit of IVT and EVT to be statistically significant over EVT alone if the time from symptom onset to expected administration of IVT was within 2 hours and 20 minutes.

2. HERMES (Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials), a meta-analysis of 5 trials (MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), found decreased odds of better disability outcomes at 90 days (mRS score distribution) with the EVT group, with longer time from symptom onset to expected arterial puncture. At 3 hours, the cOR was 2.79 (95% CI, 1.96–3.98), with an absolute risk difference (ARD) of 39.2% for lower disability scores. At 6 hours, the cOR was 1.98 (95% CI, 1.30–3.00), and the ARD was 30.2%; and at 8 hours, the cOR was 1.57 (95% CI, 0.86–2.88), with an ARD of 15.7%. Statistical significance was retained through 7 hours and 18 minutes. Among 390 patients who achieved substantial reperfusion with EVT, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76–0.93]; ARD, −6.7%) and less functional independence (OR, 0.81 [95% CI, 0.71–0.92]; ARD, −5.2% [95% CI, −8.3 to −2.1]) but no change in mortality (OR, 1.12 [95% CI, 0.93–1.34]; ARD, 1.5% [95% CI, −0.9 to 4.2]).[3]The REVASCAT trial included a 30-minute observation period before performing EVT. The available data do not directly address the question of whether patients should be observed after IVT to assess clinical response before pursuing EVT. However, one can infer that because disability outcomes at 90 days were directly associated with time from symptom onset to arterial puncture, any delay to EVT, including observing for a clinical response after IVT, should be avoided. Therefore, the recommendation is slightly modified from the 2015 endovascular update.

## Knowledge Gaps and Future Directions

- The use of IVT in the extended window (4.5–24 hours) with advanced imaging combined with EVT is less certain. In the TIMELESS trial, tenecteplase did not improve the odds of good functional outcomes compared with placebo in patients undergoing EVT in the 4.5- to 24-hour window and with ischemic penumbra as determined by perfusion imaging.[9] Given the rapid delivery of EVT in this study, other studies should confirm this finding.
- Future studies should also assess whether other thrombolytic agents perform differently than alteplase in conjunction with EVT. The Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke (DIRECT-TNK) trial will assess tenecteplase versus placebo in patients with anterior circulation LVO within 4.5 hours from onset and undergoing EVT (NCT05199194).

### 4.7.2. Endovascular Thrombectomy for Adult Patients

**Recommendations for Endovascular Thrombectomy for Adult Patients**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| Thrombectomy 0 to 6 hours after onset of symptoms, ASPECTS 3 to 10 | | |
| 1 | A | 1. In patients with AIS from anterior circulation proximal LVO of the ICA or M1, presenting within 6 hours from onset of symptoms, with NIHSS score ≥6, prestroke mRS score of 0 to 1, and ASPECTS 3 to 10, EVT is recommended to improve functional clinical outcomes and reduce mortality.[1–11] |
| Thrombectomy 6 to 24 hours after onset of symptoms, ASPECTS 6 to 10 | | |
| 1 | A | 2. In patients with AIS from anterior circulation proximal LVO of the ICA or M1 presenting between 6 and 24 hours from onset of symptoms, with NIHSS score ≥6, prestroke mRS score 0 to 1 and ASPECTS ≥6, EVT is recommended to improve functional clinical outcomes and reduce mortality.[12–14] |
| Thrombectomy 6 to 24 hours after onset of symptoms, ASPECTS 3 to 5 | | |
| 1 | A | 3. In selected patients* with AIS from anterior circulation proximal LVO of the ICA or M1, presenting between 6 and 24 hours from onset of symptoms, with age <80 years, NIHSS score ≥6, prestroke mRS score 0 to 1, ASPECTS 3 to 5, and without significant mass effect on imaging, EVT is recommended to improve functional clinical outcomes and reduce mortality.[7,8] |
| Thrombectomy 0 to 6 hours after onset of symptoms, ASPECTS 0 to 2 | | |
| 2a | B-R | 4. In selected patients† with AIS from anterior circulation proximal LVO of the ICA or M1 presenting within 6 hours from onset of symptoms, with age <80 years, NIHSS score ≥6, prestroke mRS 0 to 1, ASPECTS 0 to 2, and without significant mass effect on imaging, EVT is reasonable to improve functional clinical outcomes and reduce mortality.[8,10,11] |
| Thrombectomy 0 to 6 hours after onset of symptoms with mild preexisting disability | | |
| 2a | B-NR | 5. In patients with AIS from anterior circulation proximal LVO of the ICA or M1 presenting within 6 hours from onset of symptoms, with NIHSS score ≥6, and ASPECTS ≥6, who have a prestroke mRS score of 2, EVT is reasonable to improve functional clinical outcomes and reduce accumulated disability.[15,16] |
| Thrombectomy 0 to 6 hours after onset of symptoms with moderate preexisting disability | | |
| 2b | B-NR | 6. In patients with AIS from anterior circulation proximal LVO of the ICA or M1 presenting within 6 hours from onset of symptoms, with NIHSS score ≥6, and ASPECTS of ≥6, who have a prestroke mRS score of 3 to 4, EVT might be reasonable to improve functional clinical outcomes and reduce accumulated disability.[17–20] |
| Thrombectomy 0 to 6 hours for dominant proximal M2 division MCA occlusions | | |
| 2a | B-NR | 7. In patients with AIS from occlusion of the dominant proximal M2 division of the MCA presenting within 6 hours from onset of symptoms with a prestroke mRS score of 0 to 1, NIHSS score of ≥6, and ASPECTS of ≥6, EVT is reasonable to improve functional outcomes, but the benefits are uncertain.[21–23] |

| Recommendations for Endovascular Thrombectomy for Adult Patients (Continued) | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| Thrombectomy 0 to 6 hours for nondominant proximal M2 division MCA, distal MCA, anterior cerebral artery, and posterior cerebral artery occlusions | | |
| **3: No Benefit** | **A** | 8. In patients with AIS from occlusion of the proximal nondominant or codominant division proximal M2 segment of the MCA, or distal MCA, anterior cerebral artery (ACA), or posterior cerebral artery (PCA), EVT is not recommended to improve functional outcomes.[23,24] |

*Limited generalizability in specific subpopulations: Specific patient groups were underrepresented or excluded in the trials supporting this recommendation. Consequently, the applicability of these findings is limited in individuals >80 years, those with renal failure, patients with refractory hypertension (SBP ≥185 mm Hg or DBP ≥110 mm Hg), comorbid psychiatric or medical illnesses that confound neurological assessments, or patients with a life expectancy <3 months.[7,8]

CT hypodensity volume as a predictor of poor outcomes: In an exploratory analysis of the SELECT2 trial, a threshold of ≥26 mL of severe CT hypodensity, defined as the lower 99% CI of the contralateral thalamic gray matter (≤26 Hounsfield units), was associated with diminished treatment benefit from EVT. Patients with CT hypodensity above this threshold derived no functional benefit and instead experienced increased risks, including cerebral edema and the need for hemicraniectomy.[25]

†Limited generalizability in specific subpopulations: Specific patient groups were underrepresented or excluded in the trials supporting this recommendation. Consequently, the applicability of these findings is limited in individuals >80 years, those with significant head and neck vessel tortuosity, comorbid psychiatric or medical conditions that confound neurological assessments, seizures at stroke onset that hinder accurate NIHSS evaluations, a strong suspicion of underlying intracranial stenosis, or a life expectancy <6 months.[9]

### Synopsis

EVT for LVO in AIS has demonstrated clear benefits in improving functional outcomes and reducing mortality, warranting strong recommendations for EVT intervention in eligible patients.[1–11] Since the original 6 landmark trials were completed in 2015,[1–6] additional trials have progressively investigated the use of EVT in expanded time windows[12–14] and a larger predicted ischemic core at presentation,[7–11] supporting the expansion of EVT as reflected in these guidelines.

An essential insight of the new data presented here is that in the context of ischemic stroke, "core" refers to the volume of cerebral tissue that is irreversibly damaged or infarcted. Historically, both clinical trials and patient-selection frameworks have defined core infarction through CT and diffusion-weighted imaging (DWI) findings. However, trials investigating "large-core" AIS indicate that decreased density on NCCT, DWI abnormalities, or low cerebral blood flow (CBF) estimates should be considered predictors of cerebral infarction but are not synonymous with entirely irreversible tissue loss.[26]

Patient-level meta-analysis of the initial thrombectomy trials also endorses EVT for individuals with mild prestroke disability during the first 6 hours from symptom onset, specifically in those with small predicted cores (ASPECTS ≥6).[15,16]

Recent RCTs indicate no significant improvement in functional outcomes with EVT for medium or distal vessel occlusions,[23,24] yet there appear to be subgroups within this category for whom further investigation is needed to elucidate the potential benefits and limitations of EVT[21–23] (Figure 3).

### Recommendation-Specific Supportive Text

1. Results from multiple randomized trials of EVT using predominantly stent retriever devices support a strong recommendation (COR 1) for treating patients with LVO of the anterior circulation (ICA or MCA, M1) in the early window (0–6 hours from onset of symptoms).[1–6] The HERMES pooled patient-level analysis indicated a favorable effect of EVT over standard care, even in patients ≥80 years of age (cOR, 3.68 [95% CI, 1.95–6.92]).[27] The ASTER2[28] and COMPASS[29] trials showed that contact aspiration thrombectomy is noninferior to stent retriever use in both efficacy and safety, thus expanding the range of technical options.

   Five of 6 recent RCTs investigating large predicted core infarcts reported benefits of EVT for anterior circulation LVOs in patients with ASPECTS 3 to 5 who presented within 6 hours of symptom onset, effectively expanding the application of EVT to larger predicted core infarcts than considered in the initial trials.[7–11] The NNT to prevent 1 additional instance of functional dependence in these patients was 8. In these trials, 19.5% of patients achieved functional independence, and 36.5% achieved independent ambulation.[26] These proportions are lower than the ~50% rate of functional independence observed in earlier EVT trials that enrolled patients with smaller predicted cores, reflecting the severity of large-core presentations. Nevertheless, EVT recipients more than doubled their rate of functional independence compared with patients receiving maximum medical therapy alone (7.5%). Because of this lower magnitude of effect, in the context of large, predicted core infarcts, where the severity of the underlying condition potentially limits the effect of treatment, discussions with the patient and/or family, when feasible, are essential to balance the benefits of EVT with patients' and families' values, expectations, and desires.
2. DAWN[12] and DEFUSE-3[13] used selective imaging (of predicted core and ischemic penumbra) to identify patients for thrombectomy and establish the benefit of treatment after 6 hours from the onset of symptoms. With the selection of patients with limited predicted core and large penumbral infarcts, the effect of thrombectomy was powerful, with the NNT achieving functional independence of 2.8 in DAWN and 3.6 in DEFUSE-3. These randomized data were reinforced by the AURORA individual patient data meta-analysis,[14] combining multiple randomized stroke trials to evaluate patient outcomes. The AURORA study showed reduced disability at 90 days (adjusted cOR, 2.54







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[95% CI, 1.83–3.54]; *P*<0.0001) in favor of EVT in the extended time window of 6 to 24 hours. The study noted no evidence of treatment effect heterogeneity between patients selected in DAWN and DEFUSE-3 by volumetric mismatch criteria versus patients selected in the other included trials (ESCAPE,[1] RESILIENT,[30] Perfusion imaging selection of ischemic stroke patients for endovascular therapy [POSITIVE],[31] and REVASCAT[2]) that used different criteria, including 2 studies (ESCAPE[1] and RESILIENT[30]) that did not require mandatory baseline perfusion lesion volumetric assessments.

3. Of the 6 large predicted core infarct RCTs recently completed, 3 specifically enrolled patients in the extended 6- to 24-hour window (ANGEL ASPECTS,[8] SELECT2,[7] and TESLA). Two of these trials (ANGEL_ASPECTS and SELECT2) demonstrated the benefit of EVT for eligible participants. Even in individuals with a sizable pretreatment imaging-predicted core (ASPECTS 3–5), those treated with EVT experienced better functional outcomes than controls. Across these trials, imaging selection and inclusion criteria varied, incorporating CT and MRI ASPECTS, CT perfusion, and MRI diffusion-DWI with FLAIR mismatch (as a "tissue clock"), suggesting that multiple imaging approaches can reliably identify suitable candidates for EVT. Patients with certain characteristics were either excluded or underrepresented in the supporting trials, such as those >80 years, individuals with renal failure, refractory hypertension (SBP ≥185 mm Hg or DBP ≥110 mm Hg), comorbid psychiatric or medical conditions that confound neurological assessments, or limited life expectancies (<3 months).[7,8]

   The threshold of "severe hypodensity" identified by the exploratory analysis of the SELECT2 trial[25] suggests that patients with predicted core volumes ≥26 mL with hypodensity ≤26 HU may receive no functional benefit from EVT and instead face higher complication rates, such as cerebral edema or hemicraniectomy. Clinically, this finding underscores the importance of careful imaging-based selection, prompting clinicians to weigh these elevated risks against the potential benefits of intervention before proceeding with thrombectomy in such cases.

   In consideration of the magnitude of benefit in the context of large, predicted core infarcts, where the severity of the underlying condition potentially limits the effect of treatment, discussions with the patient and/or family, when feasible, are essential to balance the benefits of EVT with patients' and families' values, expectations, and desires.

4. Only 1 clinical trial, the LASTE study, systematically enrolled patients with an ASPECTS score 0 to 2.[9] In total, 181 patients meeting ASPECTS 0 to 2 criteria were primarily selected using MRI-DWI within 6.5 hours, a modality more sensitive to early ischemic changes than CT.[32,33] This higher sensitivity may bias toward identifying salvageable tissue, potentially leading to improved outcomes. The remaining patients with ASPECTS 0 to 2 in other positive thrombectomy trials were typically included off protocol after core laboratory adjudication and constituted approximately 7% of the overall study population.[8,10,11]

   It is important to note that LASTE[9] excluded patients ≥80 years of age, those with significant head and neck vessel tortuosity, comorbid psychiatric or medical conditions confounding neurological assessments, seizures at stroke onset that precluded accurate NIHSS evaluation, strong suspicion of underlying intracranial stenosis, or life expectancies of <6 months. In the population studied in LASTE, 13.3% achieved functional independence at 90 days after EVT, while only 7.5% did in the medical treatment group. In consideration of the magnitude of benefit in the context of very large predicted core infarcts, where the severity of the underlying condition limits the potential effect of treatment, discussions with the patient and/or family, when feasible, are essential to balance the benefits of EVT with patients' and families' values, expectations, and desires.

5. Of the landmark 2015 thrombectomy RCTs,[1–6] only MR CLEAN[6] enrolled patients with a prestroke mRS score of ≥2 (n=45). A subsequent HERMES meta-analysis pooled data from 7 RCTs (n=1764), including 199 participants with a prestroke mRS score of 1 to 2, demonstrated a significant benefit from EVT in this subgroup (cOR, 2.08 [95% CI; 1.22–3.55]).[15] Although these patients had marginally worse outcomes compared with those with a prestroke mRS score of 0, EVT still conferred meaningful improvements relative to conservative management. A separate meta-analysis of randomized and observational studies similarly found that individuals with mild baseline disability (mRS score 2) achieved better outcomes with EVT than with conservative therapy.[16] Prestroke disability does not appear to alter the likelihood of sICH or successful reperfusion.[15,16]

6. There are no completed RCTs evaluating patients with moderate prestroke disability (mRS score 3–4). Overall, good outcomes in patients with premorbid disability >2 are less frequent compared with a premorbid mRS score of 0 to 2.[17,18] Nevertheless, in 1 nonrandomized prospective cohort study and other retrospective studies, 20% to 30% of the patients returned to their premorbid mRS score, which may justify endovascular treatment.[17,18] Retrospective cohort studies of EVT versus medical management in patients with a prestroke mRS score of 3 to 5 found that revascularization with EVT improved the odds of achieving favorable outcomes at 90 days.[19,20] An analysis of the Czech national registry, including 1712

patients with a prestroke mRS score of 3 to 5, showed that these patients were less likely to receive EVT, had slower treatment times, and had worse outcomes than patients with an mRS score of 0 to 2. Still, EVT improved outcomes in patients with prestroke disability, and 32% returned to their prestroke status.[18]

7. Patients with isolated M2 occlusions account for approximately 20% of all LVOs.[21] In pooled patient-level data from the HERMES collaboration,[22] including 7 RCTs,[22,34] EVT was favorable in patients with M2 occlusions (adjusted OR, 2.39 [95% CI, 1.08–5.28]; *P*=0.03) for a 90-day mRS score of 0 to 2 (58.2% EVT versus 39.7% control). Treatment effect was more marked in dominant MCA M2 segment occlusions.[22] Dominant is defined as the M2 segment supplying 50% or more of the MCA territory. This does not refer to left/right side dominance. An analysis of the prospective MR-CLEAN Registry[35] showed that outcomes and complication rates were similar between M1 and M2 occlusions (n=1003; 244 with M2 occlusions), with no evidence of significant interaction effects in any subgroup (dominant-division or nondominant-division M2, right versus left side).[35] In another pooled patient level analysis of 3 RCTs and 2 prospective trials of patients with M2 occlusion, EVT was associated with improved functional independence when compared with medical management (68.3% versus 61.6%, aOR, 2.42 [95% CI, 1.25–4.67]; *P*=0.008).[21] This association was primarily observed in patients with a mismatch profile and those with higher stroke severity.[21]

   In the recent multicenter, prospective, randomized, parallel group, open-label design to determine the efficacy and safety of EVT for patients with ischemic stroke and symptomatic acute medium vessel intracranial occlusions (ESCAPE-MeVO Trial), of 530 patients enrolled, 122 had proximal M2 occlusions defined as the "MCA segment proximal to the point that was 1 cm distal to the MCA bifurcation."[23] Globally, this study did not show benefit of EVT across all included groups. For proximal M2 MCA, the risk ratio was 0.9 (95% CI, 0.6–1.33). However, the study has some limitations that restrict the generalizability of the data. ESCAPE-MeVO did not include considerations for dominance versus codominance or nondominance of the proximal M2 segments; the workflow times were longer than in previous trials of LVO. The study generally recruited patients with less severe symptoms at presentation, with a median NIHSS score of 8, compared with the median NIHSS score of 15 in the patients included in the previous meta-analysis who had shown benefit. There was also a lack of data on screening of cases, which limits information about patients who might have been selected for treatment outside the trial.[23]

8. Medium or distal occlusion(s) of the anterior, middle, or posterior cerebral arteries cause 25% to 40% of AIS.[36] These lesions may cause disability but are more likely to recanalize spontaneously or with IVT. Additionally, there may be an increased risk of accessing the distal vasculature. Two recent RCTs, ESCAPE-MeVO[23] and DISTAL,[24] showed no benefit of EVT over best medical management. The data from ESCAPE-MeVO indicate that the workflow times in the trial were more prolonged than in previous studies for LVO, with a median time from onset to recanalization of 359 minutes, as compared with 241 minutes in the ESCAPE trial.[23,37] Further research on the impact of reducing this time delay, the use of aspiration-first, new thrombectomy devices, or intra-arterial thrombolysis approaches on outcomes will be fundamental to evaluate the role of EVT in medium and distal vessel occlusions. DISTAL included patients with distal vertical or insular nondominant or codominant MCA M2, distal ACA (A2, A3), and PCA (P1, P2, and P3 segments). This study did not show benefit of EVT over medical management in the treatment of these patients.[24]


## Knowledge Gaps and Future Research

- Future studies to evaluate and confirm the ischemic core predictive value of specific volumes and degrees of CT hypodensity or DWI restriction in MRI are necessary to refine the selection for EVT treatment of patients with ASPECTS <6.[25,38]
- Further studies of quality-of-life outcomes and cost-benefit analysis of EVT for patients with lower ASPECTS are also necessary.
- The efficacy of EVT in medium vessel occlusions treated with faster workflows, using different techniques (aspiration-first, IA thrombolysis, or new devices) in patients with more substantial neurological deficits at presentation requires further investigation.
- The development and evaluation of new EVT techniques designed for medium and distal vessels also require further research.
- The role of EVT in patients with moderate prestroke morbidity and those with low NIHSS scores at presentation requires investigation in future RCTs.[39–41]

### *4.7.3. Posterior Circulation Stroke*

**Recommendations for Posterior Circulation Stroke**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | A | 1. In patients with AIS, with basilar artery occlusion, a baseline mRS score of 0 to 1, NIHSS score ≥10 at presentation, and PC-ASPECTS ≥6 (mild ischemic damage), EVT within 24 hours from onset of symptoms is recommended to achieve better functional outcome and reduce mortality.[1,2] |







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| Recommendations for Posterior Circulation Stroke (Continued) | | |
|---|---|---|
| COR | LOE | Recommendations |
| 2b | B-R | 2. In patients with AIS, with basilar artery occlusion, a baseline mRS score of 0 to 1, NIHSS score 6 to 9 at presentation, and PC-ASPECTS ≥6 (mild ischemic damage) the effectiveness of EVT within 24 hours to improve functional outcomes and reduce mortality is not well established.[3–5] |

### Synopsis

EVT has been established as standard of care to achieve optimal functional outcome in patients with AIS in the anterior circulation. Recently, several randomized clinical trials have investigated outcomes of EVT in the posterior circulation, specifically acute basilar occlusions. Earlier RCTs conducted in China, BEST and BASICS, showed a statistically nonsignificant direction toward benefit of EVT for acute basilar occlusions but failed to show superiority over best medical management.[4,6,7] These trials were found to have long nonconsecutive recruitment rates, as well as high crossover and treatment outside the trial rates. Two subsequent RCT Chinese studies, ATTENTION and BAOCHE, showed significant benefit and superiority of EVT over best medical management in patients with acute basilar occlusions within 12 and 24 hours from symptom onset, respectively.[1,8] Of note, the aforementioned trials were conducted in China, where prevalence of intracranial atherosclerotic disease as a causal mechanism is reported in as much as 50% of ischemic strokes in people of Asian ethnicity.[9] For more information, see Figure 3 describing the management of AIS eligibility for EVT.

### Recommendation-Specific Supportive Text

1. In ATTENTION, 340 patients with acute basilar occlusions within 12 hours from symptom onset were prospectively investigated in an RCT to receive EVT versus best medical management; the study showed a 2-fold statistically significant benefit in 90-day functional outcome for the thrombectomy group compared with the medical group (46% and 23%).[1] Although the sICH rate was 5% in the EVT group and 0% in the medical group, this trend did not reach statistical significance. Similarly, the BAOCHE RCT showed that in 217 patients within 24 hours from basilar occlusion symptoms, an mRS score of 0 to 3 was achieved in 46% of the EVT group, as opposed to 24% in the medical management group, which reached statistical significance.[8] The trial was stopped early due to the clear superiority of EVT in an interim analysis. Radiographic inclusion criteria included a posterior circulation ASPECTS score of ≥6. Similar to the anterior circulation, the PC-ASPECTS is a 10-point scale, where points are deducted for each region affected. The pons and midbrain are worth 2 points each (regardless of lateralization or extent of ischemic changes), thalami (1 point each), occipital lobes (1 point each), and cerebellar hemispheres (1 point each) (Figure 2).[2]
2. Due to low enrollment in the BAOCHE RCT, following the 61st patient, the investigators expanded the inclusion criteria to include patients with NIHSS scores ≥6. Data are limited for patients with stroke severity NIHSS scores of 6 to 9, as only 17 patients were randomized, of whom only 6 received EVT. All patients treated with EVT reached the trial defined good outcome (mRS score, 0–3), while only 6 of the 11 managed medically got these results. Globally, the study showed that in the enrolled patients who met radiographic criteria of a PC-ASPECTS score ≥6 without a pons-midbrain index ≥3 (indicating extensive infarction in the brainstem region), EVT showed favorable outcomes that reached statistical significance, over the medical management group (mRS of 0–3 was achieved in 46% of the EVT group, as opposed to 24% in the medical management group).[8] A meta-analysis of the 4 RCTs (BEST, BASICS, ATTENTION, and BAOCHE) showed the median NIHSS of ~20; however, functional outcome differences may exist among patients with basilar occlusions presenting with a low NIHSS score followed by neurological decline, as opposed to high NIHSS scores at the outset.[5] Therefore, future investigation of EVT in patients with an NIHSS stroke severity score of 6 to 9 at presentation is warranted.

## Knowledge Gaps and Future Research

- Future research is needed regarding the role of EVT in improving outcomes in patients with nonbasilar posterior circulation stroke, namely vertebral and posterior cerebral arteries.
- Research is lacking regarding the preferred endovascular technique to achieve optimal outcomes in patients with basilar ischemic strokes.
- Future studies are needed to investigate the role of EVT in patients with basilar occlusions and low NIHSS scores (defined as NIHSS <10).
- Lack of evidence exists regarding the role of EVT for basilar occlusions and low PC-ASPECTS scores (<6).

### 4.7.4. Endovascular Techniques

| Recommendations for Endovascular Techniques<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| COR | LOE | Recommendations |
| Thrombectomy general techniques | | |
| 1 | A | 1. In patients with AIS due to an LVO, EVT with stent retrievers, contact aspiration, or combination techniques is recommended to achieve rapid and adequate reperfusion.[1–4] |
| 1 | A | 2. In patients with AIS undergoing EVT, reperfusion to an extended TICI grade 2b/2c/3 is recommended as early as possible within the therapeutic window to achieve maximum functional benefit at 90 days.[1,5,6] |

| Recommendations for Endovascular Techniques (Continued) | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | B-R | 3. In patients with AIS undergoing EVT, either general anesthesia or procedural sedation are recommended to facilitate EVT.[7–9] |
| 2b | B-R | 4. In patients with AIS undergoing EVT, the use of a proximal balloon to guide catheters to achieve improved outcomes remains uncertain.[10–12] |
| 3: No Benefit | A | 5. In patients with AIS from occlusion of medium or distal vessels of the anterior, middle (non-dominant or codominant M2, M3), or posterior cerebral arteries, EVT with stent retrievers is of no benefit for improving functional outcomes.[13,14] |
| Thrombectomy adjunctive techniques | | |
| 2b | B-NR | 6. In patients with AIS undergoing EVT in the setting of tandem extracranial-intracranial anterior circulation occlusions, acute treatment of both, including emergent extracranial stenting, may be reasonable to achieve higher good functional outcome.[5,15–18] |
| 2b | B-NR | 7. In patients with AIS in the setting of failed EVT, the use of rescue intracranial balloon angioplasty and/or stenting to improve functional outcome remains uncertain.[19–21] |
| 2b | B-R | 8. In patients with AIS who achieve complete or near-complete EVT (modified TICI 2b or greater), the administration of adjunctive intraarterial thrombolytics with urokinase, alteplase, or tenecteplase may be reasonable to improve cerebral reperfusion and 90-day functional outcome.[22–25] |
| 3: No Benefit | B-R | 9. In the management of patients with AIS in the setting of LVO, preoperative administration of tirofiban before EVT is not useful to improve 90-day functional outcome.[26,27] |

### Synopsis

Several RCTs, such as COMPASS, ASTER, and ASTER 2, investigated first-line contact aspiration, versus stent retrievers, versus combination techniques and found no statistical significance in the difference in adequate and successful reperfusion.[1–3] Radiographic results of extended TICI of 2B/2C/3 are recommended for maximal functional benefit.[6] General anesthesia and procedural sedation for EVT have comparable functional outcomes and periprocedural complications based on a recent RCT.[7] However, in the extended thrombectomy window of 6 to 24 hours specifically, the data thus far are insufficient. The use of balloon-guided catheters during EVT has uncertain implications on functional outcome because the data are conflicting. In tandem lesions of the anterior circulation, a systematic review of observational studies has shown that emergent carotid stenting has some functional benefit over nonstenting, despite a higher incidence of ICH.[17] In the setting of failed EVT, defined as extended TICI 0 to 2a, the role of rescue intracranial balloon angioplasty and/or stenting to improve functional outcome remains uncertain. Several systematic reviews, meta-analyses, and large observational cohorts have shown an overall favorable direction in 90-day mRS score. However, a recent RCT in China of nearly 350 patients failed to show benefit of these rescue techniques.[28] The usefulness of administration of adjunctive intra-arterial thrombolytics, namely urokinase and tenecteplase, after successful thrombectomy remains uncertain, as data from 4 major RCT are conflicting.[22–25] Preoperative IV administration of tirofiban showed no functional benefit in 90 days and a higher incidence of symptomatic hemorrhage in a double-blind randomized placebo-control clinical trial in China of nearly 948 patients. It is therefore not recommended prior to EVT.[26]

### Recommendation-Specific Supportive Text

1. In the ASTER RCT, first-line aspiration did not show increased revascularization results compared with stent retrievers in anterior circulation thrombectomy of 381 patients.[1] In COMPASS, 270 patients at 15 sites were randomized to aspiration versus stent retrievers and reached similar functional outcomes in 90 days.[2] In ASTER 2, a combination of contact aspiration and stent retriever did not show superiority to stent retriever alone in an RCT of 408 patients.[3] A large international multicenter retrospective study showed that contact aspiration and stent retrievers had similar revascularization rates and 90-day functional outcomes.[4]
2. Although various reperfusion scores exist, the modified TICI score has been established as the assessment tool of choice, with proven value in predicting clinical outcomes.[1] Most endovascular trials used the mTICI grade 2b/3 threshold for adequate reperfusion. In the HERMES collaboration, 402 of 570 patients (71%) were successfully reperfused to mTICI grade 2b/3.[5] Recently, the modified TICI score has been extended to include a TICI 2c, in the extended TICI, which indicates near perfect perfusion.[6]
3. Recent RCTs including AMETIS and DIRECT-MT subgroup analysis compared general anesthesia to conscious sedation in EVT of patients with AIS LVO and found no statistical significance between the 2 groups' 90-day functional outcome improvement. AMETIS randomized 273 thrombectomy patients to general anesthesia versus procedural sedation and found comparable 90-day functional outcomes and major procedural complications.[7] In DIRECT-MT, a subgroup analysis of 636 patients showed comparable 90-day functional outcomes between the 2 groups.[8] In Denmark, an RCT of 128 patients showed similar primary outcomes of infarct volume growth between the 2 groups.[9]
4. Several systematic reviews, meta-analyses, and a plethora of trials confirmed procedural and reperfusion benefits with the use of balloon-guided catheters, most recently in 24 studies and 8483 patients that showed improved 90-day functional outcomes in the balloon-guided catheter group.[11] However, subgroup analysis in DAWN showed no benefit in the extended time window of 6 to 24 hours.[12] Since then, a placebo double-blind RCT, PROTECT-MT in China, showed worse functional outcomes with







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balloon-guided catheters in 329 patients.[10] Overall, the data are conflicting, and there is insufficient evidence to determine the impact of use of balloon-guided catheters on functional outcome.

5. The ESCAPE-MeVO and DISTAL trials examined the benefit of endovascular therapy in patients with medium or distal branch occlusions. ESCAPE-MeVO included patients up to 12 hours from last known well, with an NIHSS score of >5 or 3 to 5 if considered disabling, with occlusions of M2, M3, A2, A3, or P2, P3 segments with imaging evidence of salvageable tissue. DISTAL included patients up to 24 hours from last known well with similar occlusion locations, NIHSS score ≥4 or lower if symptoms were disabling. Both allowed treatment with IVT, with 65% receiving this treatment in DISTAL and 58% in ESCAPE-MeVO. Presentation NIHSS values were generally low, with median values of 6 and 7. Both trials failed to demonstrate improved outcomes with endovascular therapy relative to medical management for 90-day mRS scores 0 to 1 (EVT versus medical management: 35% vs 38%, DISTAL; 42% versus 43%, ESCAPE-MeVO). ESCAPE-MeVO using stent-retrievers for first pass suggested harm with EVT, as mortality was significantly greater (HR, 1.82 [95% CI, 1.06–3.12]) and rates of hemorrhage were greater in the EVT groups. These findings suggest stent retrievers should not be routinely offered to patients who met criteria for these 2 randomized trials.[13,14]
6. Tandem occlusion emergent revascularization has shown benefit for EVT over medical management alone. In the HERMES meta-analysis, 122 of 1254 patients (risk ratio, 1.81 [95% CI, 0.96–3.4]) and in THRACE, 24 of 196 patients (risk ratio, 1.82 [95% CI, 0.55–6.07]) (risk ratio, 1.34 [95% CI, 0.87–2.07]) had tandem occlusions that were treated emergently.[5,15] In HERMES, there was heterogeneity in the endovascular management of the proximal extracranial occlusion (no revascularization of versus angioplasty versus stenting). In TITAN, a retrospective analysis from nearly 20 centers comprising 395 patients with AIS caused by tandem lesions who underwent EVT, an mTICI grade 2b/3 was achieved in 76.7% of patients; at 90 days, 52.2% achieved an mRS score of 0 to 2.[16] Recently, a systematic review and meta-analysis of 46 observational studies showed that emergent carotid stenting in tandem occlusions was associated with higher good functional outcomes, despite the higher risk of ICH.[17] PICASSO, an international survey of 220 physicians, demonstrated multiple areas of uncertainty in the emergent medical and endovascular management of tandem carotid occlusions.[18]
7. The ANGEL-REBOOT RCT in China failed to show superiority of rescue balloon angioplasty or stenting in 348 patients who underwent EVT with TICI 0 to 2a revascularization, as there was no improvement in 90-day mRS score and higher complication rates. However, a major trial limitation was the use of off-label tirofiban, which could have affected the results.[19] Several other meta-analyses of nonrandomized controlled trials showed low level evidence of functional improvement. Most recently, a prospective multicenter observational international cohort study, RESCUE ICAS, showed that functional independence at 90 days was significantly higher in the stenting group (42.2% versus 28.4%), with no statistical significance in hemorrhagic complications.[20] Similarly, a recent analysis of a multicenter retrospective pooled cohort of patients with anterior LVO (2015–2021) with propensity score matching showed that rescue stenting had a favorable shift in the overall mRS distributions (adjusted cOR, 0.74 [95% CI, 0.60–0.91]; *P*=0.006) and no difference in 3-month mortality.[21] Overall, rescue balloon angioplasty and/or stenting may be considered in rescue thrombectomy; however, the true benefit in functional outcome and mortality is not clear.
8. CHOICE, a placebo double-blind RCT investigating intra-arterial alteplase administration after successful EVT showed favorable 90-day mRS scores in the IA alteplase group, without a concomitant increase in ICH. However, the study terminated early due to challenges in the maintenance of enrollment and placebo drugs during the COVID pandemic. No timing from last known normal was added as enrollment was based on EVT decision criteria.[22] Most recently, 3 clinical trials, POST-UK, ATTENTION-IA, and POST-TNK showed lack of benefit from adjunctive intraarterial administration of urokinase and tenecteplase, after complete or near-complete thrombectomy.[23–25] The dosages used in the trials were 100 000 IU urokinase and 0.0625 mg/kg, with a maximum of 6.25 mg of tenecteplase, within 24 hours from symptom onset. Therefore, the role of adjunctive intraarterial thrombolysis after thrombectomy reperfusion remains uncertain.
9. In a double-blind, placebo-controlled RCT of 55 centers in China, RESCUE-BT, administration of IV preoperative tirofiban versus placebo in the setting of LVO prior to EVT showed no functional benefit in 90 days.[26] A meta-analysis of 7 RCTs nonspecific to LVO showed that IV tirofiban administration was associated with higher 90-day functional outcome and lower NIHSS at 7 days, but a higher incidence of ICH.[27] It included studies with inconsistent methodologies and variable protocols for the administration of tirofiban, some of which were 24-hour infusions.

## Knowledge Gaps and Future Research

- Future research is needed regarding revascularization techniques in AIS thrombectomy in the posterior circulation.

- Additional evidence is required to evaluate the functional outcome differences between revascularization results of mTICI 2b/2c/3, and whether the additional benefit to achieve a TICI 3 rather than 2c or 2b is warranted.
- Further prospective randomized trials are required to determine the preferred anesthesia modality for optimal functional outcomes in EVT within the extended 6- to 24-hour window.
- Additional research trials are required to investigate an additional thrombectomy window in the patient population >24 hours from symptom onset.
- Emerging evidence will determine the role of EVT and recommended techniques in medium and distal vessel occlusions.
- The benefit of EVT in populations not adequately evaluated by these 2 trials remains incompletely characterized. In specific, there remains uncertainty in the population of patients who have more substantial stroke deficits (ie, higher NIHSS scores than those of the above studies) or in whom thrombolysis was not performed, as this subgroup was the minority population in these trials.
- There remain open questions on the optimal devices and techniques to be used in treatments of the medium and distal vessels. The above studies relied heavily on stent retrievers, and future work may examine treatment effect associated with alternative approaches, including catheter-based aspiration.
- Nomenclature and categorization of intracranial branching patterns remain inconsistently defined. Given prior data supporting treatment for proximal, larger M2 occlusions, the distinctions between the types of M2s that benefit from endovascular reperfusion and those that do not need to be further clarified.

### 4.7.5. Endovascular Thrombectomy in Pediatric Patients

**Recommendations for Endovascular Thrombectomy in Pediatric Patients**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-NR | 1. In pediatric patients ≥6 years with acute neurological symptoms and ischemic stroke due to LVO and within 6 hours from symptom onset, EVT can be effective if performed by experienced neurointerventionalists to improve functional outcomes.[1–4] |
| 2a | B-NR | 2. In pediatric patients ≥6 years with acute neurological symptoms and ischemic stroke due to LVO, 6 to 24 hours from symptom onset, and with potentially salvageable brain tissue, EVT can be effective to improve functional outcomes.[1–3] |
| 2b | B-NR | 3. In pediatric patients aged 28 days to 6 years with acute neurological symptoms, including first-time seizure and AIS due to LVO, within 24 hours from symptom onset, and with potentially salvageable brain tissue, EVT performed by neurointerventionalists with pediatric experience may be reasonable to improve functional outcomes.[1–3] |

#### *Synopsis*

AIS is a highly impactful cause of brain injury in pediatric patients that has been associated with elevated rates of long-term consequences.[5] The recommendations presented here for hyperacute pediatric AIS are based on updated literature published since the last guidelines and expert consensus reviews. Although no randomized clinical trials have been completed in this population, there is moderate-quality evidence, meta-analyses of such studies, and expert consensus on the importance of considering hyperacute stroke interventions in pediatric patients. The establishment of these recommendations is intended for centers with experience in managing pediatric patients and interventionalists with pediatric endovascular intervention experience. (Figure 3 describes the management of AIS eligibility for EVT.)

#### *Recommendation-Specific Supportive Text*

1. In the absence of data from a randomized trial, which is likely unfeasible,[6] several well-designed retrospective studies[2,7] and a meta-analysis of these studies[4] have demonstrated safety of EVT in children with arterial ischemic stroke. In addition, recent evidence from a population-based study has shown that the majority of children with LVO stroke have moderate to severe disability or death at 3 months and long term.[8] Finally, the large prospective multicenter Save ChildS Pro registry[1] has shown that EVT in children with LVO results in better functional outcomes than medical management alone, especially in children ≥6 years, presenting <6 hours after symptom onset, and with a PedNIHSS score ≥6. The rationale for using a 6-year cutoff for EVT recommendations in children is based on the population included in the retrospective multicenter Save ChildS study[2] and anatomic studies that evaluated the caliber of the access and cerebral vessels in pediatric patients of different ages.[9] In this study, the mRS score at discharge was higher in children 0 to 6 years of age (3.5; IQR, 1.0–5.1) than in the whole study cohort including all age groups (mRS, 1.0; IQR, 0.2–2.0). The Save ChildS study results likely reflect the smaller vessel caliber in children younger than 6 years, which requires even more skilled neurointerventionalists with pediatric experience compared with children older than 6 years in whom intracranial vessels are nearly adult sized.[9]
2. In children, perfusion imaging has been shown to be feasible, but thresholds for defining penumbra and "core" may be different from those of adults and are not yet established.[10] Nonetheless, results from the prospective multicenter Save ChildS Pro registry[1] and a well-designed matched case-control study[3] that included patients 6 to 24 hours from symptom onset suggest that EVT is associated with better outcomes than best medical treatment







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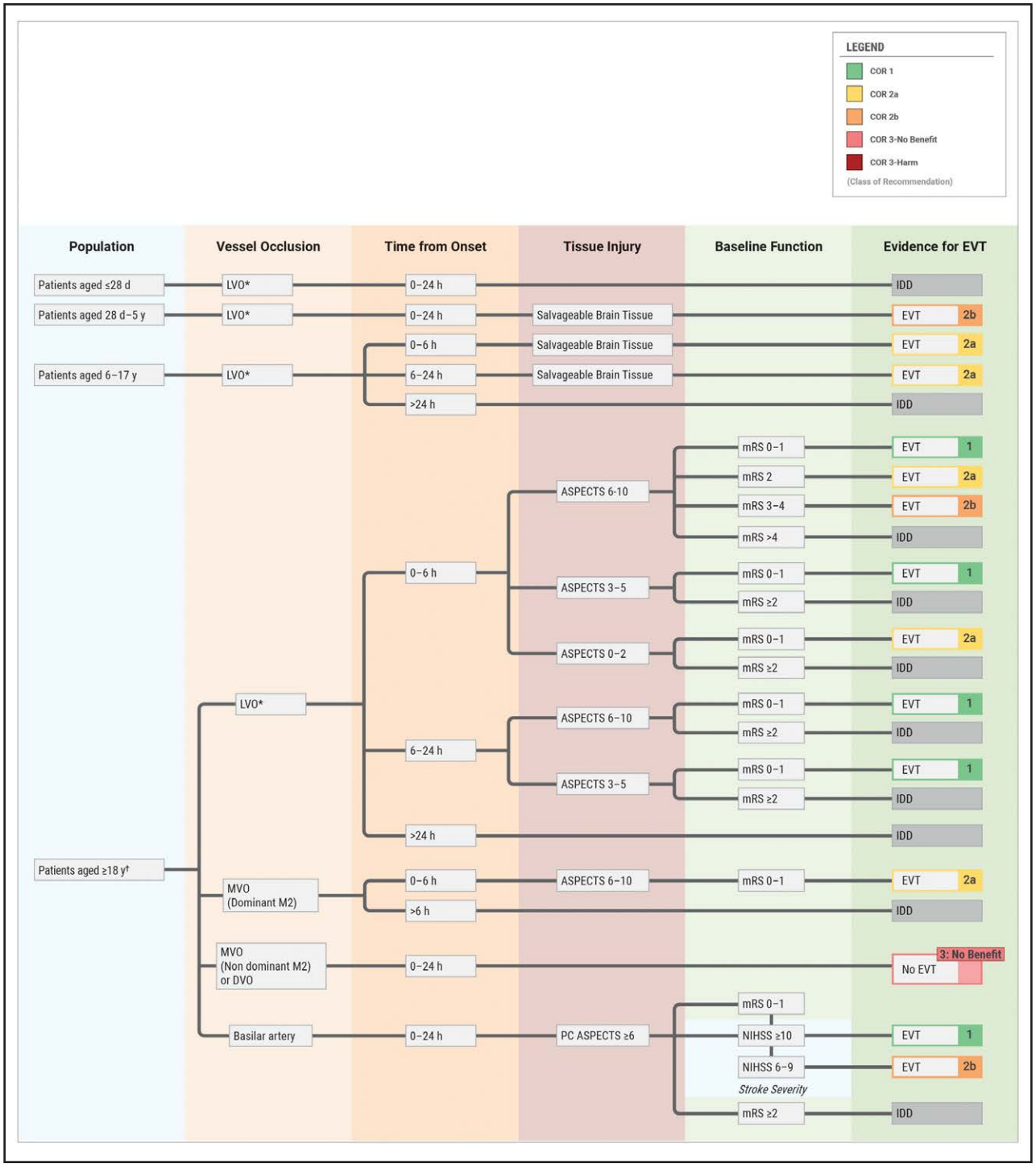


**Figure 3. Algorithm for management of AIS eligibility for EVT.**

*LVO of the anterior circulation. †In patients with NIHSS scores ≥6, unless specified in the graphic. DVO indicates distal vessel occlusion; EVT, endovascular thrombectomy; IDD, insufficient data to determine; LVO, large vessel occlusion; mRS, modified Rankin scale; MVO, medium vessel occlusion; and NIHSS, National Institutes of Health Stroke Scale.

if there is a mismatch between clinical deficit and infarct.

3. For children <6 years there is an ongoing debate whether EVT can be performed safely. However, there is some evidence from observational studies that children between 28 days and 6 years can benefit from EVT if adequately selected and performed cautiously by experienced neurointerventionalists.[1–3,11] For neonates (<28 days), there are case reports of EVT, but there is no systematic evidence on potential efficacy or harm of hyperacute recanalization therapies.

## Knowledge Gaps and Future Research

- Comprehensive registries of pediatric patients treated with hyperacute interventions for AIS should be maintained by centers providing those services and studied with rigorous methodologies through collaborative efforts among those institutions. Future research should also consider including children in thrombectomy trials. Significant knowledge gaps include, among others, establishing thresholds for perfusion parameters in children for hyperacute treatment selection and defining selection criteria for treatment of very young children (<2 years) and neonates or those children with arteriopathic etiologies such as focal cerebral arteriopathy.
- Medical education programs to improve knowledge and skills in early recognition of AIS in pediatric patients should be included in the pathways for pediatric stroke and systematically evaluated.

## 4.8. Antiplatelet Treatment

| Recommendations for Antiplatelet Treatment<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| General principles for early antiplatelet therapy | | |
| 1 | A | 1. In patients with AIS, administration of aspirin is recommended within 48 hours after stroke onset to reduce risk of death and dependency.[1–3] |
| 2b | B-NR | 2. In patients with AIS who have received IVT, the risk of antiplatelet therapy in the first 24 hours after IVT (with or without mechanical thrombectomy) is uncertain. Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IVT is known to provide substantial benefit or when withholding such treatment is known to cause substantial risk. |
| 2b | B-R | 3. In patients with AIS, the efficacy of IV tirofiban to improve clinical outcomes is not well established.[4,5] |
| 3: Harm | B-R | 4. In patients with AIS, the administration of IV abciximab is not recommended due to increased bleeding complications.[6,7] |
| Early secondary prevention | | |
| 1 | A | 5. In patients with noncardioembolic AIS or TIA, antiplatelet therapy is indicated in preference to oral anticoagulation to reduce the risk of recurrent ischemic stroke and other cardiovascular events, while minimizing the risk of bleeding.[8,9] |
| 1 | C-EO | 6. In patients with noncardioembolic AIS or TIA, the selection of an antiplatelet agent for early secondary stroke prevention should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics. |
| 2a | B-R | 7. In patients with AIS and extracranial carotid or vertebral arterial dissection, treatment with either antiplatelet or anticoagulant therapy for at least 3 months is reasonable to prevent recurrent stroke.[10–12] |
| 2b | B-NR | 8. For patients already taking aspirin at the time of noncardioembolic ischemic stroke or TIA, the effectiveness of increasing the dose of aspirin or changing to another antiplatelet medication is not well established.[13,14] |
| 3: No Benefit | B-R | 9. In patients with minor (NIHSS score ≤3) noncardioembolic AIS or high-risk TIA (ABCD² score ≥4), ticagrelor is not recommended over aspirin to reduce the composite endpoint of stroke, myocardial infarction, or death.[15] |
| 3: Harm | B-R | 10. In patients with noncardioembolic ischemic stroke, treatment with triple antiplatelet therapy (aspirin and clopidogrel and dipyridamole) for secondary stroke prevention should not be administered due to increased risk of bleeding.[16] |
| 3: Harm | B-NR | 11. In patients with ischemic stroke and AF without active CAD or recent intravascular stent, the routine addition of antiplatelet therapy to oral anticoagulation is potentially harmful because of increased bleeding risk and is not recommended.[17,18] |
| Dual antiplatelet therapy for minor AIS and high-risk TIA | | |
| 1 | A | 12. In patients with minor (NIHSS score ≤3) noncardioembolic AIS or high-risk TIA (ABCD² score ≥4) who did not receive IVT, DAPT (aspirin and clopidogrel with loading dose of clopidogrel) should be initiated early (within 24 hours after symptom onset) and continued for 21 days, followed by single antiplatelet therapy (SAPT) to reduce the 90-day risk of recurrent ischemic stroke.[19–25] |
| 2b | B-R | 13. In patients with recent (<24 hours) minor (NIHSS score ≤5) noncardioembolic AIS or high-risk TIA (ABCD² score ≥6 or symptomatic intracranial or extracranial ≥50% stenosis of an artery that could account for TIA) who did not receive IVT, DAPT with ticagrelor (including loading dose) plus aspirin for 30 days may be considered to reduce the risk of 30-day recurrent stroke.[26] |
| 2a | B-R | 14. In patients with minor (NIHSS score ≤5) noncardioembolic AIS or high-risk TIA (ABCD² score ≥4) within 24 to 72 hours from stroke onset, or NIHSS score of 4 to 5 within 24 hours from onset, who did not receive IVT, with presumed atherosclerotic cause (≥50% stenosis of intracranial or extracranial stenosis that was likely to have accounted for clinical presentation or acute new infarctions on imaging of presumed large artery atherosclerosis origin), DAPT (clopidogrel and aspirin) for 21 days followed by SAPT is reasonable to reduce the 90-day risk of recurrent stroke.[27] |
| 2b | B-R | 15. In patients with minor (NIHSS score ≤3) noncardioembolic AIS or high-risk TIA (ABCD² score ≥4) within 24 hours after symptom onset who did not receive IVT and who carry the CYP2C19 loss-of-function allele, DAPT with ticagrelor and aspirin for 21 days (followed by ticagrelor monotherapy) may be reasonable in preference over DAPT with clopidogrel and aspirin to reduce the 90-day risk of recurrent stroke.[28] |
| Antiplatelet therapy in the setting of IVT | | |
| 3: Harm | B-R | 16. In patients with AIS who are otherwise eligible for IVT or mechanical thrombectomy, aspirin is not recommended as a substitute for acute stroke treatment to improve patient outcomes. |
| 3: Harm | B-R | 17. In patients with AIS who are eligible for IVT, IV aspirin should not be administered concurrently or within 90 minutes after the start of IVT given the risk of hemorrhage. |
| 3: No Benefit | B-R | 18. In patients with AIS treated with IVT within 3 hours after symptom onset, adjunctive treatment with IV eptifibatide is not recommended to reduce disability at 3 months.[29,30] |





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### *Synopsis*

Patients with noncardioembolic AIS should be placed on antiplatelet therapy for prevention of recurrent stroke. The use of triple therapy (aspirin, clopidogrel, and dipyridamole) or the use of anticoagulation is not associated with clinical benefit and increases the risk of bleeding. For patients with minor AIS or high-risk TIA, short-term (21–90 days) DAPT followed by SAPT has been demonstrated to be beneficial to reduce the risk of early recurrent stroke if initiated soon after stroke (within 24 hours) and with a loading dose of clopidogrel (300 or 600 mg). Continuing DAPT beyond 90 days is not beneficial for reducing recurrent stroke and is associated with increased risk of bleeding.[31] The treatment approach for DAPT in AIS based upon the trial evidence is summarized in Figure 4 and Table 9.

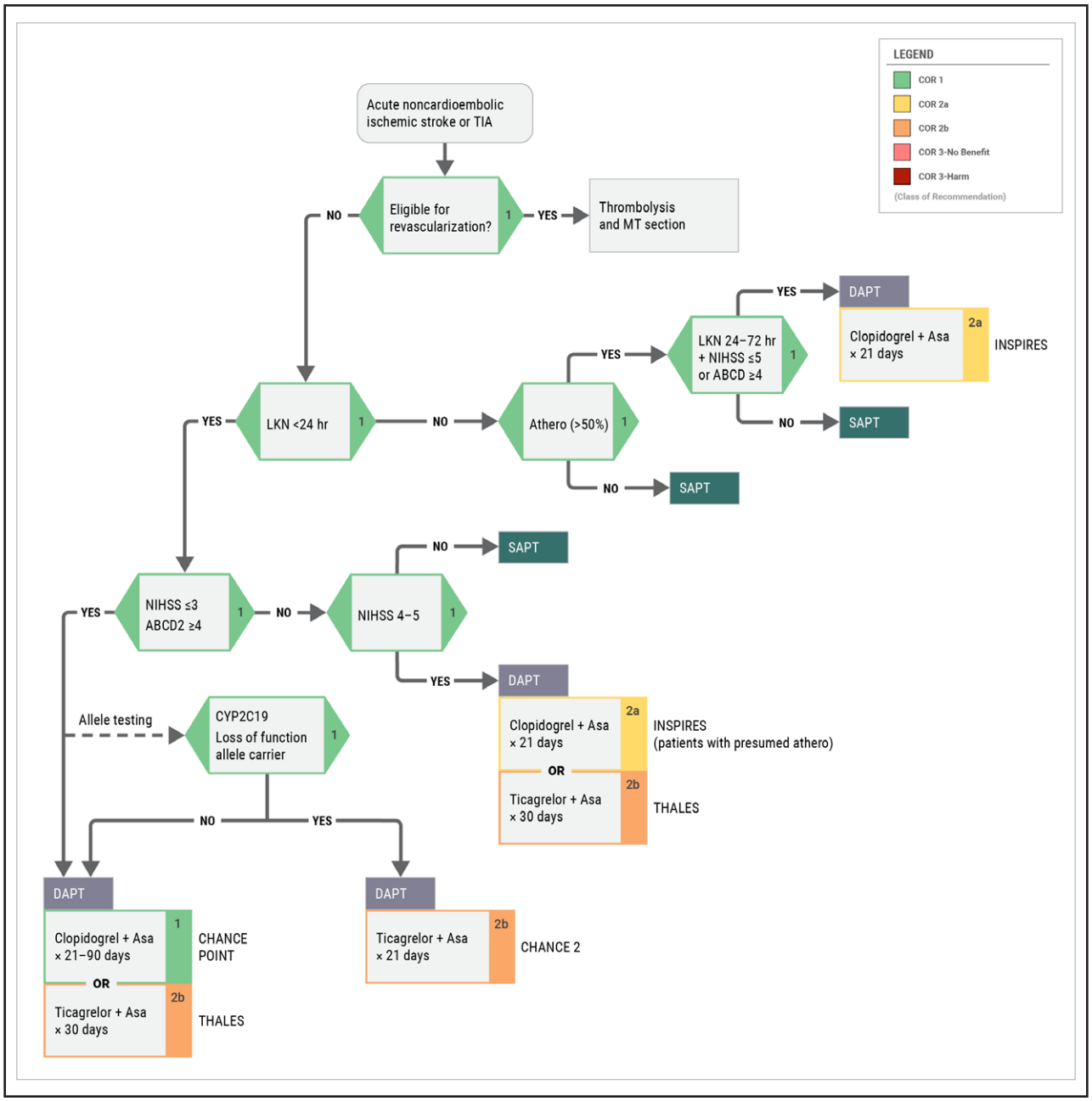


**Figure 4. DAPT for minor noncardioembolic AIS and TIA.**

ABCD2 indicates Age, Blood Pressure, Clinical Features, Duration, and Diabetes (TIA risk score); AIS, acute ischemic stroke; Asa, aspirin; Athero, atherosclerosis; CHANCE, Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events; CHANCE 2, Clopidogrel versus Ticagrelor in High-risk Patients with Acute Nondisabling Cerebrovascular Events; DAPT, Dual Antiplatelet Therapy; INSPIRES, Innovative Stroke Prevention and Intervention Research Study; LKN, last known normal; MT, mechanical thrombectomy; NIHSS, National Institutes of Health Stroke Scale; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; SAPT, Single Antiplatelet Therapy; THALES, Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death; and TIA, transient ischemic attack.

**Table 9. DAPT Trials**

| AIS DAPT trial | Inclusion | Drug/duration | LKN | NNT |
|---|---|---|---|---|
| CHANCE[19] | AIS (NIHSS ≤3) or TIA (ABCD ≥4) | Clopidogrel (300 mg load then 75 mg/d) + Asa (75 mg) x 21 d followed by clopidogrel | 24 h | 28 |
| POINT*[21] | AIS (NIHSS ≤3) or TIA (ABCD ≥4) | Clopidogrel (600 mg load then 75 mg/d) + Asa (50–325 mg/d) x 90 d | 12 h | 67 |
| THALES*[26] | AIS (NIHSS ≤5) or TIA (ABCD ≥6) | Ticagrelor (180 mg load then 90 mg twice daily) + Asa (300–325 mg load then 75–100 mg/d) x 30 d | 24 h | 91 |
| CHANCE 2*[28] | AIS (NIHSS ≤3) or TIA (ABCD ≥4) and CYP2C19 loss-of-function allele | Ticagrelor (180 mg load then 90 mg twice daily) + Asa (75–300 mg load then 75mg/d) x 21 d followed by ticagrelor | 24 h | 63 |
| INSPIRES*[27] | AIS (NIHSS ≤5) or TIA (ABCD ≥4), presumed athero | Clopidogrel (300 mg load then 75 mg/d) + Asa (100–300 mg load then 100mg/d) x 21 d followed by clopidogrel | 72 h | 53 |

*Slight increased risk of bleeding.

ABCD indicates Age, Blood Pressure, Clinical Features, Duration (TIA risk score); AIS, acute ischemic stroke; Asa, aspirin; athero, atherosclerosis; CHANCE, Clopidogrel in High-risk patients with Acute Nondisabling Cerebrovascular Events; CHANGE 2, Clopidogrel versus Ticagrelor in High-risk Patients with Acute Nondisabling Cerebrovascular Events; DAPT, Dual Antiplatelet Therapy; INSPIRES, Innovative Stroke Prevention and Intervention Research Study; LKN, last known normal; NIHSS, National Institutes of Health Stroke Scale; NNT, number needed to treat; POINT, Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; THALES, Acute Stroke or Transient Ischemic Attack Treated with Ticagrelor and ASA for Prevention of Stroke and Death; and TIA, transient ischemic attack.

The administration of antiplatelet therapy within the first 24 hours after IVT in patients with AIS remains a topic of ongoing investigation. Current guidelines advise against early antiplatelet use after IVT due to concerns about increased hemorrhagic risk. However, emerging evidence suggests that, in certain clinical scenarios, early antiplatelet therapy may be beneficial without significantly elevating the risk of ICH. Given these findings, initiating antiplatelet therapy within 24 hours after IVT might be considered in patients with concomitant conditions where such treatment is known to provide substantial benefit or where withholding it could pose significant risks. Clinical judgment should guide decision-making, balancing the potential advantages of early antiplatelet therapy against the individual patient's bleeding risk.



### *Recommendation-Specific Supportive Text*

*General Principles*

1. The clinical benefit and safety of aspirin for AIS was established by 2 large mega-stroke trials, International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST). Both trials initiated aspirin within 48 hours after onset. IST randomized 19,435 patients with AIS to 4 arms in a factorial design: 1) aspirin 300 mg daily, 2) subcutaneous heparin (half to 5000 IU twice daily or 12 500 IU twice daily), 3) both aspirin and heparin, or 4) neither (control).[1] The aspirin group had significantly fewer recurrent ischemic strokes within 14 days (2.8% versus 3.9%; $P<0.001$), no difference in hemorrhagic strokes (0.9% versus 0.8%), and a significant reduction in death or recurrent stroke (11.3% versus 12.4%; $P<0.05$). CAST randomized 20 000 patients with AIS to aspirin 160 mg/day (4 weeks) versus placebo.[2] Aspirin was associated with a reduction in combined in-hospital death or nonfatal stroke at 4 weeks (5.3% versus 5.9%; $P=0.03$). A subsequent Cochrane meta-analysis of 8 trials (n=41 483), of which IST and CAST contributed 98% of data, confirmed that aspirin within 48 hours of stroke onset was associated with a significant decrease in death or dependency (OR, 0.95 [95% CI, 0.91–0.99]; $P=0.01$).[3]
2. A recent meta-analysis[32] encompassing 8 studies with 2134 participants evaluated the impact of early antiplatelet therapy initiated within 24 hours after IVT in patients with AIS. The analysis revealed that early antiplatelet therapy was associated with significantly higher odds of excellent neurological recovery, defined as an mRS score of 0 to 1, compared with standard antiplatelet initiation (OR, 1.81 [95% CI, 1.10–2.98]; $P=0.02$). Importantly, there were no significant differences between early and standard antiplatelet groups regarding sICH (OR, 1.74 [95% CI, 0.91–3.33]; $P=0.10$) and mortality (OR, 0.88 [95% CI, 0.62–1.24]; $P=0.47$). However, a nonsignificant trend toward increased sICH in the early antiplatelet group was noted, suggesting a potential risk that warrants further investigation. The studies included in the analysis varied in their choice of antiplatelet agents, with some using glycoprotein IIb/IIIa inhibitors like tirofiban and eptifibatide, while others used combinations of aspirin and clopidogrel or aspirin alone. This heterogeneity underscores the need for further large-scale RCTs to determine the optimal antiplatelet regimen and timing, particularly in the context of different thrombolytic agents and endovascular interventions.
3. The data on the efficacy of tirofiban, an IV glycoprotein IIb/IIIa inhibitor, in AIS are inconclusive. The SaTIS trial[4] randomized 260 patients with AIS to IV tirofiban versus placebo within 3 to 22 hours after symptom onset. The primary outcome was the rate of HT and did not differ between either group (OR, 1.18 [95% CI, 0.66–2.06]). Mortality after 5 months was significantly lower in patients treated with tirofiban (2.3% versus 8.7%; OR, 4.05 [95% CI, 1.1–14.9]). There was no difference in functional outcome after 1 week and after 5 months. The TREND trial[5]





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randomized 425 patients with noncardioembolic AIS within 24 hours of onset and found that tirofiban decreased the risk of early neurological deterioration, without increasing the risk of sICH or systematic bleeding. However, the benefit of tirofiban on early neurological deterioration did not translate into a significant change in the 24- or 72-hour NIHSS score or in the 90-day mRS outcomes.

4. The AbESTT-II trial was a phase 3 randomized trial comparing abciximab, an IV glycoprotein IIb/IIIa inhibitor, with placebo within 6 hours. The trial was terminated early by the data monitoring board due to an unfavorable risk-benefit profile after 808 of the planned 1800 patients were enrolled. There was no increase in favorable clinical outcomes at 3 months (33% placebo versus 32% abciximab; *P*=0.944), but there was a significant increase in sICH or fatal ICH, within 5 days of enrollment (5.5% versus 0.5%; *P*=0.002).[7] A subsequent Cochrane review of glycoprotein IIb/IIIa inhibitors that were initiated within 6 hours of stroke onset included 3 trials of abciximab (n=1215) and also showed that that abciximab did not reduce long-term death or dependency (OR, 0.97 [95% CI, 0.77–1.22]) or death from all causes (OR, 1.08 [95% CI, 0.77–1.53]) but was associated with a significant increase in sICH (OR, 4.6 [95% CI, 2.01–10.54]).[6]

### *Early Secondary Prevention*

5. The WARSS trial included 2206 cryptogenic stroke patients (noncardioembolic and without high-grade carotid stenosis) who were randomized to warfarin (international normalized ratio [INR] goal, 1.4–2.8) versus aspirin 325 mg daily.[9] There was no difference in the primary endpoint (2-year recurrent ischemic stroke or death) between the groups (17.8% warfarin versus 16% aspirin; HR, 1.13 [95% CI, 0.92–1.38]). A subsequent Cochrane review meta-analysis of 8 oral anticoagulant therapy trials (n=5762) of patients with TIA or nondisabling cardioembolic AIS compared vitamin K antagonists (warfarin, phenprocoumon, or acenocoumarol) of various intensities with antiplatelet therapy.[8] Intensity of anticoagulation was defined as low intensity (INR, 1.4–2.8), medium intensity (INR, 2.0–3.6), and high intensity (INR, 3.0–4.5). This meta-analysis showed no benefit of oral anticoagulation (in any intensity) over antiplatelet therapy (medium intensity: risk ratio, 0.80 [95% CI, 0.56–1.14]; high intensity: risk ratio, 1.02 [95% CI, 0.49–2.13]), but both medium-intensity and high-intensity anticoagulation were associated with a significantly higher risk of bleeding complications (medium intensity: risk ratio, 1.93 [95% CI, 1.27–2.94]; high intensity: risk ratio, 9.0 [95% CI, 3.9–21]).
6. Expert consensus suggests that the choice of antiplatelet medication for early secondary stroke prevention in noncardioembolic patients with AIS or TIA should be individualized to the patient based upon factors that will improve compliance and adherence to treatment, such as tolerability and cost.
7. The Cervical Artery Dissection in Stroke Study (CADISS) Trial enrolled 250 patients with extracranial carotid and vertebral dissection with symptom onset within the last 7 days and randomized patients to antiplatelet therapy versus anticoagulation therapy.[10] This was a pragmatic treatment trial, and the choice of antiplatelet agents or anticoagulation was at the discretion of the local physician. Treatment was open label, and the primary endpoint was ipsilateral stroke or death from any cause within 3 months. There were no significant differences between treatment groups for any outcome. The recurrent stroke rate at 1 year was low at 6 (2.4%), with 4 in the antiplatelet group and 2 in the anticoagulation group. The low event rate suggests that any absolute effect difference between treatment approaches would be difficult without extremely large numbers. A subsequent systemic review and meta-analysis of 11 studies (n=5039) noted that anticoagulation was associated with a lower ischemic stroke risk (risk ratio, 0.63 [95% CI, 0.43–0.94]; *P*=0.02; $I^2$=0%) but higher major bleeding risk (risk ratio, 2.25 [95% CI, 1.07–4.72]; *P*=0.03, $I^2$=0%).[11] In an individual patient data meta-analysis (n=444) of 2 randomized clinical trials, CADISS and Cervical Artery Dissection in Stroke Study and the Biomarkers and Antithrombotic Treatment in Cervical Artery Dissection (TREAT-CAD), there were fewer primary endpoints in the anticoagulation group versus the antiplatelet group (1.4% versus 4.4%; OR, 0.33 [95% CI, 0.08–1.05]; *P*=0.06), but the finding was not statistically significant.[12] The secondary endpoint of ischemic stroke was significant, and anticoagulation was associated with fewer ischemic strokes (0.5% versus 4.0%; OR, 0.14 [95% CI, 0.02–0.61]; *P*=0.01) but nominally more bleeding events (2 versus 0). Therefore, based upon these limited data, it is reasonable to treat patients with AIS due to dissection with either anticoagulation or antiplatelet therapy.
8. For patients already taking aspirin at the time of a noncardioembolic AIS, there are limited nonrandomized data to support the effectiveness of increasing the dose of aspirin or changing to another SAPT. An analysis of a stroke registry database in South Korea of 1172 patients found that, compared with the aspirin monotherapy group, there was a reduction in the composite vascular event primary endpoint in the group that was switched from aspirin to another antiplatelet agent (HR, 0.50 [95% CI, 0.27–0.92]; *P*=0.03) and the group for whom another antiplatelet agent was

added to aspirin (HR, 0.40 [95% CI, 0.24–0.66]; *P*<0.001).[14] In a systemic review and meta-analysis, 5 studies with 8723 patients with AIS or TIA found that the addition of or a switch to another antiplatelet agent, versus aspirin monotherapy, was associated with reduced risks of major adverse cardiovascular events (HR, 0.68 [95% CI, 0.54–0.85]) and recurrent stroke (HR, 0.70 [95% CI, 0.54–0.92]). However, high-quality randomized evidence to support changing or increasing antiplatelet medication remains lacking.

9. The SOCRATES (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) trial compared ticagrelor versus aspirin within 24 hours of minor noncardioembolic AIS (NIHSS score ≤5) or high-risk TIA (ABCD$^2$ score ≥4).[15] The primary composite endpoint of stroke, myocardial infarction, or death within 90 days occurred in 6.7% of the ticagrelor group versus 7.5% of the aspirin group (HR, 0.89 [95% CI, 0.78–1.01]; *P*=0.07). Major bleeding (0.5% ticagrelor versus 0.6% aspirin) and ICH (0.2% ticagrelor and 0.3% aspirin) were similar between groups. SOCRATES failed to demonstrate superiority of ticagrelor monotherapy. However, as ticagrelor event rates were numerically less than aspirin, and there were no safety differences in the 2 groups, ticagrelor may be a reasonable alternative in patients with AIS who have contraindications to aspirin.
10. The TARDIS trial (n=3096) was an international randomized blinded endpoint trial of patients with AIS or TIA within 48 hours after onset comparing triple antiplatelet therapy (aspirin 75 mg, clopidogrel 75 mg, and dipyridamole 200 mg twice daily) for 30 days versus standard antiplatelet therapy (clopidogrel or aspirin plus dipyridamole).[16] The trial was stopped early by the data monitoring committee, due to futility. The incidence and severity of recurrent stroke or TIA did not differ between the triple therapy and guideline therapy groups (6% versus 7%; adjusted cOR, 0.90 [95% CI, 0.67–1.20]; *P*=0.47), but triple antiplatelet therapy was associated with more bleeding and increased severity of bleeding (adjusted cOR, 2.54 [95% CI, 2.05–3.16]; *P*<0.0001).
11. In patients with AIS with AF, anticoagulation monotherapy is recommended to prevent ischemic strokes. However, the addition of antiplatelet therapy to oral anticoagulation is commonly practiced. In a retrospective cohort analysis of 10093 patients discharged on warfarin after an AF admission using data from Medicare claims, almost 20% of patients with AF using warfarin were discharged on additional antiplatelet therapy, and this addition was associated with increased major bleeding rates (1.3%–1.9%; *P*=0.052).[18] The SPORTIF III (n=3407) and SPORTIF IV (n=3922) trials evaluated ximelagatran versus warfarin in patients with AF and allowed low-dose aspirin to be taken in conjunction with the study anticoagulation medication at the physician's discretion.[17] In a pooled analysis of SPORTIF III and SPORTIF IV, combining aspirin with either anticoagulant did not decrease primary events rates but was associated with higher rates of major bleeding in either anticoagulant arm (1.5%/year with warfarin versus 4.95%/year with warfarin plus aspirin; *P*=0.004; and 2.35%/year with ximelagatran and 5.09%/year versus ximelagatran plus aspirin; *P*=0.046). A cohort study of 24 436 patients with new onset AF and at least 1 risk factor for stroke from the international multicenter observational GARFIELD-AF registry found no benefit of anticoagulation plus antiplatelet therapy in reducing acute coronary syndromes; however, over 1 year, patients treated with anticoagulation plus antiplatelet therapy had significantly higher incidence rates of stroke (adjusted HR, 1.49 [95% CI, 1.01–2.20]) and any bleeding event (adjusted HR, 1.41 [95% CI, 1.17–1.70]) than those treated with anticoagulation monotherapy.[33] Although the routine addition of antiplatelet therapy to anticoagulation for patients with stroke is likely harmful overall, there may be specific indications or clinical scenarios where the additional benefit of antiplatelet therapy may outweigh the increased risk of bleeding (ie, active coronary artery disease or recent stent placement). Therefore, clinicians should consider careful risk/benefit analysis to identify select patients who may benefit from combination anticoagulation and antiplatelet therapy for stroke prevention in atrial fibrillation.

### *DAPT and Minor AIS*

12. Two large randomized trials, CHANCE (Clopidogrel in High Risk Patients With Acute Nondisabling Cerebrovascular Events) and POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke), established the benefit of early short-term DAPT with clopidogrel plus aspirin over SAPT for minor noncardioembolic AIS (NIHSS score ≤3) or high-risk TIA (ABCD$^2$ score ≥4).[25] CHANCE was a Chinese trial (n=5170) of DAPT (clopidogrel loading dose of 300 mg followed by 75 mg plus aspirin 75 mg for 21 days followed by clopidogrel alone) versus aspirin alone (75 mg for 90 days) within 24 hours after stroke onset.[19] DAPT was associated with a decreased rate of recurrent stroke (ischemic or hemorrhagic) at 90 days over aspirin (8.2% versus 7%; HR, 0.68 [95% CI, 0.570.81]; *P*<0.001) but with an identical rate of moderate-severe hemorrhage in both groups (0.3%; *P*=0.73). In a post-hoc analysis of CHANCE, DAPT was associated with improved 90-day functional outcome (absolute reduction of poor outcome, 1.70% [95% CI, 0.03–3.42])

compared with aspirin alone.[20] The POINT trial (n=4881) replicated the benefit of DAPT (clopidogrel plus aspirin) that was demonstrated in the CHANCE trial but in an international population.[21] In contrast to CHANCE, POINT initiated DAPT earlier (within 12 hours after symptom onset), used a higher loading dose of clopidogrel (600 mg), had longer duration of DAPT (90 days), and variable aspirin doses (50–325 mg/day). The composite primary endpoint was ischemic stroke, myocardial infarction, or death resulting from a vascular event within 90 days. Compared with aspirin alone, DAPT resulted in fewer ischemic events (5% versus 6.5%; HR, 0.75 [95% CI, 0.59–0.95]; *P*=0.02) but more major hemorrhages (0.9% versus 0.4%; HR, 2.32 [95% CI, 1.10–4.87]; *P*=0.02). Unlike CHANCE, which showed improved 90-day functional outcomes with DAPT, there was no significant difference in disability at 90 days seen in POINT (14.3% versus 14.7%; OR, 0.97 [95% CI, 0.82–1.14]; *P*=0.69).[24] A secondary analysis of CHANCE showed that the majority of benefit occurred within the first 2 weeks, as DAPT reduced the 1-week risk of new ischemic stroke by 35% (HR, 0.64 [95% CI, 0.52–0.79]; *P*<0.001), and the effect decreased during the second week (*P*=0.25), whereas the risk of bleeding was constant within the 3 weeks.[22] Similarly, a post-hoc analysis of POINT confirmed that the initially high early event rate decreased markedly, whereas the rate of major hemorrhage remained constant. Using a model-based approach, the optimal change point for ischemic events in POINT was calculated to be 21 days (DAPT versus aspirin 0–21 days HR, 0.65 [95% CI, 0.50–0.85]; *P*=0.0015; versus 22–90 days HR, 1.38 [95% CI, 0.81–2.35]; *P*=0.24), which supports limiting DAPT use to 21 days to maximize benefit and minimize risk.[23]

13. The THALES trial (Ticagrelor and Aspirin or Aspirin Alone in AIS or TIA) randomized 11 016 patients with noncardioembolic mild-moderate AIS (NIHSS score ≤5) or high-risk TIA (ABCD$^2$ score ≥6) or symptomatic intracranial or extracranial arterial stenosis (≥50% narrowing that could account for TIA) within 24 hours after symptom onset to DAPT with ticagrelor plus aspirin versus aspirin alone for 30 days.[26] Ticagrelor loading dose was 180 mg followed by 90 mg twice daily, and the aspirin regimen was 300 to 325 mg on the first day followed by 75 to 100 mg daily. DAPT with ticagrelor plus aspirin was associated with a decrease in the primary outcome of composite of stroke or death within 30 days (5.5% versus 6.6%; HR, 0.83 [95% CI, 0.71–0.96]; *P*=0.02) but was also associated with increased risk of severe bleeding (0.5% versus 0.1%; *P*=0.001). The rates of disability did not differ significantly between the 2 groups.
14. The INSPIRES trial (n=6100) enrolled Chinese patients with presumed symptomatic atherosclerosis (>50% stenosis) and patients with minor AIS (NIHSS score ≤5) or high-risk TIA (ABCD$^2$ score ≥4) within 24 to 72 hours after onset or for patients with an NIHSS score of 4 to 5, within 24 hours after onset.[27] Patients were randomized to DAPT (clopidogrel and aspirin) for 21 days followed by clopidogrel versus aspirin 100 mg only for 90 days. Loading dose of clopidogrel was 300 mg and of aspirin was 100 to 300 mg. Among patients with mild AIS or high-risk TIA of presumed atherosclerotic cause, combined clopidogrel and aspirin therapy initiated within 72 hours after stroke onset was associated with a lower risk of recurrent stroke at 90 days than aspirin alone (7.3% versus 9.2%; HR, 0.79 [95% CI, 0.66–0.94]; *P*=0.008) but was also associated with a higher risk of moderate-to-severe bleeding (0.9% versus 0.4%; HR, 2.08 [95% CI, 1.07–4.04]; *P*=0.03).
15. The CHANCE 2 trial was a Chinese trial of 6412 patients with minor noncardioembolic AIS (NIHSS score ≤3) or a high-risk TIA (ABCD$^2$ score ≥4) who also carried the CYP2C19 loss-of-function allele.[28] In this cohort of clopidogrel nonresponders, CHANCE 2 demonstrated that the DAPT regimen with ticagrelor plus aspirin was superior to the DAPT combination of clopidogrel plus aspirin in decreasing the risk of recurrent stroke within 90 days (6.0% versus 7.6%; HR, 0.77 [95% CI, 0.64–0.94]; *P*=0.008). Ticagrelor was associated with more total bleeding events than clopidogrel (5.3% versus 2.5%; HR, 2.18 [95% CI, 1.66–2.85]), although the risk of severe or moderate bleeding did not differ between the 2 treatment groups (0.3% versus 0.3%; HR, 0.82 [95% CI, 0.34–1.98]).

### *Thrombolysis*

16. In patients with AIS who are otherwise eligible for IVT or mechanical thrombectomy, aspirin is not recommended as a substitute for AIS treatment to improve patient outcomes. For a detailed evidence review on the efficacy of AIS revascularization therapy, please refer to the sections related to thrombolysis and mechanical thrombectomy.
17. Early administration of IV aspirin during thrombolysis has not improved stroke outcomes and can increase the risk of bleeding. In the ARTIS trial, 300 mg of IV aspirin given within 90 minutes of alteplase was stopped early after enrolling 642 of the planned 800 patients because sICH was higher in the aspirin arm (4.3% versus 1.6% with standard treatment; risk ratio, 2.78 [95% CI, 1.01–7.63]; *P*=0.04), with no benefit in functional outcomes at 3 months. These findings reflect broader evidence that platelet inhibition combined with active fibrinolysis may heighten hemorrhagic risks without offsetting improvements

in recovery. Consequently, many clinicians postpone aspirin administration until 24 hours after fibrinolysis or once imaging has ruled out intracranial bleeding, a strategy that maintains the long-term prophylactic advantages of aspirin while reducing early hemorrhage concerns. While research continues to explore optimal timing or patient subgroups, current data do not support very early use of IV aspirin in conjunction with alteplase.

18. The CLEAR stroke trial was a pilot safety trial multicenter randomized dose-escalation study of 94 patients with AIS treated within 3 hours after symptom onset with IV tissue-type plasminogen activator (tPA) and combination eptifibatide. The combination group appeared safe, with 1 sICH (1.4% [95% CI, 0–4.3]) versus 2 sICH (8.0% [95% CI, 0–19.2]) in the tPA only arm ($P$=0.17).[30] The MOST trial was a phase 3, adaptive. single-blind, randomized, controlled clinical trial in the United States that randomized patients with AIS treated with IVT within 3 hours after symptom onset and had an NIHSS score ≥6 to receive adjunctive IV argatroban, eptifibatide, or placebo within 75 minutes after thrombolysis. Adjunctive treatment with IV argatroban or eptifibatide did not reduce poststroke disability (90 day mean [±SD] utility-weighted mRS scores were 5.2±3.7 with argatroban, 6.3±3.2 with eptifibatide, and 6.8±3.0 with placebo) but was associated with increased 90-day mortality (argatroban 24%, eptifibatide 12%, placebo 8%).[29]

## Knowledge Gaps and Future Research

- The efficacy of ticagrelor monotherapy has not been shown to be superior to aspirin alone for composite outcome of stroke, MI, or death but is likely equivalent given the similar event rates and safety profile. Future studies evaluating the noninferiority of ticagrelor monotherapy in reducing recurrent stroke would be helpful.
- DAPT has been demonstrated to be beneficial in patients with minor AIS (NIHSS score ≤5) when initiated early (within 72 hours). However, the use of DAPT in clinical practice has been variable and routinely extended beyond clinical trial eligibility criteria. In the READAPT prospective cohort study (n=1070) of patients with minor AIS or high-risk TIA treated with DAPT at 51 Italian centers, 32.2% had late (>24 hours) DAPT initiation; 63.2% patients did not receive loading doses of clopidogrel, and overall, only 7.8% met the DAPT RCT inclusion/exclusion criteria.[34] Future randomized trials are needed to evaluate whether there is clinical benefit of DAPT in these untested scenarios, including delayed initiation (>72 hours), in severe strokes (NIHSS score >5), based upon certain subtypes (large artery atherosclerosis), or in those populations that were excluded in the DAPT trials (such as those patients with high-grade carotid stenosis or patients who received thrombolysis).
- The reliability of testing for clopidogrel loss of function in patients with stroke and whether the results of these tests should guide clinical decision-making in choice of antiplatelet regimen for stroke prevention needs further study.
- Randomized clinical trials to provide evidence that changing or increasing antiplatelet medication is beneficial in patients with AIS are needed.
- Future randomized trials could evaluate the benefit of combination antiplatelet and anticoagulation in AF for stroke prevention.
- Despite early indications that IV tirofiban may enhance recanalization rates when used with IVT, definitive data on long-term safety and functional benefits remain limited. Additional research is needed to determine optimal patient selection (eg, those with LVO or who are undergoing bridging therapies), establish dosing regimens, and clarify the interplay of tirofiban's platelet inhibition with thrombolytics to mitigate hemorrhagic risk. Ongoing large multicenter trials aim to validate these preliminary safety findings, define net clinical benefit, and refine treatment protocols.
- There have been no RCTs of anticoagulation versus antiplatelets in children with arterial ischemic stroke, a major gap in the current evidence.

## 4.9. Anticoagulants

**Recommendations for Anticoagulants**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | A | 1. In carefully selected (eg, milder severity) patients with AIS with atrial fibrillation, a strategy of early oral anticoagulation poststroke is low risk and is reasonable compared with a strategy of delayed anticoagulation, although the efficacy of early anticoagulation for prevention of early recurrent stroke is not established.[1–3] |
| 2b | B-NR | 2. In patients with an AIS and ipsilateral, high-grade ICA stenosis, the benefit of urgent anticoagulation is not well established.[4,5] |
| 2b | C-LD | 3. In patients with AIS with an ipsilateral, nonocclusive, extracranial intraluminal thrombus, the safety and efficacy of short-term anticoagulation are not well established.[6–8] |
| 2b | C-LD | 4. In patients with AIS who experience HT, initiation or continuation of anticoagulation may be considered depending on the specific clinical scenario and underlying indication.[9–11] |
| 3: No Benefit | A | 5. In patients with AIS, the use of argatroban is not effective as an adjunctive therapy with IVT to improve long-term functional outcomes.[12–15] |
| 3: No Benefit | A | 6. In patients with AIS, early anticoagulation (within 48 hours of stroke onset) does not reduce the likelihood of early neurological worsening or increase the likelihood of a favorable functional outcome and is not recommended.[4,16–24] |

### *Synopsis*

Anticoagulation (the pharmacological inhibition of the coagulation cascade with IV or oral medications) has been







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tested extensively in the treatment of AIS. The underlying principle is that anticoagulation may prevent early recurrent stroke, prevent neurological worsening, reduce the risk of thrombus propagation, and potentially counter the phenomenon of incomplete microcirculatory reperfusion. However, in general, these theoretical benefits have not been borne out in the medical literature. Among patients with AIS and AF who are selected for anticoagulation poststroke, a strategy of early initiation of a DOAC rather than delayed initiation is safe, although the efficacy of this approach in early recurrent stroke prevention is not established.[1–3] While sometimes practiced on an ad hoc basis, short term-anticoagulation of patients with undifferentiated stroke is not beneficial in either AIS associated with large artery atherosclerotic stenosis or with nonocclusive, intraluminal thrombus.[4,6–8] Argatroban has been tested in numerous prospective, interventional studies as an adjunctive therapy alongside IVT.[12–15] However, the benefits of this agent have yet to be demonstrated. Early anticoagulation (within 48 hours) does not confer a benefit with respect to long-term functional outcomes.[4,16–24]

### *Recommendation-Specific Supportive Text*

1. In the Early versus Late Initiation of Direct Oral Anticoagulants in Post-Ischemic Stroke Patients with Atrial Fibrillation (ELAN) trial,[1] "early anticoagulation" (within 48 hours of AIS onset in minor/moderate AIS and on day 6/7 in those with major AIS) versus "later anticoagulation" (day 3/4 after a minor AIS, day 6/7 after moderate AIS, or day 12–14 after major AIS) led to a numerical (but not statistically significant) reduction in recurrent AIS, systemic embolism, major bleeding, sICH, or vascular death (risk difference, −1.18 [95% CI, −2.84 to 0.47]). In the Optimal Timing of Anticoagulation After AIS with Atrial Fibrillation (OPTIMAS) trial,[2] 3648 participants with AIS and AF were randomized to "early" DOAC therapy (≤4 days of onset) or "delayed" DOAC therapy (7–14 days of onset). Early DOAC therapy was noninferior to delayed DOAC therapy. The Timing of Oral Anticoagulant Therapy in AIS with Atrial Fibrillation (TIMING) trial[3] randomized participants to early (≤4 days of onset) or delayed (5–10 days from onset) anticoagulation. The primary outcome occurred in 6.9% of participants with early anticoagulation and 8.7% of participants with delayed anticoagulation, suggesting that early anticoagulation was noninferior to delayed anticoagulation.
2. The Trial of Org 10172 in Acute Stroke Treatment (TOAST) trial[4] randomized participants with AIS to either danaparoid (a heparin analog) or placebo. While the primary analysis showed no benefit of danaparoid, a prespecified subgroup analysis[5] found that patients with AIS associated with ipsilateral large artery atherosclerosis enjoyed an apparent benefit from danaparoid. A favorable outcome was seen in 53.8% of participants treated with danaparoid compared with 38.0% of participants treated with placebo (*P*=0.023; Fisher exact test). However, this finding has not been replicated in subsequent studies, and the total body of literature does not support the approach of urgent anticoagulation for patients with AIS associated with an ipsilateral large artery atherosclerosis mechanism.
3. The optimal management of ipsilateral, nonocclusive, extracranial, intraluminal thrombus is not known. Short-term anticoagulation is pursued on an ad hoc basis by some practitioners. Several moderately well-designed observational studies[6–8] have suggested that short-term anticoagulation is not associated with excessive harm, but there are no well-conducted prospective studies to clarify this question further.
4. Several observational studies suggest that antithrombotic therapy can be safely initiated or continued in patients with AIS and HT. In a prospective, open-label study of 60 patients with AF and either mild to moderate AIS with an NIHSS score <9 (n=49) or TIA (n=11) who were treated with rivaroxaban within 14 days of onset, 50 were available for follow-up at 7 days after drug initiation. None developed symptomatic HT. Of the 23 with AIS who had HT at baseline, 5 demonstrated asymptomatic radiographic progression, and 18 showed neither clinical nor radiographic progression. Of the remaining 27 who did not have HT at baseline, 3 developed asymptomatic HT.[9] A retrospective stroke registry analysis identified 222 patients with AIS and HT. The frequency of composite events (neurological deterioration, vascular events, and death) at 1 month was significantly lower in patients treated with antithrombotic therapy compared with those who were not (1.6% versus 11.1%; *P*=0.041). Neither antiplatelet (n=72) nor anticoagulant (n=28) treatment after HT was associated with enlargement of the original HT or development of new HT or neurological deterioration.[10] Individual assessment of the clinical indication, benefits, and associated risks is warranted.[10,11]
5. In the Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke (ARTSS-2) trial,[13] patients treated with alteplase were randomized to either argatroban or placebo. There was no difference in the proportion of participants with sICH among the placebo (10%), low-dose argatroban (13%), or high-dose argatroban (7%) arms. The Multi-Arm Optimization of Stroke Thrombolysis (MOST) trial[14] was a phase 3, multi-arm, single-blind, randomized, controlled clinical trial conducted in the United States. Patients with AIS who received IVT were randomized to argatroban (100 µg/kg bolus + 3 µg/kg/min for 12 hours), eptifibatide (not discussed further), or placebo. In total, 59 of 514 (11.5%) patients received argatroban.

At 90 days, the mean utility-weighed mRS score was 5.2 in argatroban-treated participants and 6.8 in placebo-treated participants. The proportion of participants with sICH was 4% in the argatroban group and 2% in the placebo group. In the ARAIS trial,[15] 817 participants with AIS who were treated with IVT were randomized to argatroban (100 µg/kg bolus followed by an infusion of 1 µg/kg/min for 48 hours) or placebo. In total, 63.8% of participants in the argatroban group and 64.9% of participants in the placebo group had an mRS score of 0 to 1 at 90 days, with no difference in sICH across groups.

6. Historically, early anticoagulation (generally within 48 hours of stroke onset but no later than 14 days of acute stroke onset) has been posited to reduce the risk of early recurrent stroke, reduce the risk of neurological worsening, and potentially improve functional outcomes. However, numerous well-conducted clinical trials[4,16–24] as well as an individual participant data meta-analysis of the 5 largest trials[25] failed to demonstrate a net benefit for this approach. Since the publication of the prior guidelines, a further systematic review has been released.[26] In total, this review included 28 trials with 24 025 participants treated with either unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), a heparinoid, oral anticoagulants, or direct thrombin inhibitors. There was no evidence that early anticoagulation reduced the odds of the endpoints of death or functional dependence (OR, 0.98 [95% CI, 0.92–1.03]). There was moderate evidence that early anticoagulation was associated with a moderate reduction in early recurrent stroke (OR, 0.75 [95% CI, 0.65–0.88]) but was associated with higher odds of sICH (OR, 2.47 [95% CI, 1.90–3.21]) and of extracranial hemorrhage (OR, 2.99 [95% CI, 2.24–3.99]).

## Knowledge Gaps and Future Research

- The safety and usefulness of oral factor XIa inhibitors in the treatment of AIS are unknown. Factor XIa inhibitors are a newer drug class that are being tested for various conditions within cardiovascular medicine. The principle behind this drug class is that they may confer an anticoagulant benefit without increasing bleeding risk (to the same extent as vitamin K antagonists, direct thrombin inhibitors, or factor Xa inhibitors). Two recent exploratory clinical trials[27,28] examined their use in patients with high-risk TIA or minor stroke, forming the basis for ongoing confirmatory studies. However, there is no evidence on the use of factor XIa inhibitors for the treatment of AIS.
- Argatroban may warrant future study to improve long-term functional outcomes in patients with AIS who exhibit early neurological deterioration. A recent prospective, randomized, open-label, blinded-end point clinical trial examined the use of argatroban in this context.[29] This trial was conducted between April 2020 through July 2022. It was conducted in a majority Han Chinese population. The trial enrolled 628 participants with AIS who exhibited early neurological deterioration (defined as a worsening of ≥2 points on the NIHSS within 48 hours of stroke onset). Both groups received antiplatelet therapy within guidelines. Where participants received IVT, enrollment could only occur at least 24 hours after IVT was completed. The primary end point was a good functional outcome (defined as an mRS score of 0–3 at 90 days postenrollment). Of 314 participants randomized to argatroban, 80.5% achieved a good functional outcome. Of 314 randomized to no argatroban, 73.3% achieved a good functional outcome, a difference that was statistically significant (risk difference, 7.2% [95% CI, 0.6–14.0]). There was no difference in the proportion of patients experiencing sICH between the 2 groups (3/317 [0.9%] in the argatroban group and 2/272 [0.7%] in control group; $P$=0.78). Several methodological attributes of this trial are noteworthy. First, because participants, caregivers, and those delivering the intervention were aware of the treatment assignment, it is possible that deviations from the intended intervention may have occurred. Indeed, while 22 patients from the intervention arm did not complete study procedures per protocol, 42 patients in the control arm did not complete study procedures per protocol (of whom 31 participants received argatroban). Second, because trial participants and treating practitioners were aware of treatment assignment, it is possible that ascertainment of the primary outcome could have difference systematically between the 2 groups, although the final functional outcome was measured by blinded adjudicators. Finally, this trial was conducted on an exclusively Han Chinese population, and it is not clear that the results can be generalized to other racial or ethnic designations. A replication of this trial is warranted.
- There is a lack of prediction tools to aid in selecting patients for early as opposed to delayed anticoagulation in patients with AIS and AF. The ELAN trial indicated that early anticoagulation may be superior to delayed anticoagulation. In this trial, participants were subdivided based on whether their index stroke was "mild," "moderate," or "severe" based on infarct sizes and locations. However, it is likely that there may be other patient-specific factors that could be used to identify those at especially high risk of early recurrence (which may indicate that early anticoagulation is preferable) or at especially high risk of hemorrhagic complications (which may indicate that delayed anticoagulation is preferable).
- The optimal adjunctive strategies for IVT in the era of tenecteplase are not known. The majority of the literature examining adjunctive anticoagulation in patients who have received IVT has included patients who received IV alteplase. It is not known whether this







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literature can be extrapolated to patients who received IV tenecteplase, a newer molecule that exhibits more favorable pharmacokinetics and higher fibrin specificity than alteplase. (Please note that in the MOST trial, only 12% [7/59] of argatroban-treated patients received tenecteplase, and the balance received alteplase).

- There may be special populations in whom early anticoagulation (within 48 hours) is warranted. Although a strategy of early anticoagulation (within 48 hours) in patients with undifferentiated stroke is not recommended, there may be a population of patients in whom such a strategy is warranted. Such patients may include those with intracardiac thrombi (within the left atrium or left ventricle), patients with left ventricular assist devices, or those with mechanical cardiac valves (aortic or mitral).
- There is a lack of high-level evidence on concomitant full-dose anticoagulation (LMWH or DOACs) with IVT.
- The ideal strategy for initiating or resuming antithrombotics/anticoagulants concomitantly or postthrombolysis, including its timing and dose, is unknown, and guidelines will likely evolve as new trial data emerge.

## 4.10. Volume Expansion/Hemodilution, Vasodilators, and Hemodynamic Augmentation

**Volume Expansion/Hemodilution, Vasodilators, and Hemodynamic Augmentation**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 3: No Benefit | A | 1. In patients with AIS, hemodynamic augmentation using hemodilution,[1] high-dose albumin,[2,3] or chemical vasodilators such as pentoxifylline is not recommended to improve functional clinical outcomes. |
| 3: No Benefit | B-R | 2. In patients with AIS, mechanical hemodynamic augmentation with counterpulsation devices[4] or sphenopalatine ganglion stimulation[5,6] is not recommended to improve functional clinical outcomes. |

### *Synopsis*

In the ischemic brain, loss of cerebral autoregulation results in a theoretical advantage to hemodynamic augmentation. Such augmentation during ischemic stroke may preserve the ischemic penumbra and support pial-pial collaterals. However, hemodynamic augmentation has not demonstrated improved clinical outcomes in RCTs.

### *Recommendation-Specific Supportive Text*

1. Attempts to medically augment blood flow include the randomized study of hemodilution, high-dose albumin, and chemical vasodilators such as pentoxifylline. With all approaches studied, patients treated with these measures did not benefit in terms of functional outcome or mortality.
2. Mechanical approaches at augmentation of blood flow have also been unsuccessful in improving patients' functional outcomes. While studies showed that external counterpulsation was safe in a limited number of patients with acute stroke, it produced unpredictable effects on MCA flow measured by transcranial Doppler and improvements in NIHSS score that were independent of counterpulsation pressures used. Studies of sphenopalatine ganglion stimulation also demonstrated safety within 24 hours of onset. However, while patients with cortical stroke may have had nominally more favorable outcomes, results did not achieve statistical significance for improved 3-month disability.

## Knowledge Gaps and Future Research

- The development of techniques for accurate, region-specific, real-time measures of cerebral perfusion is necessary.
- Future research should focus on an improved understanding of collateral dynamics in stroke, particularly during acute interventions.
- Confirmatory studies could evaluate the impact of isosorbide mononitrate and cilostazol on patient outcomes after lacunar stroke (as studied in LACI-2)[7] and their possible roles in acute therapy and for other stroke subtypes.
- Contributions of baseline hydration status and intravascular volume repletion to stroke risk, progression, and recurrence would be helpful.

## 4.11. Neuroprotective Agents

**Recommendation for Neuroprotective Agents**
**Referenced studies that support the recommendation are summarized in the online data supplement.**

| COR | LOE | Recommendation |
|---|---|---|
| 3: No Benefit | A | 1. At present, in patients with AIS, the use of pharmacological or nonpharmacological neuroprotective treatments is not recommended to improve functional outcome.[1–5] |

### *Synopsis*

Since the 2019 update to the AIS guidelines, there have been several studies that have targeted different mechanisms of action related to neuroprotection. While the studies have been neutral or negative with respect to the primary outcomes, secondary and hypothesis-generating analyses from several studies support continued investigation in these areas. Given that each target has unique biology, the experience to date highlights the importance of iterative learning about patient selection and accounting for potential interactions with thrombolysis and/or EVT.

### *Recommendation-Specific Supporting Text*

1. Since the 2019 update to the AIS guidelines, several clinical trials have been completed that encompass various hypothesized mechanisms of action. For example, nerinetide targets glutamate excitotoxicity by uncoupling the postsynaptic density 95 protein.[1]

In a phase 3 trial, there was no difference in the primary outcome, although subgroup analysis showed potential for an effect in selected patients, which was confirmed in a meta-analysis of 3 randomized trials.[6] Uric acid is a free radical scavenger intended to reduce oxidative stress in the setting of thrombolysis. Although it did not increase the proportion of patients with excellent outcome, median mRS scores were lower in the treatment group.[2] Anti-inflammatory therapies, including ApTOLL[3] and stem cell therapy,[4,5] were reported as safe but have not been studied in pivotal trials.[3–5] Combination therapy with sublingual edaravone and dexborneol showed efficacy in a phase 3 trial in mild stroke patients from 1 country, but generalizability to other populations is not known.[7] RIC has shown conflicting results in 2 separate clinical trials.[8,9] While studies have demonstrated hypothesis-generating and/or preliminary evidence of efficacy, further studies are needed to demonstrate pivotal evidence. At present, none of the trials have demonstrated sufficient evidence to warrant use in clinical practice.

## Knowledge Gaps and Future Research

Neuroprotection has garnered renewed interest in the era of reperfusion. Current knowledge gaps and areas for future research that need to be addressed for any neuroprotection strategy include:

- Validated preclinical outcome measures and robust study designs that can increase the likelihood of successful human clinical trials in neuroprotection
- Role of the timing of treatment initiation, including in the prehospital setting and before or after reperfusion
- Role of patient selection based on stroke severity and acute infarct volume
- Role of combination pharmacotherapy that targets independent mechanisms of action
- Confirmatory pivotal studies based on the secondary analyses or preliminary efficacy of compounds, including nerinetide, uric acid, edaravone-dexborneol, and ApTOLL

## 4.12. Emergency Carotid Endarterectomy, Carotid Angioplasty, and Stenting Without Intracranial Clot

**Recommendation for Emergency Carotid Endarterectomy, Carotid Angioplasty, and Stenting Without Intracranial Clot**
**Referenced studies that support the recommendation are summarized in the online data supplement.**

| COR | LOE | Recommendation |
|---|---|---|
| 3: No Benefit | B-NR | 1. In patients with AIS or unstable neurological status (eg, stroke in evolution) caused by a high-grade carotid stenosis or occlusion without intracranial occlusion, emergent carotid endarterectomy (within 48 hours) is not beneficial to improve functional outcomes.[1–3] |

### *Synopsis*

The recommendation presented here for emergency carotid endarterectomy (within 48 hours) without intracranial clot is based on updated literature published since the last guidelines and a new meta-analysis.[1] The recommendations to perform carotid endarterectomy between 2 days and 2 weeks are covered in the AHA/ASA secondary prevention guidelines.[4] Additionally, the information regarding emergent carotid artery stenting during stroke thrombectomy to gain access or after EVT to maintain patency is discussed in the technique section under tandem lesions.

### *Recommendation-Specific Supportive Text*

1. Since the 2019 AIS guideline, a new meta-analysis[1] including 3 RCTs and 68 observational cohorts (n=232 952) reported that when carotid endarterectomy was performed within 2 days of symptom onset (versus days 3–14), there were higher rates of 30-day stroke (OR, 1.57 [95% CI, 1.3–1.9]) and death (OR, 5.19 [95% CI, 4.1–6.6]). This is in line with the previous results of the Swedish national registry[2] and the UK national registry.[3] Therefore, the recommendation was changed from the previous version to a COR 3.

# 5. IN-HOSPITAL MANAGEMENT OF AIS: GENERAL SUPPORTIVE CARE

## 5.1. Stroke Units

**Recommendation for Stroke Units**
**Referenced studies that support the recommendation are summarized in the online data supplement.**

| COR | LOE | Recommendation |
|---|---|---|
| 1 | B-R | 1. In patients with AIS of all ages, treatment within an organized inpatient stroke care unit supported by a specialty trained, interdisciplinary care team (ie, acute stroke units, rehabilitation stroke units, comprehensive stroke units, and mixed rehabilitation units) that incorporates standardized stroke care order sets and protocols is recommended to reduce the odds of poor outcomes and death.[1–16] |

### *Synopsis*

The role that the organized stroke unit care plays in the reduction of death, disability, and institutionalization of patients with acute stroke has been demonstrated via multiple randomized trials and meta-analyses.[1–3,17–20] The benefits have been independent of age, sex, and stroke type or severity.[3,21,22] The main characteristics distinct to an organized specialized inpatient stroke care unit include multidisciplinary team (including caregivers) care with weekly meetings, involvement of caregivers in rehabilitation, education, and training (staff and caregivers), specialization of staff (interest in stroke and rehabilitation), earlier and intensive onset of therapy, and medical investigation/treatment protocols[1] (Figure 5). Over the







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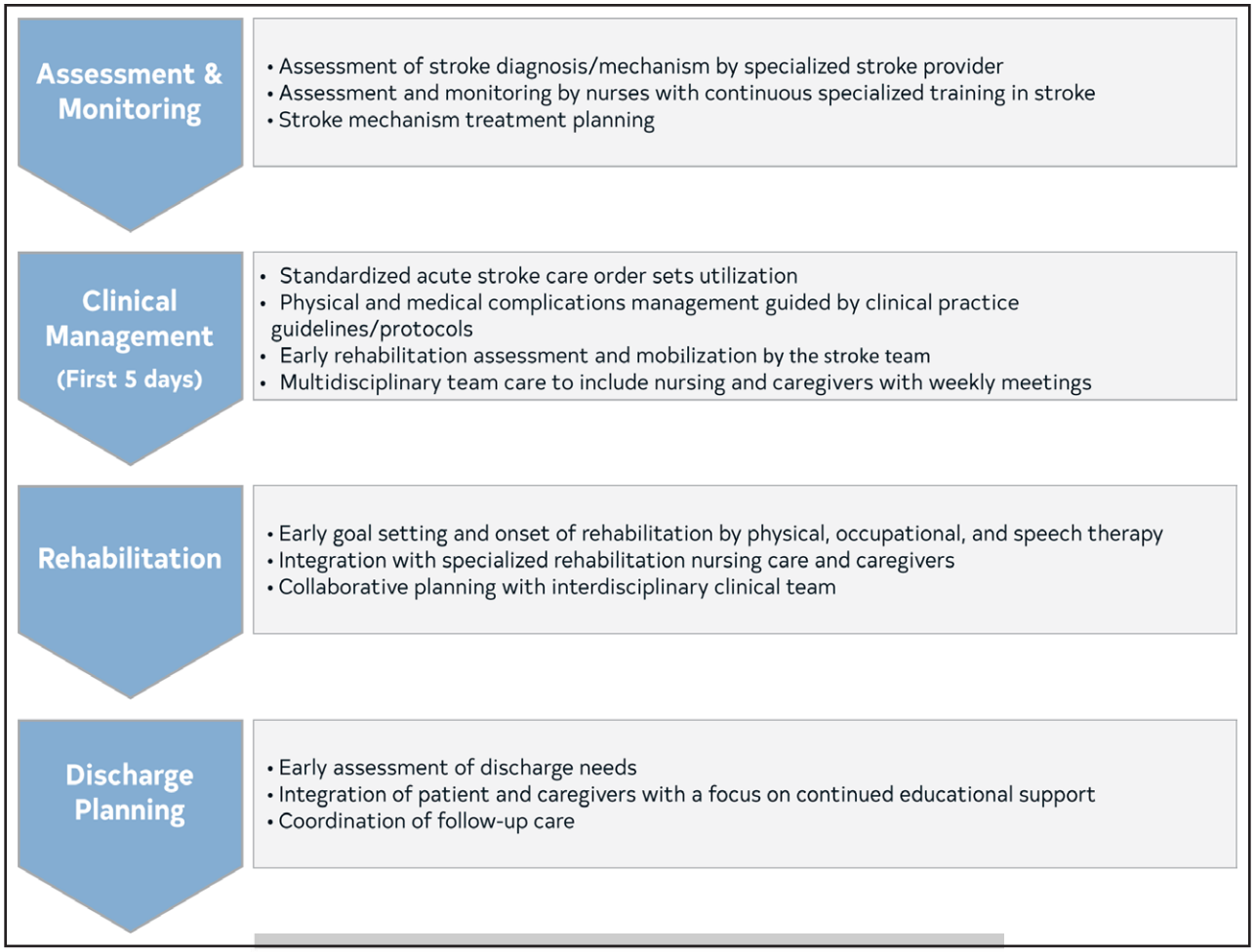


**Figure 5. Characteristics of an organized specialized inpatient care unit: flow diagram.**



years, multiple observational studies have revealed the effective implementation and operation of stroke units in the "real world" setting.[5,6,9–13] In addition, several studies have demonstrated successful implementation of stroke units in low- and middle-income countries with improvement in patient outcomes.[23–27] Stroke units were broadly defined in earlier studies as the incorporation of a "multidisciplinary team of specialists in the care of stroke patients which could apply to an isolated ward (stroke ward) or a mobile stroke team." Although it is challenging to evaluate differences in models of stroke unit implementation, evidence suggests that benefits are strongest in geographically colocalized units.[2,3,28]

### *Recommendation-Specific Supportive Text*

1. In 2020, the Stroke Unit Trialists' Collaboration conducted an updated systematic review that included 29 trials consisting of 5902 participants and compared organized inpatient care with alternative service. Direct pairwise comparisons and a network-analysis approach were used to assess the various types of organized inpatient care intervention. There was no effect on length of stay; however, patients with stroke cared for within an organized inpatient care unit were more likely to survive, be independent, and reside at home at the end of scheduled follow-up (median, 1 year). The benefits were independent of patient age, sex, initial stroke severity, stroke type, or duration of follow-up and were most evident in organized inpatient care units based in geographically colocalized units.[3] Several large, multicenter observational studies have also demonstrated a reduction in mortality, morbidity, and a greater likelihood of discharge home for patients treated in stroke units relative to a conventional ward/general ward.[5,10,12,13]

## Knowledge Gaps and Future Research

- Future research should focus on evaluating the effectiveness of newer stroke unit models, such as hyperacute stroke units, which integrate the hyperacute phase of care, to determine their impact on patient outcomes, including mortality, functional recovery, long-term quality of life, and health care resource utilization.[29] Understanding the effectiveness of these

units can inform best practices and optimize stroke care delivery.
- Further research is needed to evaluate the specific components of stroke unit care that contribute most to improved patient outcomes, such as early mobilization, specialized stroke teams, early rehabilitation, and intensive monitoring.[3] Additionally, there is a need to investigate the barriers to implementing organized stroke units in low- and middle-income countries, including resource constraints, workforce shortages, and infrastructure challenges.[30] Addressing these gaps will help develop tailored strategies to enhance stroke care globally and reduce disparities in treatment access and outcomes.

## 5.2. Dysphagia

**Recommendations for Dysphagia**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-EO | 1. In patients with AIS, performing a bedside swallow screening prior to initiation of liquid or food intake is recommended to screen for patients at increased risk for aspiration. |
| 2a | C-LD | 2. In patients with AIS, it is reasonable for dysphagia screening to be performed by speech pathologists or other trained health care professionals.[1] |
| 2a | B-NR | 3. In patients with AIS who have failed or are unable to participate in a bedside swallow screening due to neurological disabilities, it is reasonable to perform an endoscopic examination of swallowing function to aid in determination of dysphagia severity and aspiration risk.[2–4] |
| 2b | B-NR | 4. In patients with AIS, an oral hygiene protocol may be reasonable to reduce the risk for pneumonia.[5,6] |
| 2a | B-R | 5. In patients with stroke with dysphagia, treatment with pharyngeal electrical stimulation (PES), can be beneficial to reduce dysphagia severity and decrease the risk of aspiration.[7–9] |
| 2a | B-R | 6. In patients with severe stroke with dysphagia requiring tracheotomy and mechanical ventilation, treatment with PES, after ventilator weaning can be beneficial to decrease dysphagia severity, reduce the risk of aspiration, and expedite decannulation.[7,9–11] |

### *Synopsis*

Dysphagia is common after stroke and, until recently, no treatment has existed to reduce dysphagia severity or aspiration risk. Bedside screening for dysphagia may play an important role in preventing aspiration and pneumonia through the early identification of at-risk patients[12]; however, screening, formal endoscopic evaluation, and instituting oral intake restrictions will not prevent aspiration or hospital-acquired pneumonia in all patients with neurogenic dysphagia. Implementation of oral hygiene has been shown to reduce pneumonia risk in observational studies,[5,6] but the equivalency or superiority of specific oral hygiene methods remains unknown. Importantly, new research evaluating the use of PES has demonstrated reduced dysphagia severity, aspiration risk, and length of stay, with significantly more patients able to safely resume an oral diet.[7–9] PES is delivered as 3 consecutive, once-daily treatments (with an optional second course of treatment), and the PES tube can be used like other nasogastric tubes to deliver medications and tube feedings.[7,9] In patients with severe stroke requiring intubation with mechanical ventilation, PES treatment has resulted in reduced dysphagia severity, decreased aspiration risk, and a reduction in the time required to successfully decannulate patients, thereby decreasing length of stay.[7,10,11]

### *Recommendation-Specific Supportive Text*

1. Although clinical trial findings are lacking to show bedside swallow screening may prevent aspiration,[3,4,13,14] observational studies suggest that screening may reduce the incidence of pneumonia.[12] There is inherent logic in screening patients for signs of dysphagia prior to initiating oral intake. Preliminary bedside screening for dysphagia may also guide selection of additional definitive testing[15] and aid in selection of appropriate nutritional management.[2]
2. Acute stroke hospitals differ in their access to resources and services and make use of various educated and trained professionals (eg, speech pathologists) to support dysphagia screening. Expanding the number of qualified professionals may improve adherence to dysphagia screening in patients with AIS.[1]
3. Bedside screening may help to identify patients with stroke who could benefit from endoscopic assessment of swallowing function.[2–4] Although endoscopy may not be necessary in all patients with acute stroke, it may aid in understanding the cause and severity of dysphagia and guide the determination of patient management.
4. No randomized clinical trial data have evaluated the use of a specific oral hygiene protocol in relation to the development of pneumonia in patients with stroke. However, observational studies suggest that oral hygiene may be important for reducing pneumonia risk.[5,6]
5. Several studies have demonstrated a reduction in both dysphagia severity and aspiration risk after treatment with PES in patients with acute stroke.[7–9] This new intervention is applied via nasogastric tube and may lessen the risk of pneumonia through improved airway clearance, resulting in safe swallowing ability and improved oral feeding ability.[7,8]
6. PES has been tested in patients with severe stroke who required intubation with mechanical ventilation, which may further worsen dysphagia. PES treatment resulted in reduced dysphagia severity, decreased aspiration risk, and expedited decannulation in patients with severe stroke.[7,9–11]

## Knowledge Gaps and Future Research

- Insufficient evidence currently exists to recommend 1 specific dysphagia screening method over another.







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Additional research demonstrating superiority or equivalency of specific methods would be beneficial to aid the clinical diagnosis of dysphagia.
- Evaluation of standardized oral hygiene protocols for superiority and/or equivalency in pneumonia prevention is recommended in patients with AIS with and without neurogenic dysphagia.

## 5.3. Nutrition

**Recommendations for Nutrition**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | B-R | 1. In patients with AIS, enteral diet should be started within 7 days of admission after an AIS.[1–6] |
| 1 | B-NR | 2. In patients with AIS, nutritional screening is recommended to direct nutritional management early into hospitalization, preferably within 48 hours of admission, with a nutritional screening or assessment tool that has been validated in patients with acute stroke.[2–9] |
| 2a | B-NR | 3. In patients with AIS with dysphagia, it is reasonable to use nasogastric tubes initially for feeding within the first 7 days and to place percutaneous gastrostomy tubes in patients with longer anticipated persistent inability to swallow safely (>2–3 weeks).[1] |

### *Synopsis*

Prestroke nutritional status and nutritional support during hospitalization may play an important role in determining stroke outcomes. Observational studies of hospitalized patients with stroke show that undernourishment, malnutrition, and underweight status at the time of stroke hospitalization are associated with worse outcomes than normal weight and overweight status.[2,4–6,10]

Additionally, increased waist-hip ratio in men, but not body mass index, has been associated with worse stroke outcomes at hospital discharge[3] in patients with acute stroke. The FOOD 1 trial[1] showed that the addition of nutritional supplements alongside a normal hospital diet offers no additional benefit to patients without dysphagia. The FOOD 2[1] trial demonstrated a trend toward improved outcomes with institution of early nutrition within the first 7 days of hospitalization for patients requiring tube feedings. The FOOD 3[1] trial showed that early percutaneous gastrostomy tube insertion was not beneficial compared with nasogastric tube management. Several nutritional screening and assessment tools have been tested and validated in patients with stroke that can offer direction to stroke team prescribers on nutritional management during hospitalization.[7–9,11]

### *Recommendation-Specific Supportive Text*

1. Only 1 RCT exists to provide direction for nutritional management of AIS. The Feed Or Ordinary Diet (FOOD) trial was a study made up of 3 separate clinical trials published together in a single publication.[1] The FOOD 1 study enrolled patients without swallowing dysfunction into 2 groups. Both groups received "normal hospital diets," and the target group also received nutritional supplements. The study found no difference in primary outcomes (mRS <3; all-cause death) between use of supplements versus no supplements in these patients. FOOD 2 examined the benefit of provision of early nutrition (recommended within 3 days of admission if possible) versus withholding nutrition for at least 7 days in patients requiring tube feedings, finding a trend ($P$=0.09) in the absolute risk reduction of death when enteral feeding was commenced within 7 days of admission in patients with dysphagia who require tube feeding. Observational data also demonstrate an association between nutritional status and stroke outcome, making the early institution of nutrition an important aspect of AIS management.[1–4,6]
2. Several observational studies highlight significant risk for death or poor outcome in malnourished and undernourished patients with AIS.[2–6,10] Nutritional screening performed within the first 24 hours from hospital admission can identify patients with malnutrition who are at increased risk of poor stroke outcomes, aiding in direction of nutritional management during hospitalization. Several validated nutritional screening and assessment tools are available to determine nutritional status in AIS, including the Mini Nutritional Assessment (MNA),[7] the Controlling Nutritional Status Score (CONUT),[8] the Geriatric Nutritional Risk Index (GNRI),[11] and the Malnutritional Universal Screening Tool (MUST).[9]
3. The FOOD 3 trial[1] examined whether early percutaneous gastrostomy tube placement was superior to early placement of a nasogastric tube of any size lumen. FOOD 3 found an increased absolute risk for death and/or poor outcome in patients with early percutaneous gastrostomy tube placement compared with nasogastric feeding tube placement. Careful weighing of the risks of early percutaneous gastronomy versus the benefits of initiation of recovery activities, including earlier discharge to rehabilitation, is warranted.

## Knowledge Gaps and Future Research

- Nutritional status in patients with stroke with dysphagia who have undergone treatment with PES is an area in need of future exploration and has yet to be reported in any published literature.

## 5.4. Deep Vein Thrombosis Prophylaxis

| Recommendations for Deep Vein Thrombosis Prophylaxis Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | B-R | 1. In patients with AIS who have impaired mobility and do not have contraindications to intermittent pneumatic compression (IPC), IPC in addition to routine care is recommended over routine care alone to reduce the risk of deep vein thrombosis (DVT).[1,2] |
| 2a | B-R | 2. In patients with AIS who have impaired mobility, either prophylactic-dose subcutaneous heparin (UFH or LMWH) is reasonable to reduce the risk of VTE.[3] |
| 2b | A | 3. In patients with AIS who have impaired mobility, the benefit of prophylactic-dose subcutaneous heparin (UFH or LMWH) over no prophylactic-dose heparin is not well established to increase overall survival.[2] |
| 2b | B-R | 4. In patients with AIS who have impaired mobility and who are selected for prophylactic anticoagulation, the benefit of prophylactic-dose LMWH over prophylactic-dose UFH to prevent DVT is uncertain.[4–6] |
| 3: Harm | B-R | 5. In patients with AIS who have impaired mobility, elastic compression stockings cause harm, including skin breakdown, ulceration, and tissue necrosis, compared with usual care.[7–9] |

### *Synopsis*

DVT is a potentially life-threatening complication of impaired mobility, a frequent result of AIS. DVT can lead to circulatory stasis, venous insufficiency, chronic pain, or pulmonary embolism (PE; when peripheral venous thrombi migrate to the pulmonary circulation). As part of a broader suite of interventions to minimize complications of impaired mobility, reducing the risk of DVT is an important objective of acute stroke management. On the basis of a large, well-conducted clinical trial (CLOTS3[1]), it is recommended that IPCs are used to reduce venous stasis in the extremities and thereby reduce the risk of DVT in patients with AIS. The use of chemical prophylaxis (LMWH or UFH) is not well-established in patients with AIS, and it is unclear whether the use of such prophylaxis improves survival. However, the literature from general hospitalized medical populations support pharmacological DVT prophylaxis as a measure to reduce the occurrence of DVT compared with no pharmacological prophylaxis.[3] A lack of field- and clinician-level equipoise around this question may complicate the design of studies to address this question further in patients with AIS.[2] Among patients selected to receive pharmacological prophylaxis, there are no data to suggest that LMWH is superior to UFH or vice versa.[4–6] The use of elastic compression stockings for DVT prophylaxis should be avoided because they have been shown in multiple clinical trials to cause skin breakdown and ulceration.[7–9]

### *Recommendation-Specific Supportive Text*

1. The Clots in Legs Or sTockings after Stroke (CLOTS)-3 trial[1] was a multicenter, randomized, controlled, clinical trial conducted in the United Kingdom between 2008 and 2012. The objective of the trial was to determine whether IPCs were effective in reducing the risk of DVT in patients who experienced an acute stroke (either ischemic or hemorrhagic stroke). The study population comprised patients with acute stroke who were immobile (defined as the inability to use the toilet without assistance) and who could be enrolled between day 0 and day 3 after symptom onset. The study intervention was IPC with a widely available device, and the control group consisted of no IPC. The primary endpoint of the study was composed of 1) proximal DVT detected on screening ultrasound within 30 days of enrollment or 2) any symptomatic DVT within the first 30 days of enrollment. In total, 2876 patients were enrolled, >80% of whom had an AIS, with a median age of 76 years. The primary endpoint was seen in 8.5% of patients randomized to IPC and 12.1% of patients randomized to no IPC (risk difference, −3.6 [95% CI, −1.4 to −5.8]). During the treatment period, 11% of those randomized to IPC died compared with 13% of those randomized to no IPC ($P$=0.057). There was a small but significantly increased risk of skin breakdown in those randomized to IPC care (3% in IPC group versus 1% in control group; $P$=0.002).
2. A systematic review and meta-analysis[3] that included all hospitalized medical patients (including, but not limited to, those with acute stroke) additionally found that the use of pharmacological DVT prophylaxis may reduce the occurrence of PE (OR, 0.70 [95% CI, 0.56–0.87]), but there was no significant benefit with respect to mortality (risk ratio, 0.93 [95% CI, 0.86–1.00]) and an increased risk of any bleeding (risk ratio, 1.28 [95% CI, 1.05–1.56]) and of major bleeding events (OR, 1.61 [95% CI, 1.23–2.10]), suggesting no net benefit.
3. A systematic review and meta-analysis[2] including 14 clinical trials examined the use of pharmacological DVT prophylaxis (UFH, LMWH, and another heparinoid) in patients with AIS. It was found that the routine use of prophylactic-dose anticoagulants (heparin, LMWH, or other heparinoids) did not reduce the risk of death or reduce the level of global disability. The routine use of prophylactic anticoagulants did reduce the intermediate endpoints of symptomatic PE (OR, 0.69 [95% CI, 0.49–0.98]) and DVT (OR, 0.21 [95% CI, 0.15–0.29]). However, there was a corresponding increased risk of both ICH (OR, 1.68 [95% CI, 1.11–2.55]) and extracranial hemorrhage (OR, 1.65 [95% CI, 1.00–2.72]).







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4. In the Prophylaxis of Thromboembolic Events by Certoparin (PROTECT) trial,[4] 545 patients with AIS were included within 24 hours of stroke onset. Participants were randomized to certoparin or UFH. The primary endpoint of the study was a composite of proximal DVT, PE, or death related to VTE. In total, 7.0% of patients in the certoparin group and 9.7% of patients in the UFH group developed a primary endpoint ($P$=0.0011). These results met the prespecified margins for noninferiority of certoparin over UFH. Major bleeding rates did not differ between the 2 groups. The Prevention of VTE After AIS With LMWH Enoxaparin (PREVAIL) trial[5] included 1762 patients with AIS and impaired mobility at study screening who could be enrolled within 48 hours of symptom onset. Participants were randomized to enoxaparin 40 mg administered subcutaneously daily or to UFH administered subcutaneously twice daily. The primary endpoint was a composite of DVT or PE. The rate of the primary endpoint was 10% in those patients randomized to enoxaparin compared with 18% in those randomized to UFH ($P$=0.0001). However, the rate of extracranial hemorrhage was 1% in those treated with enoxaparin and 0% in those treated with UFH. A systematic review and meta-analysis[6] of 9 trials enrolling a total of 3137 participants found that enoxaparin reduced the occurrence of DVT when compared with UFH but that there was no significant difference with respect to the rates of PE, sICH, or death. In summary, the published literature suggests that LMWH is likely associated with a small but significant reduction in the occurrence of DVT when compared with UFH but this is accompanied by an increased risk of extracranial hemorrhage without a clear net benefit on mortality or the level of global disability.
5. In a small clinical trial[9] of 98 patients with acute stroke (ischemic or hemorrhage) who were immobile at study screening, 65 patients were randomized to usual care plus graded compression stockings (GPCs) and 32 patients were randomized to usual care alone. Of those randomized to GPCs, 7 of 65 (10.8%) developed a DVT compared with 7 of 32 (21.9%) in the group assigned to usual care alone (OR, 0.43 [95% CI, 0.14–1.36]). In the CLOTS 1 trial,[7] 2518 patients with acute stroke (ischemic or hemorrhagic) who could be enrolled within 1 week after symptom onset were included. Participants were randomized to thigh-length GPCs or avoidance of thigh-length GPCs. The primary endpoint was DVT in the popliteal or femoral veins. In total, 10% of patients randomized to GPCs developed a primary endpoint compared with 10.5% of patients randomized to usual care only. Skin breaks, skin ulceration, skin blistering, and skin necrosis occurred more commonly in those randomized to GPCs (5%) than those randomized to usual care only (1%). In the CLOTS 2 trial,[8] 3114 patients with acute stroke (ischemic or hemorrhagic) were randomized to either thigh-length GPCs or below-knee stockings. The primary endpoint was DVT in the popliteal or femoral veins. In total, 6.3% of patients with thigh-length GPCs developed a primary end point compared with 8.8% of those with below-knee GPCs. However, skin complications occurred in 3.9% of patients randomized to thigh-length GPCs compared with 2.9% of those with below-knee GPCs.

## Knowledge Gaps and Future Research

- Designing fully powered trials to determine the efficacy of pharmacological DVT prophylaxis over no prophylaxis with respect to mortality and global disability is likely to be extremely challenging. However, this question could be studied using highly pragmatic trial designs embedded within stroke quality assurance registries or through leveraging newer electronic medical record–linked datasets, which offer the potential to generate adequate sample sizes while capturing sufficient data to account for confounding by patient and by center.
- There may be subgroups of patients with AIS for whom LMWH is preferable over UFH. Development of risk prediction tools (weighing the potential benefit of LMWH with respect to VTE prevention against the potential harms of increased bleeding risk) may allow this decision to be more precisely tailored on a patient level.
- At present, the optimal dosing regimen for UFH (3 times per day or 2 times per day) is not known. The difference between 2 groups is likely to be small and may be substantially influenced by individual patient-level factors, including clinical and demographic parameters. Thus, such a study may be addressed through the use of large sources of real-world data or highly pragmatic comparative effectiveness studies.
- The use of factor XIa inhibitors for pharmacological DVT prophylaxis in patients with AIS has not been studied.
- There are no data to support choice DVT prophylaxis in pediatric patients with AIS.

## 5.5. Depression

| Recommendations for Depression<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | B-NR | 1. In patients with AIS, administration of a structured depression inventory is recommended to routinely screen for poststroke depression (PSD), although the optimal timing of screening is uncertain.[1–4] |
| 1 | B-R | 2. In patients diagnosed with PSD, treatment with antidepressants and/or nonpharmacological interventions (ie, psychotherapy, noninvasive brain stimulation, acupuncture) is recommended to improve depressive symptoms.[5–17] |

### *Synopsis*

PSD is common in patients with ischemic stroke, with a prevalence of 31%, and is associated with increased disability and mortality compared with non-PSD patients.[18–20] Early identification and treatment are critical and have led to the use of various self-rating and health care-professional interview scales. In 2014, a meta-analysis of studies identified several depression screening tools with high sensitivity but low specificity.[2] In addition, the optimal timing, setting, and follow-up were unknown. The scales commonly used were not explicitly designed for patients with stroke, who may have various physical or stroke-related somatic symptoms, and cognitive or speech difficulties, which add layers of complexity. Over the years, a few PSD-specific scales have been developed but are not widely used.[21–23] To date, data have shown that each of the commonly used PSD scales has distinct advantages in the diagnosis of PSD.[1] The best method for PSD screening in patients with aphasia and cognitive impairments is unknown.

### *Recommendation-Specific Supportive Text*

1. In 2024, a meta-analysis of studies evaluating 10 depression screening tools (32 studies, N=3865) found that each scale had different degrees of benefit in diagnosing PSD based on depression type and time of screening. The Patient Health Questionnaire-9 (PHQ-9) demonstrated higher diagnostic accuracy when evaluating any PSD type and during the first 2 months after stroke. Higher diagnostic accuracy was noted with the Hamilton Depression Scale (HDS) in the chronic phase (>2 months) after stroke and in the major depression classification. Due to the heterogeneity of studies included, data were insufficient to assess PSD in patients with combined aphasia and cognitive impairments.[1]
2. In a meta-analysis of RTCs evaluating the overall efficacy of pharmacological antidepressant treatment, patients receiving antidepressants had greater improvement in various depressive symptoms compared with patients receiving placebo, but antidepressants were less well tolerated.[16] In several network meta-analyses, selective serotonin reuptake inhibitors (SSRIs) and tricyclic antidepressants were more effective than placebo, with paroxetine noted to potentially be the best choice for treatment of PSD.[11,12] Given the associated adverse reactions and reduced tolerability with antidepressant therapy for PSD, alternative non-pharmacological forms of treatment have been evaluated independently and in combination with pharmacological therapy.[5,24–28] Shen et al showed that repeated transcranial magnetic stimulation (rTMS) was effective in PSD treatment in a meta-analysis of 22 RCTs.[15] When comparing forms of acupuncture to antidepressant therapy in PSD, several meta-analyses revealed that acupuncture was just as effective as pharmacological therapy.[6–8] In a meta-analysis of 13 RTCs, the combined therapy of acupuncture with antidepressants led to a significant reduction in the HDS score when compared with antidepressant therapy alone.[9] When comparing antidepressant therapy alone with the combination of low frequency (≤10 Hz) rTMS and antidepressant therapy, a meta-analysis of 34 RTCs revealed a significant reduction in the HDS score and higher total effective rate in the combination group.[10]

## Knowledge Gaps and Future Research

Future research is warranted in the following areas:

- Several PSD screening scales, such as the Stroke Aphasic Depression Questionnaire (SADQ) and the Aphasia Depression Rating Scale (ADRS), have been developed for patients with stroke and aphasia and/or cognitive impairments.[29] Most have demonstrated feasibility in the clinical setting but were unable to sufficiently establish reliability and validity, thus limiting their widespread adoption and clinical use. Future research is needed to address these limitations, with thoughtful consideration of methodological strategies, such as larger sample sizes, to ensure the accuracy and generalizability of these screening tools.[30]
- The gold standard for confirming a diagnosis of PSD is a structured psychiatric interview, which assesses whether a patient meets the depression criteria outlined in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM).[31] To replace the DSM as the gold standard, PSD screening scales must demonstrate high diagnostic accuracy, strong validity/reliability, and high sensitivity/specificity. Further research is needed to evaluate whether any of the current PSD screening scales can meet these rigorous criteria and effectively replace the DSM-based diagnostic process.
- There is a significant knowledge gap regarding the optimal timing and setting for screening and diagnosing PSD, as most studies varied in when and where assessments were conducted.[1,2,32] Further research is needed to determine whether early screening during acute hospitalization or later assessments in outpatient or community settings yield more accurate diagnoses.[18] Additionally, studies should explore the impact of different health care environments, such as stroke rehabilitation units versus primary care clinics, on the identification and management of PSD.[33]
- Recent studies have explored the use of serum biomarkers, such as brain-derived neurotrophic factor, cortisol, and inflammatory markers, for screening and diagnosing PSD, offering promising insights







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into potential biological correlates of the condition. However, the feasibility and accuracy of these biomarkers in clinical practice remain uncertain due to variability in study designs, small sample sizes, and inconsistent findings across populations.[31,34] Further research is needed to standardize biomarker measurement techniques, validate their diagnostic use, and determine their integration into existing PSD screening protocols.[33]

## 5.6. Other In-Hospital Management Considerations

**Recommendations for Other In-Hospital Management Considerations**
**Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | C-EO | 1. For select patients with AIS and their families, referral to palliative care resources is reasonable as appropriate. |
| 3: No Benefit | A | 2. In patients with AIS, routine use of prophylactic antibiotics has not been shown to be beneficial in improving functional outcomes.[1–5] |
| 3: Harm | C-LD | 3. In patients with AIS, routine placement of indwelling bladder catheters should not be performed because of the associated risk of catheter-associated urinary tract infections (UTIs).[6] |

### *Synopsis*

Medical complications after stroke are associated with increased mortality and worse functional outcomes.[7,8] A key component of poststroke supportive care during hospitalization is prevention of these complications, which may include infections, VTE, and other systemic conditions common after stroke. Many of these are specifically covered in more detail in other sections of the guideline.

Patients with AIS are at particularly high risk for complications related to immobility, such as skin breakdown and the development of pressure ulcers. As such, specific recommendations for regular skin assessments using objective risk scales and measures to minimize skin injury have been incorporated into both the guidelines for adult stroke rehabilitation and recovery as well as the care of the patient with AIS comprehensive nursing care scientific statement.[9,10]

Other recommendations to minimize in-hospital complications after stroke not included elsewhere in the guideline include caution around the routine use of prophylactic antibiotics and indwelling bladder catheters. Although studies support decreased incidence of systemic infection with prophylactic antibiotics, improvement in functional outcome or mortality has not been consistently demonstrated.[11] There are robust data demonstrating lower incidences of catheter-associated UTIs with removal of indwelling catheters in hospitalized patients,[12] although specific evidence surrounding patients poststroke is limited.

### *Recommendation-Specific Supportive Text*

1. It is reasonable for health care professionals to ascertain and include patient-centered preferences in decision-making, especially during prognosis formation and considering interventions or limitations in care. See the 2014 AHA/ASA palliative care statement for additional information.[13]
2. Three large RCTs demonstrated no effect of preventive antimicrobial therapy on functional outcome. The PASS (Preventive Antibiotics in Stroke Study) trial showed no difference in the primary endpoint of distribution of functional outcome scores on the mRS score at 3 months (adjusted cOR, 0.95 [95% CI, 0.82–1.09]; $P$=0.46) despite an overall reduction in the incidence of infection (OR, 0.57 [95% CI, 0.38–0.85]; $P$=0.005), including reducing the number of UTIs (OR, 0.34 [95% CI, 0.26–0.46]; $P$<0.001) but no significant decrease in the rate of poststroke pneumonia (OR, 0.91 [95% CI, 0.73–1.13]; $P$=0.385).[1] In STROKE-INF (Antibiotics to Prevent Infection in Stroke), prophylactic antibiotics did not affect the incidence of the primary endpoint of poststroke pneumonia (adjusted OR, 1.21 [95% CI, 0.71–2.08]; $P$=0.489) or the secondary endpoint of mRS score of 0 to 2 at 90 days (adjusted OR, 0.87 [95% CI, 0.6–1.24]; $P$=0.448).[2] The PRECIOUS (Prevention of infections and fever to improve outcome in older patients with acute stroke) trial also did not show benefit of prophylactic ceftriaxone on functional outcome of mRS score at 90 days (adjusted cOR, 0.99 [95% CI, 0.77–1.27]; $P$=0.93).[5] Several meta-analyses, including these trials and other smaller RCTs, all demonstrated a reduction in infection but no change in functional outcome.[11,14,15]
3. Bladder dysfunction, including urinary incontinence, voiding difficulties, and impaired awareness of bladder needs, is common after stroke, with estimates exceeding one-third of patients in the acute period.[16,17] Both urinary incontinence and indwelling bladder catheters are strong independent risk factors for poor outcome at 3 months.[18,19] UTIs may occur in up to 15% of patients after acute stroke.[20,21] Catheter-associated infections remain particularly common in hospitalized patients despite being classified by the Centers for Medicare & Medicaid Services (CMS) as a preventable condition. Although data specific to poststroke patients are limited, given the prevalence of UTIs (especially catheter-associated UTIs) in hospitalized patients as well as the association of indwelling catheters with poor outcome after acute stroke,[6] avoidance or judicious early removal of indwelling catheters is recommended.

## 5.7. Rehabilitation

| Recommendations for Rehabilitation<br>Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | A | 1. In patients with AIS, in-hospital, formal, interdisciplinary assessment and provision of rehabilitation at a level appropriate for the individual patient is recommended to improve functional recovery.[1] |
| 3: No Benefit | A | 2. In patients with AIS, SSRIs are not effective for improving motor recovery or functional status.[2–5] |
| 3: Harm | B-R | 3. In patients with AIS, high-dose, very early mobilization within 24 hours of stroke onset is not recommended to improve the odds of a favorable outcome at 3 months and may be harmful.[6–8] |

### *Synopsis*

Globally, stroke is a leading cause of long-term disability, and although some patients achieve meaningful recovery, many do not regain independent function. In the United States, more than two-thirds of patients receive post-stroke rehabilitation services after hospital discharge.[9] Patients with stroke have highly variable degrees of impairment and a diverse range of individualized needs. A comprehensive and multidisciplinary program designed to assess the appropriate intensity and modality of rehabilitation is thus critical for optimizing recovery after stroke. A dedicated and detailed review of best clinical practices in stroke rehabilitation, including postdischarge care, can be found in the AHA adult stroke rehabilitation and recovery guideline.[10] In-hospital interdisciplinary evaluation for the appropriate level of rehabilitation after stroke is associated with improved functional outcomes.[1] However, very early (<24 hours after stroke onset) mobilization has not been shown to provide functional benefit, and high doses resulted in worse outcomes in 1 RCT.[8]

Multiple adjunctive pharmacological and nonpharmacological therapies have been studied to improve rehabilitation and recovery after stroke. Early administration of SSRIs after stroke has been studied extensively but has not shown benefit in improving functional outcomes in patients without depressive symptoms.

### *Recommendation-Specific Supportive Text*

1. Patients with AIS admitted to organized inpatient stroke units, most of which include interdisciplinary assessments of rehabilitation, are more likely to be independent and live at home. Inpatient rehabilitation after AIS (especially when initiated within 3 days of admission) has been shown to improve activities of daily living.[11] Multiple guidelines support multidisciplinary inpatient evaluation for the appropriate level of rehabilitation after stroke,[10,12] and early adherence to these guidelines has been associated with improved functional recovery.[13]
2. For patients with weakness after stroke but without depression, a few small RCTs initially demonstrated benefit of early SSRI administration in conjunction with physical therapy for improving motor recovery.[14] However, several larger RCTs[2–4] and a subsequent meta-analysis did not find a significant difference in functional outcome with fluoxetine as compared with placebo. In a Cochrane systematic review including more than 13 000 participants, there were no significant differences between the treatment and placebo groups for either disability (standardized mean difference, −0.0 [95% CI, −0.05 to 0.05]) or independence (risk ratio, 0.98 [95% CI, 0.93–1.03]).[5] There is evidence supporting decreased risk of developing depression with early initiation of SSRIs; however, this did not alter motor recovery or reduce dependency overall. Additionally, all 3 recent RCTs showed increased risk of bone fractures,[2–4] and 1 also demonstrated a higher risk of falls (20 [3%] versus 7 [1%]; *P*=0.018) and epileptic seizures (10 [2%] versus 2 [<1%]; *P*=0.038) at 6 months with fluoxetine.[3]
3. The AVERT (A Very Early Rehabilitation Trial) RCT compared high-dose, very early mobilization with standard-of-care mobility.[8] High-dose mobilization protocol interventions included the following: mobilization was initiated within 24 hours of stroke onset, whereas usual care typically was 24 hours after the onset of stroke; there was a focus on sitting, standing, and walking activity in the intervention arm; and there were at least 3 additional out-of-bed sessions compared with usual care. Favorable outcome at 3 months after stroke was defined as an mRS score of 0 to 2. A total of 2104 patients were randomly assigned (1:1). The results of this RCT showed that patients in the high-dose, very early mobilization group had less favorable outcomes (46% versus 50%; adjusted OR, 0.73 [95% CI, 0.59–0.90]; *P*=0.004) than those in the usual care group: 8% versus 7% of patients died in the very early mobilization group, and 19% versus 20% had a nonfatal serious adverse event with high-dose, very early mobilization. A meta-analysis including AVERT and several other very small RCTs did not show benefit in functional outcome with very early mobilization after stroke.[6]

## Knowledge Gaps and Future Research

- Although challenging to study, the optimal in-hospital dose, frequency, and timing of rehabilitation initiation after stroke are unclear and warrant further investigation. Data are limited regarding standardized methods for individualized needs assessments based on stroke severity and level of function in the inpatient setting.
- Using wearable forms of technology, including accelerometers, virtual reality, activity monitors, and pressure sensors in conjunction with machine learning may help patients and clinicians optimize movements and







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refine the classification of appropriate therapy level after disabling stroke.
- Research outcomes for in-hospital stroke rehabilitation have largely focused on motor recovery, functional outcomes, and death. Other outcome measures affecting dependence and disability should be considered, including those surrounding cognition, communication, and quality of life.

## 6. IN-HOSPITAL MANAGEMENT OF AIS: TREATMENT OF ACUTE COMPLICATIONS

### 6.1. Brain Swelling (General Recommendations)

**Recommendations for Brain Swelling (General Recommendations) Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 1 | C-EO | 1. In patients with large cerebral or cerebellar infarctions at high risk for developing brain swelling and herniation, an early discussion of care options and possible outcomes should take place with patients (if feasible) and family or next of kin to ascertain patient-centered preferences in shared decision-making, especially during prognosis formation and when considering interventions or limitations in care. |
| 1 | C-EO | 2. In patients with large cerebral or cerebellar infarctions, close monitoring of the patient for signs of neurological worsening during the first days after stroke is recommended to rapidly evaluate the need for potential interventions. |
| 1 | C-LD | 3. In patients with large cerebral or cerebellar infarctions who are at increased risk for malignant brain swelling, early transfer to an institution with appropriate neurosurgical and critical care expertise is recommended to ensure timely treatment.[1] |

#### *Synopsis*

Brain swelling after ischemic stroke is a severe and life-threatening complication. It is more likely to occur within the first week from stroke in patients with large cerebral and cerebellar infarcts. Therefore, early discussion of care options and neurological monitoring in a facility with neurosurgical and critical care expertise is recommended.

#### *Recommendation-Specific Supportive Text*

1. Brain swelling in patients with large cerebral or cerebellar infarction can cause major and life-threatening complications. Although less severe swelling can be managed medically, decompressive surgery is effective in reducing mortality in cases of severe brain swelling.[2] Nevertheless, there is evidence that persistent morbidity is common. Therefore, a discussion with the patient (or next of kin) about the potential benefit of interventions and the overall prognosis with or without these interventions can help ascertain patient-centered preferences in shared decision-making, especially during prognosis formation and when considering interventions or limitations in care.
2. A substantial proportion of patients with large cerebral or cerebellar infarctions exhibit neurological deterioration from cerebral edema. In 1 study, nearly 70% of neurological deterioration occurred in the first 48 hours from the ischemic stroke, and only 6% occurred on day 6 or afterwards.[3] Therefore, in patients with large cerebral or cerebellar infarctions, close neurological monitoring is crucial in the first few days to detect neurological deterioration from cerebral edema and evaluate the need for potential interventions.
3. In patients with brain swelling due to large hemispheric or cerebellar infarction, decompressive surgery within 48 hours is effective in reducing mortality in cases of severe brain swelling.[2] Additionally, a retrospective study showed that patients who underwent decompressive craniectomy beyond 72 hours (compared with within 48 hours) had increased odds of poor outcome at discharge.[4] Therefore, it is recommended that patients with large cerebral or cerebellar infarctions at risk of malignant brain swelling be cared for at an institution with neurosurgical and critical care expertise.

#### Knowledge Gaps and Future Research

- Identifying the group of patients at risk of brain swelling who may benefit from transfer to facilities with neurosurgical and critical care expertise is essential.
- The optimal duration of intensive neurological monitoring in patients at risk for brain swelling needs to be determined.

### 6.2. Brain Swelling (Medical Management)

**Recommendations for Brain Swelling (Medical Management) Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | C-LD | 1. In patients with large cerebral or cerebellar infarctions and neurological decline from brain swelling, the use of osmotic therapy as a bridge to a surgical intervention is reasonable to improve functional outcome and reduce mortality. |
| 3: No Benefit | B-R | 2. In patients with large hemispheric infarction 18 to 70 years of age, the use of IV glibenclamide does not result in improved functional outcome and is not recommended.[1] |
| 3: Harm | C-LD | 3. In patients with large cerebral or cerebellar infarctions and brain swelling, hypothermia, barbiturates, or corticosteroids should not be administered to treat brain swelling due to the lack of evidence of efficacy and potential of increased adverse effects. |

### *Synopsis*

Medical management is an important aspect of the treatment of brain swelling in patients with large cerebral or cerebellar infarcts and is often a bridge to more definitive neurosurgical treatments.

### *Recommendation-Specific Supportive Text*

1. Several nonrandomized studies in patients with cerebral edema from large ischemic or other causes have shown that the use of osmotic therapy (mannitol or hypertonic saline) was associated with a reduction in intracranial pressure.[2–6]
2. The IV glibenclamide for cerebral edema after large hemispheric stroke (CHARM) trial[1] randomized 535 patients with AIS ages 18 to 85 years who were at risk for cerebral edema (ASPECTS score of 1–5 or infarct core 80–300 mL on CT perfusion or MRI) to IV glibenclamide versus placebo. The trial showed that IV glibenclamide did not improve mRS score at 90 days using shift analysis (cOR, 1.17 [95% CI, 0.80–1.71]; *P*=0.42) or 90-day mortality (hazard ratio, 1.20 [95% CI, 0.85–1.70]; *P*=0.30).
3. There are limited data on the use of barbiturates, hypothermia, or corticosteroids to treat brain swelling in patients with large cerebral or cerebellar infarctions. A meta-analysis of 6 RCTs demonstrated that the use of hypothermia as a neuroprotectant agent in patients with ischemic stroke was not associated with improved functional outcome but increased odds of pneumonia.[7] A single arm retrospective study of 60 patients treated with barbiturate therapy for increased intracranial pressure due to large hemispheric infarcts showed a reduction of intracranial pressure in nearly 80% of patients, but only 6% of patients survived. Adverse effects include hypotension requiring pressors in 33% of patients and pneumonia in 17% of patients.[8] Further trials are necessary to evaluate the safety and efficacy of these interventions. Several studies investigating conventional or large doses of corticosteroids in patients with ischemic stroke showed no clinical benefit but increased infectious complications.[9–12]

## Knowledge Gaps and Future Directions

- A comparison of the safety and efficacy of mannitol and hypertonic saline in patients with brain swelling is required.
- The optimal duration of brief hyperventilation in patients with brain swelling should be determined.

## 6.3. Supratentorial Infarction (Surgical Management)

**Recommendations for Supratentorial Infarction (Surgical Management) Referenced studies that support the recommendations are summarized in the online data supplement.**

| COR | LOE | Recommendations |
|---|---|---|
| 2a | B-NR | 1. In patients with large territorial cerebral infarctions at high risk for developing brain swelling and herniation, decreased level of consciousness attributed to brain swelling is a reasonable trigger for decompressive hemicraniectomy selection.[1] |
| 1 | A | 2. In patients ≤60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours from brain swelling despite medical therapy, decompressive craniectomy with dural expansion is beneficial to reduce mortality and improve functional outcome.[2–6] |
| 2b | B-R | 3. In patients >60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours from brain swelling despite medical therapy, decompressive craniectomy with dural expansion may be considered to reduce mortality.[3,7–9] |
| 2b | B-NR | 4. In patients with AIS who received IV tPA thrombolysis and develop malignant cerebral edema despite medical therapy, early decompressive craniectomy within 48 hours may still be considered without additional safety concerns.[10,11] |

### *Synopsis*

Malignant cerebral edema after unilateral MCA infarctions carries significant morbidity and mortality rates, severely impacting patient functional outcomes. A plethora of RCTs (Decompressive Craniectomy in Malignant Middle Cerebral Artery Infarction [DECIMAL], Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery [DESTINY], Hemicraniectomy after Middle Cerebral Artery Infarction with Life-threatening Edema Trial [HAMLET], Hemicraniectomy and Durotomy Upon Deterioration From Infarction-Related Swelling Trial [HeADDFIRST], and Hemicraniectomy for Malignant Middle cerebral Artery Infarction [HeMMI]) have established that early surgical decompression within 48 hours results in a statistically significant benefit of survival and functional recovery in 12 months for patients ≤60 years of age.[2–6] However, in the >60 years of age group, early surgical decompression failed to show improvement in functional outcomes, despite the statistically significant survival benefit.[7] The positive effect of early decompression remains, despite administration of IV tPA.[11] Although the optimal trigger







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for patient surgical selection has not been well-established, a decrease in level of consciousness compared with baseline has been used in most of these studies. Unlike elective craniotomy procedures, decompression for malignant cerebral edema in patients with AIS is most beneficial without tight dural closure. An open dural closure with expansion has been associated with more efficient procedures, lower complications, and similar rates of infection and cerebrospinal fluid (CSF) leaks.[12]

### *Recommendation-Specific Supportive Text*

1. The pooled results and analysis of several RCTs investigating early decompressive craniectomy versus medical management of cerebral edema after MCA infarction demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction.[1] The trigger for decompression in these trials included an observation of decreased level of consciousness, although this was not the primary clinical factor of randomization.
2. Surgical decompression within 48 hours after cerebral ischemia with malignant edema has been established as standard of care based on earlier European RCTs, DECIMAL, DESTINY, and HAMLET.[2–4] Subsequently, the HeADDFIRST, Slezins, and HeMMI RCTs confirmed prior findings.[5,6] The pooled results of the first 3 RCTs demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction in patients <60 years of age, with an absolute risk reduction in mortality of 50% (95% CI, 34–66) at 12 months.[1] At 12 months, moderate disability or better (mRS score, 2 or 3) was achieved in 43% (22/51) of the surgical group and 55% (22/40) of survivors compared with 21% of the total medical group and 75% of the medical survivors. Subsequently, several systematic reviews and meta-analyses confirmed that early surgical decompression led to a considerable reduction in death and severe disability and a reduction of moderate disability.[13–15] A recent systematic review and meta-analysis of 4 studies and 368 patients showed a reduced likelihood of complications and procedural duration in the open-dura group with no higher incidence of CSF leak or infections.[12]
3. Based on the aforementioned RCTs, patients >60 years of age can have an almost 2-fold reduction in mortality (76% in the nonsurgical group versus 42% in the surgical group in DESTINY II) when decompressive craniectomy for malignant MCA infarction is performed within 48 hours of stroke onset. However, functional outcomes in older adult patients seem to be worse in this age group. At 12 months, moderate disability (mRS score, 3) was achieved in 6% of the total surgical group and 11% of survivors compared with 5% of the total medical group and 20% of the medical survivors. At 12 months, independence (mRS score, ≤2) was not achieved by any survivors in either group.[3] Subsequently, a systematic review and meta-analysis of 9 RCTs and 425 patients included new studies, such as ZHAO/DESTINY II/Li, and showed that in the >60-year-old patient group, surgical decompression within 48 hours led to a statistically significant increase in survival rate yet failed to show statistical significance in favorable functional recovery.[7–9]
4. A post-hoc analysis of the ENCHANTED RCT showed that administration of IV tPA at different dosages did not affect patient outcome or mortality; therefore, there was no associated increased risk with surgery.[10] In addition, a systematic review of 4 studies (98 patients) who underwent decompressive surgery for malignant edema due to ischemic stroke showed that IV tPA did not affect mortality, functional outcome, or minor and major hemorrhagic complications, providing evidence that surgical decompression is still a viable option in these patients.[11]

## Knowledge Gaps and Future Research

- Future research is needed regarding the role of early surgical decompression in improving functional outcome in patients >60 years old with malignant edema from cerebral ischemia.
- Lack of high-level evidence exists to determine whether radiographic changes versus clinical deterioration are optimal triggers for decompressive craniectomy.
- Future research is required to determine the role of surgical decompression in patients with extensive cerebral edema after AIS due to carotid occlusions, those with HT of ischemic stroke, and in patients on antiplatelet medications for indications such as recently placed stents.
- Researchers should investigate the combination of medical osmotic therapy with surgical decompression.

## 6.4. Cerebellar Infarction (Surgical Management)

| Recommendations for Cerebellar Infarction (Surgical Management) Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | C-LD | 1. In patients with cerebellar infarction and obstructive hydrocephalus, ventriculostomy is recommended to improve neurological function and decrease mortality. Concomitant or subsequent decompressive craniectomy may or may not be necessary on the basis of factors such as the size of the infarction, neurological condition, degree of brainstem compression, and effectiveness of medical management.[1–3] |
| 1 | B-NR | 2. In patients with cerebellar infarction causing neurological deterioration from brainstem compression or volumes ≥35 mL, decompressive suboccipital craniectomy with dural expansion should be performed to improve outcomes and decrease mortality.[1–7] |

### *Synopsis*

Cerebellar infarction can result in cerebellar edema, which may cause mass effect on the fourth ventricle, leading to obstructive hydrocephalus and subsequent brainstem compression. Size and location of the infarct are related to the magnitude of mass effect. Treatment of symptomatic hydrocephalus or brainstem compression through surgical interventions such as CSF diversion or decompressive craniectomy can decrease mortality, and these conditions must be identified early with rapid surgical consultation, which may require early transfer.[1–4,8]

### *Recommendation-Specific Supportive Text*

1. Ventriculostomy is a well-recognized effective treatment for the management of acute obstructive hydrocephalus and is often effective in isolation in relieving symptoms, even among patients with acute cerebellar infarction.[1,2] Thus, in patients who develop symptoms of obstructive hydrocephalus from cerebellar infarction, emergency ventriculostomy is a reasonable first step in the surgical management paradigm. If CSF diversion by ventriculostomy fails to improve neurological function, decompressive suboccipital craniectomy should be performed.[1–3] Although a risk of upward herniation exists with ventriculostomy alone, it can be minimized with conservative CSF drainage or subsequent decompression if the cerebellar infarction causes significant swelling and mass effect.[1,2]
2. The data support decompressive cerebellar craniectomy for the management of acute ischemic cerebellar stroke with mass effect.[1–3] This surgery is indicated as a therapeutic intervention in cases of neurological deterioration caused by swelling as a result of cerebellar infarction that cannot be otherwise managed with medical therapy or ventriculostomy in the setting of obstructive hydrocephalus.[1,2] Surgical therapy led to significant differences in mortality and functional outcomes in patients with severe disease.[8] In patients with cerebellar infarct volumes of 35 mL or greater, surgical treatment was associated with a significant improvement in favorable outcomes at 1-year follow-up.[4] Furthermore, in 1 retrospective multicenter study, patients treated with necrosectomy (eg, resection of necrotic ischemic tissue) had better functional outcomes than those patients who underwent decompressive craniectomy alone (65.3% versus 27.9%, respectively; $P<0.001$).[7]

### Knowledge Gaps and Future Research

- Currently, there is no universal definition of swelling and/or infarct volume(s) available to support a decision for surgery. This varies by study.
- CSF diversion by external ventricular drainage is considered medical management in some studies and surgical intervention in others, making it difficult to define outcomes after "surgical" treatment broadly across studies.
- There are no rigorous studies that examine surgical technique, including size and location of craniectomy, use of expansile duraplasty versus dural substitute.

## 6.5. Seizures

| Recommendations for Seizures Referenced studies that support the recommendations are summarized in the online data supplement. | | |
|---|---|---|
| **COR** | **LOE** | **Recommendations** |
| 1 | C-LD | 1. In adult patients with an unprovoked seizure after AIS, management that includes antiseizure medication is recommended on the basis of specific patient characteristics to reduce the risk of seizure recurrence. |
| 3: No Benefit | C-LD | 2. In adult patients with AIS, prophylactic treatment with antiseizure medication is not recommended to prevent seizures or improve functional outcome.[1,2] |

### *Synopsis*

Ischemic stroke increases the risk of seizure, which can occur early within the first week or later as an unprovoked poststroke seizure.[3] Poststroke seizure is associated with an increased risk of mortality and disability.[4] There are insufficient data to inform the pharmacological management of early seizures or recommend the routine use of EEG for monitoring during







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acute hospitalization. Risk factors for an unprovoked poststroke seizure include early seizure, stroke severity, and cortical involvement.[5] Antiseizure medication is reasonable to initiate after an unprovoked poststroke seizure, with medication choice and duration dependent on patient-specific factors.

### *Recommendation-Specific Supportive Text*

1. Given the lack of high-quality evidence to support specific antiseizure medication choice, the selection should be based on patient-specific factors that include potential for drug interactions and adverse effects. The duration of antiseizure medication therapy should be individualized to each patient. Considerations to guide the duration of therapy include the length of seizure freedom, the severity of seizure, and the presence and/or severity of adverse effects from the medication.
2. There is insufficient evidence to evaluate the effectiveness of prophylactic antiseizure medication to prevent poststroke seizure or improve functional recovery after stroke. A prospective randomized, placebo-controlled trial that evaluated levetiracetam for preventing poststroke seizures was terminated early due to lack of enrollment.[1] Another randomized, placebo-controlled trial tested the efficacy of diazepam on functional recovery at 3 months[2] and was negative for the primary outcome. Seizure frequency was a secondary endpoint in that trial, with post-hoc analysis reporting a lower rate of seizure with diazepam but only in the subgroup of patients with anterior circulation stroke with cortical involvement.[6]

## Knowledge Gaps and Future Research

- Seizures are reported to alter metabolic homeostasis in the brain, but it is unknown whether preventing early seizures during acute ischemia can preserve brain tissue and/or improve functional recovery.
- For unprovoked seizures that occur after the acute ischemic period, the comparative effectiveness of different antiseizure medications and the appropriate duration of therapy are unknown.
- The role for prophylactic antiseizure medications may be different in children because of their higher risk of seizures and needs to be studied.

## AHA/ASA STROKE COUNCIL'S SCIENTIFIC STATEMENTS OVERSIGHT COMMITTEE

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## ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel. Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on October 21, 2025, and the American Heart Association Executive Committee on December 8, 2025. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 215-356-2721 or email Meredith.Edelman@wolterskluwer.com

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*Stroke Council Scientific Statements Oversight Committee Member at guideline initiation. Term ended July 2025.

**Appendix 1. Guideline Writing Group Relationships With Industry and Other Entities (Relevant)**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| **Category A–**Chair cannot have ANY relevant relationships (modest or significant) in the categories of ownership interest, equity interest, royalty income, stock, stock options speaker's bureau, honoraria, expert witness, consultant/advisory board, or relevant research support from industry. Research funded by federal sources or not-for-profits is allowed on a case by case basis. The appropriate oversight committee (eg, Guideline Task Force or Manuscript Oversight Committee) will review and evaluate the relationship. Government-sponsored or university managed DSMB allowed. Vice Chair can have modest or significant RWI in the categories of speakers' bureau, honoraria, consultant/advisory board, and expert witness. SIGNIFICANT relationships in category of personal investments (equity interest, royalty income, ownership, stock, stock options) are not allowed; modest RWI in this category is allowed). | | | | | | | | |
| Shyam Prabhakaran, Chair | The University of Chicago Medicine | None | None | None | None | None | None | None |
| Nestor Gonzalez, Vice Chair | Cedars-Sinai Medical Center | None | None | None | None | None | None | None |
| Kori Zachrison, Vice Chair | Massachusetts General Hospital | None | None | None | None | None | None | None |
| A majority of the writing group members must be free of a conflict in any category (modest or significant); if there is an even number of writing group members, at least 50% + 1 must be free of any conflicts. | | | | | | | | |
| **Category B (WG Members Who Have No Conflicts)** | | | | | | | | |
| Anne Alexandrov | University of Tennessee Health Science Center | None | None | None | None | None | None | None |
| Sherita Chapman | University of Virginia | None | None | None | None | None | None | None |
| Alexandra Czap | McGovern Medical School at UT Health | None | None | None | None | None | None | None |
| Oana Dumitrascu | Mayo Clinic | None | None | None | None | None | None | None |
| Karen Johnston | University of Virginia School of Medicine | None | None | None | None | None | None | None |
| Vivien Lee | The Ohio State University | None | None | None | None | None | None | None |
| Thabele Leslie-Mazwi | University of Washington | None | None | None | None | None | None | None |
| Brian Mac Grory | Duke University School of Medicine | None | None | None | None | None | None | None |
| Tracy Madsen (*SAEM* rep) | Brown University | None | None | None | None | None | None | None |
| Soojin Park (*NCS* rep) | Columbia University | None | None | None | None | None | None | None |
| Stephanie Parker | UT Health | None | None | None | None | None | None | None |
| Natalia Pérez de la Ossa | Hospital de la Santa Creu i Sant Pau (Spain); Universidad Autónoma de Barcelona (Spain) | None | None | None | None | None | None | None |
| Mathew Reeves | Michigan State University | None | None | None | None | None | None | None |
| Tania Saiz | Patient Representative | None | None | None | None | None | None | None |
| Dana Schwartzberg | Patient Representative | None | None | None | None | None | None | None |
| Phillip A. Scott | University of Michigan | None | None | None | None | None | None | None |
| Peter B. Sporns | Northwestern University | None | None | None | None | None | None | None |
| Sabrina Times | American Heart Association | None | None | None | None | None | None | None |
| Stacey Wolfe | Wake Forest School of Medicine | None | None | None | None | None | None | None |
| Shadi Yaghi | Brown University; Jersey Shore University Medical Center | None | None | None | None | None | None | None |
| **Category C (WG Members Who Have Conflicts)** | | | | | | | | |
| Opeolu Adeoye | Washington University School of Medicine in St. Louis | None | None | None | None | Sense Diagnostics† | None | None |
| Sameer Ansari (*SNIS* rep) | Northwestern University | None | None | None | None | Clearvoya† | Hyperfine Research† | None |
| Koto Ishida (*AAN* rep) | NYU Langone Health | None | None | None | None | None | Terumo Medical Corporation* | None |

(*Continued*)







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**Appendix 1. Continued**

| Writing group member | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Ashutosh Jadhav *(SVIN* rep) | St. Joseph's Hospital and Medical Center; HonorHealth Research Institute | None | None | None | None | Gravity Medical Technology* | Basking Biosciences*; Johnson and Johnson* | None |
| Brenda Johnson | Johns Hopkins Hospital | None | None | None | None | None | Genentech† | None |
| W. Taylor Kimberly | Massachusetts General Hospital | Hyperfine Research† | None | None | None | None | Astrocyte Pharmaceuticals† Ji Xing Pharmaceuticals* Remedy Pharmaceuticals* | None |
| Pooja Khatri | University of Cincinnati College of Medicine | None | None | None | None | None | Basking Biosciences† | None |
| Bijoy Menon | The University of Calgary (Canada) | None | None | None | None | Circle NVI† | Neurastasis* | None |
| Eva Mistry | University of Cincinnati | None | None | None | None | None | Silver Creek Pharmaceuticals, Inc† | None |
| Sunil Sheth | University of Texas Health | None | None | None | None | Motif Neurosciences* | Imperative Care* Penumbra, Inc.* Viz.AI* | None |
| Stavropoula Tjoumakaris *(AANS/CNS* rep) | Thomas Jefferson University | None | None | None | None | None | MicroVention, Inc.† | None |

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12 months, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest (<$5000).

†Significant (≥$5000).

AAN indicates American Academy of Neurology; AANS/CNS, American Association of Neurological Surgeons/Congress of Neurological Surgeons NCS, Neurocritical Care Society; SAEM, Society for Academic Emergency Medicine; SNIS, Society of NeuroInterventional Surgery; SOC, Stroke Oversight Committee; and SVIN, Society of Vascular and Interventional Neurology.

**Appendix 2. Peer Review Committee Relationships With Industry and Other Entities (Comprehensive)**

| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Enrique C. Leira, Chair | University of Iowa | ASA† | None | None | None | None | None | Fundacio de Recerca Clinic Barcelona-Institut d'Imvestigacions Biomediques August Pi i Sunyer (End Point Review Committee)* Patent – WO2005046758 A2* NIH NINDS (Freeox Biotech trial PI)* |
| Joseph P. Broderick, Vice Chair | University of Cincinnati | NIH NINDS† Genentech (institution)* | Novo Nordisk† | None | None | None | Basking BioScience (consultant)* Brainsgate (consultant)* Kroger Prescription Plans, Inc (consultant)* F. Hoffmann-La Roche (consultant)* | None |
| Antonio Arauz | Instituto Nacional de Neurología y Neurocirugía Manuel Velasco Suárez (Mexico) | None | None | None | None | None | None | None |
| Agnieszka Ardelt | MetroHealth | None | None | None | None | None | None | None |
| Mona Bahouth (*SOC* liaison) | Johns Hopkins School of Medicine | None | None | None | None | None | None | None |
| Anna Finley Caulfield (NCS rep) | Stanford University | None | None | None | None | None | None | None |
| Layne Dylla (*SAEM* rep) | Yale School of Medicine | TET Medical† | None | None | None | None | None | None |
| Colin P. Derdeyn | University of Virginia | University of Virginia | None | None | None | None | Euphrates Vascular (stock)* | Prenumbra, Inc. (DSMB)† Siemens Healthcare (travel)† Basking BioSciences (DSMB)* |
| Michael Frankel | Emory University | None | None | None | Frankel & Solloum, PLLC† Scrudder, Bass, Quillian, Horlock, Lazarus, & Adele LLP (Medical malpractice defense case)† | None | None | None |
| Heather J. Fullerton | University of California, San Francisco | NIH NINDS† AHA/Bugher | None | None | None | None | Bayer (consultant on clinical trial design) Genentech/Roche (consultant on clinical trial design) | None |
| Waldo Guerrero (*SVIN* rep) | University of South Florida | None | None | None | None | None | None | None |

(*Continued*)







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**Appendix 2. Continued**

| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Edward C. Jauch | MAHEC/ University of North Carolina Health Sciences | None | None | None | Medical Malpractice (stroke care case)* | None | Rapid.AI (imaging consultant)*<br>Medtronic (panel discussion ISC)*<br>HCA Healthcare† | None |
| Kimberly P. Kicielinski | Medical University of South Carolina | None | None | None | None | None | None | Elsevier (Editor-in-Chief)† |
| Yvonne Labram (Lay rep) | AHA Patient Ambassador | None | None | None | None | None | None | None |
| Patrick Lyden | University of Southern California | None | None | Boehringer International† | None | None | Apex Innovations (Consultant)* | None |
| Elisabeth B. Marsh | Johns Hopkins School of Medicine | NIH†<br>AHA† | None | None | None | None | None | AHA (Stroke Editorial Board)*<br>ANA (Associate Editor & Board of Directors)*<br>AAN (Quality Committee)* |
| William J. Meurer | University of Michigan | | | | | | | |
| J. Mocco | Icahn School of Medicine at Mount Sinai | MicroVention, Inc. (PI)*<br>PCORI (Institution)†<br>Penumbra, Inc. (PI)*<br>Stryker (PI)* | None | None | None | Blinktbi (Stock)†<br>Borvo (stock)*<br>Cerebrotech (Stock)*<br>CVAid (Equity)*<br>E8(Stock)*<br>Echovaten (Stock)*<br>Endostream (Stock)†<br>Imperative Care, Inc (Stock)†<br>Neurolutions (Stock)*<br>NTI Managers (Stock)*<br>Perflow (Consultant/ Equity)*<br>Q'Apel (Stock)†<br>Radical (Stock)*<br>Sim&Cure (Stock)*<br>Songbird (Stock)*<br>Spinaker (Stock)†<br>Tulavi (Stock)*<br>Vastrax (Stock)†<br>Viseon, Inc. (Stock)†<br>Viz.ai (Stock)†<br>Whisper (Stock)* | Synchron (Consultant-CMO)*<br>Perflow (Consultant/ Equity)* | None |

(*Continued*)

**Appendix 2. Continued**

| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Aditya Pandey (*AANS/CNS* rep) | University of Michigan | NIH NINDS† Medtronic (Institution)† | None | None | None | FlexDex Surgical (stock) † NextGen Biologics (stock) † | None | Patent (Histotripsy tech)* |
| Alejandro A. Rabinstein | Mayo Clinic | None | None | None | None | None | AstraZeneca (consultant)* Chiesi Farmaceutici (consultant)† Shionogi Inc (consultant)* | NCS (Neurocritical Care Associate Editor)† AMA (JAMA Open Associate Editor)† Boston Scientific Corporation (End Point Review Committee)† Wolters Kluwer Health, Inc. (UpToDate Section Editor)† |
| Karen Rapp | University of California, San Diego | NIH† | None | None | None | None | None | None |
| Christopher T. Richards | University of Cincinnati | NIH NINDS† | None | None | None | None | ASH (consultant; educational sessions, Spouse)† CE Synergy (Consultant, Ad board or educational session, Spouse)* Duke University (Consultant, Educational sessions, Spouse)* Health Resources in Action (Consultant, Ad board or educational session, Spouse)* Innovative Healthcare Institute LLC (Consultant, Ad board or educational session, Spouse)* Interactive Forums, Inc (Consultant, Ad board or educational session, Spouse)* Prehospital Guidelines Consortium (Consultant, Commissioned systematic review, Self)* | None |
| Marcelo Rocha | University of Pittsburgh | NIH NINDS† | None | None | None | None | None | ANA (Assistant Editor)* |
| Regina Royan | University of Michigan | None | None | None | None | None | AMA (consultant)† | None |
| Edgar A. Samaniego | University of Iowa | None | None | None | None | None | iSchemaView* Johnson & Johnson† Medtronic† MicroVention† Rapid Medical† | None |
| Navdeep S. Sangha (*AAN* rep) | Kaiser Permanente Southern California Permanente Group | None | None | None | None | None | None | None |

(*Continued*)







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**Appendix 2. Continued**

| Peer reviewer | Employment | Research grant | Other research support | Speakers' bureau/ honoraria | Expert witness | Ownership interest | Consultant/ advisory board | Other |
|---|---|---|---|---|---|---|---|---|
| Clemens Schirmer (*SNIS* rep) | Geisinger Comprehensive Stroke Centers | Balt USA, LLC (STEM clinical trial)† Cerenovus† Medtronic Vascular, Inc. (EMBOLISE, INSPIRE, ELEVATE clinical trials)† Microvention† MIVI Neuroscience (Evaq clinical trial)† NIH* Prenumbra, Inc.† Route 92 Medical, Inc.† Stryker Corporation* | None | Werfen USA LLC* | None | Neurotechnology Investors* REIST (investment club)† | Balt USA, LLC (consultant)† Medtronic Vascular, Inc. (consultant)† Microvention, Inc* Stryker Corporation (consultant)* Viz.AI* | None |
| Alexis N. Simpkins | Cedars-Sinai Medical Center | Cedars-Sinai Medical Center† NIH† Bristol-Myers Squibb Foundation (award)† | None | None | None | None | NIH NINDS (DSMB)* | ASA (Stroke Special Section Co-Editor)* Stroke: Vascular and Interventional Neurology (Associate Editor)* UpToDate* eNeurologicalScience (Assistant Editor)* Genetics and Omics of Stroke for Frontiers Neurology (Review Editor)* JACC Advances (Editorial Consultant)* AAN (Leadership Alumni Newsletter Associate Editor)* Journal of Neuroimaging (Editorial Board Member)* Neurology (Editorial Board Member)* |
| Christopher Streib | University of Minnesota | NIH† | None | None | None | None | None | None |
| David Tirschwell | University of Washington | NIH† | None | None | None | None | None | None |
| Elizabeth Zink | Johns Hopkins Hospital | None | None | None | None | None | None | None |



This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $5000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $5000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest (<$5000).

†Significant (≥$5000).

AAN indicates American Academy of Neurology; AANS/CNS, American Association of Neurological Surgeons/Congress of Neurological Surgeons; AHA, American Heart Association; AMA, American Medical Association; ANA, American Neurological Association; ASH, American Society of Hematology; NCS, Neurocritical Care Society; NIH, National Institutes of Health; NINDS, National Institute of Neurological Disorders and Stroke, SAEM, Society for Academic Emergency Medicine; SNIS, Society of NeuroInterventional Surgery; SOC, Stroke Oversight Committee; and SVIN, Society of Vascular and Interventional Neurology.

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## 4.6. IV Thrombolytics

### 4.6.1. Thrombolysis Decision-Making

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### 4.6.2. Choice of Thrombolytic Agent

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## 4.7. Endovascular Thrombectomy

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### 4.7.5. Endovascular Thrombectomy in Pediatric Patients

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## 6. In-Hospital Management of AIS: Treatment of Acute Complications

### 6.1. Brain Swelling (General Recommendations)

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### 6.5. Seizures


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