JAMA Clinical Guidelines Synopsis

Management of Patients With Acute Ischemic Stroke

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GUIDELINE TITLE 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke

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PRIOR VERSION 2013

DEVELOPER American Heart Association (AHA)/American Stroke Association (ASA)

FUNDING SOURCE AHA/ASA

TARGET POPULATION Adult patients with acute arterial ischemic stroke

MAJOR RECOMMENDATIONS

- Regional systems of stroke care should be developed that include health care facilities providing initial emergency care and those capable of endovascular stroke treatment, to which rapid transport can be arranged when appropriate (high-quality evidence; strong recommendation).
- Intravenous alteplase is recommended for patients meeting detailed eligibility requirements within 3 hours of ischemic stroke onset (high-quality evidence; strong recommendation) and between 3 and 4.5 hours of ischemic stroke onset (moderate-quality evidence; strong recommendation).
- Mechanical thrombectomy with a stent retriever is recommended for patients with a causative occlusion of the internal carotid artery or proximal middle cerebral artery with at least moderately severe presenting stroke deficits (National Institutes of Health Stroke Scale [NIHSS] score ≥6) and absence of evidence of widespread established infarction on brain imaging, when endovascular treatment can be initiated within 6 hours of symptom onset (high-quality evidence; strong recommendation).
- Mechanical thrombectomy with a stent retriever is also recommended for certain acute ischemic stroke (AIS) patients presenting at later times (moderate- to high-quality evidence; strong recommendation).

Summary of the Clinical Problem

Acute stroke is a time-critical clinical condition and a leading cause of long-term disability. There has been rapid progress in the treatment of AIS recently, with high-quality clinical evidence from randomized trials providing support for endovascular interventions. Much of this evidence has come since the publication of previous AIS management guidelines by the AHA in 2013.

Characteristics of the Guideline Source

These guidelines were developed by a writing group appointed by the AHA Stroke Council's Scientific Statements Oversight Committee, relying on systematic review of identified clinical questions by an independent evidence review committee (**Table**).[1] The recommendations were approved by the full writing group and reviewed prior to release by 4 external reviewers and by the Stroke Council Leadership Committee. Members of the writing group were required to disclose conflicts of interest and to recuse themselves from discussions or votes on related topics. The AHA/ASA, the funding source for the guideline, is partly supported by contributions from pharmaceutical companies and medical device manufacturers.

Table. Guideline Rating

Standard	Rating
Establishing transparency	Fair
Management of conflict of interest in the guideline development group	Good
Guideline development group composition	Fair
Clinical practice guideline–systematic review intersection	Good
Establishing evidence foundations and rating strength for each of the guideline recommendations	Good
Articulation of recommendations	Good
External review	Fair
Updating	Poor
Implementation issues	Fair

Evidence Base

The guidelines, broadly addressing the treatment of AIS, include more than 100 specific recommendations, each presented with the strength of the recommendation and level of the quality of supporting evidence. Many of the recommendations are unchanged from the previous guidelines and address a number of important details regarding the care of AIS patients. Four recommendations are highlighted herein because they exemplify the broad significance for systems of stroke care or because they represent notable advances in acute stroke management.

Regional systems of stroke care are supported by this guideline and have already been instituted in many areas. These systems are supported by observational data, as randomized trials addressing their efficacy would be difficult, if not impossible. Thus, the supporting quality of evidence is lower than stated in this guideline.

The strong recommendation for treatment of AIS with intravenous alteplase within the first 4.5 hours of stroke symptoms is supported by individual participant data meta-analysis of multiple trials.[2] The benefits of intravenous alteplase are modest in magnitude, with an absolute increase in achievement of disability-free outcome at

90 days of about 13% vs placebo in patients treated within 3 hours of stroke onset, and diminishing benefits at later times.[2]

The guideline strongly recommends use of endovascular thrombectomy (EVT) in treatment of AIS for patients who have occlusion of the internal carotid artery or proximal middle cerebral artery with at least moderately severe presenting stroke deficits (NIHSS score ≥6) and absence of evidence of widespread established infarction on brain imaging. This recommendation applies when endovascular treatment can be initiated within 6 hours of symptom onset. The recommendation is supported by 6 well-designed prospective randomized trials showing benefits of EVT vs conventional care.[3] Meta-analysis of pooled data from 5 of the randomized trials shows reduced disability at 90 days, with a number needed to treat of 2.6 to reduce the modified Rankin score by at least 1 level.[4]

The guideline makes recommendations regarding use of EVT for patients with AIS with a longer interval after symptom onset. For this recommendation, the guideline cites and applies 2 recent major studies (the DAWN and DEFUSE 3 trials) of patients in the greater-than-6-hour time window.[5,6] Patients in these studies had a large mismatch between the extent of brain tissue threatened by ischemia but not yet infarcted and the core infarction (based on advanced imaging). In these trials, EVT was found to be of substantial benefit in improvement in 90-day outcome. Patients for whom this recommendation applies are those presenting in the 6- to 16-hour interval meeting inclusion criteria for either cited trial (class I recommendation) and for patients presenting within 16 to 24 hours of symptom onset meeting the criteria of the DAWN trial (class IIa recommendation).

Benefits and Harms

These guidelines codify elements of AIS treatment in an accessible and well-referenced way that will promote and standardize evidence-based care for stroke. However, the geographical distribution of centers capable of delivering some of the forms of acute stroke care, particularly EVT, is nonuniform, making application of the endovascular intervention components of the guidelines limited. This highlights the challenge of broadly implementing all aspects of these guidelines.

Discussion

These guidelines have generated substantial controversy,[7] much of which concerns the class III (not recommended) designation assigned to routine use of certain diagnostic studies such as brain magnetic resonance imaging and echocardiography. The controversy led to the unusual decision to withdraw substantial portions of these recommendations.[8] The published correction to the guidelines stated that the sponsoring organizations (AHA/ASA) were preparing "clarifications, modifications and/or updates" and promised that a revised guideline would be posted. As of this writing, the revised guideline remains unavailable. This retraction of portions of a document produced through a vetted writing committee and approved by peer reviewers and the AHA's council raises concerns regarding the influence of AHA's stakeholders on the evidence-based, systematically vetted process by which these guidelines were produced, or regarding whether there were other unstated issues with the process itself.

Areas of Future Study or Ongoing Research

Judging from the controversies generated from class III recommendations assigned in the original version of these guidelines, further outcomes-based research is needed to define the benefits of diagnostic tests that are frequently used in evaluation of acute stroke, including brain magnetic resonance imaging, intracranial vascular imaging, and echocardiography, among others. Uncertainty remains about use of alteplase in acute stroke of indefinite duration, and newly reported and future studies will further clarify the appropriate treatment of these patients.[9]

Related guidelines

AHA/ASA Guidelines for the Management of Spontaneous Intracerebral Hemorrhage
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REFERENCES

1. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke. *Stroke*. 2018;49(3):e46-e110. doi:10.1161/STR.0000000000000158

2. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke. *Lancet*. 2010;375(9727):1695-1703. doi:10.1016/S0140-6736(10)60491-6

3. Prabhakaran S, Ruff I, Bernstein RA. Acute stroke intervention. *JAMA*. 2015;313(14):1451-1462. doi:10.1001/jama.2015.3058

4. Goyal M, Menon BK, van Zwam WH, et al. Endovascular thrombectomy after large-vessel ischaemic stroke. *Lancet*. 2016;387(10029):1723-1731. doi:10.1016/S0140-6736(16)00163-X

5. Nogueira RG, Jadhav AP, Haussen DC, et al. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378(1):11-21. doi:10.1056/NEJMoa1706442

6. Albers GW, Marks MP, Kemp S, et al. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378(8):708-718. doi:10.1056/NEJMoa1713973

7. Shaw G. Why reactions from vascular neurologists on the new stroke guidelines are mixed. *Neurol Today*. 2018;18(6):35-37. doi:10.1097/01.NT.0000532094.90952.27

8. Correction to: 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49(6):e233-e234. doi:10.1161/STR.0000000000000172

9. Thomalla G, Simonsen CZ, Boutitie F, et al. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379(7):611-622. doi:10.1056/NEJMoa1804355