

Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Endorsed by the Society for Academic Emergency Medicine and The Neurocritical Care Society

William J. Powers, MD, FAHA, Chair; Alejandro A. Rabinstein, MD, FAHA, Vice Chair; Teri Ackerson, BSN, RN; Opeolu M. Adeoye, MD, MS, FAHA; Nicholas C. Bambakidis, MD, FAHA; Kyra Becker, MD, FAHA; José Biller, MD, FAHA; Michael Brown, MD, MSc; Bart M. Demaerschalk, MD, MSc, FAHA; Brian Hoh, MD, FAHA; Edward C. Jauch, MD, MS, FAHA; Chelsea S. Kidwell, MD, FAHA; Thabele M. Leslie-Mazwi, MD; Bruce Ovbiagele, MD, MSc, MAS, MBA, FAHA; Phillip A. Scott, MD, MBA, FAHA; Kevin N. Sheth, MD, FAHA; Andrew M. Southerland, MD, MSc, FAHA; Deborah V. Summers, MSN, RN, FAHA; David L. Tirschwell, MD, MSc, FAHA; on behalf of the American Heart Association Stroke Council

Background and Purpose—The purpose of these guidelines is to provide an up-to-date comprehensive set of recommendations in a single document for clinicians caring for adult patients with acute arterial ischemic stroke. The intended audiences are prehospital care providers, physicians, allied health professionals, and hospital administrators. These guidelines supersede the 2013 Acute Ischemic Stroke (AIS) Guidelines and are an update of the 2018 AIS Guidelines.

Methods—Members of the writing group were appointed by the American Heart Association (AHA) Stroke Council's Scientific Statements Oversight Committee, representing various areas of medical expertise. Members were not allowed to participate in discussions or to vote on topics relevant to their relations with industry. An update of the 2013 AIS Guidelines was originally published in January 2018. This guideline was approved by the AHA Science Advisory and Coordinating Committee and the AHA Executive Committee. In April 2018, a revision to these guidelines, deleting some recommendations, was published online by the AHA. The writing group was asked review the original document and revise if appropriate. In June 2018, the writing group submitted a document with minor changes and with inclusion of important newly published randomized controlled trials with >100 participants and clinical outcomes at least 90 days after AIS. The document was sent to 14 peer reviewers. The writing group evaluated the peer reviewers' comments and revised when appropriate. The current final document was approved by all members of the writing group except when relationships with industry precluded members from voting and by the governing bodies of the AHA. These guidelines use the American College of Cardiology/AHA 2015 Class of Recommendations and Level of Evidence and the new AHA guidelines format.

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 statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 12, 2019, and the American Heart Association Executive Committee on October 3, 2019. 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 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

The online-only Data Supplements are available with this article at <https://www.ahajournals.org/doi/suppl/10.1161/STR.0000000000000211>.

The American Heart Association requests that this document be cited as follows: Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e000000-e000000. doi: 10.1161/STR.0000000000000211.

The expert peer review of AHA-commissioned documents (eg, scientific statements, clinical practice guidelines, systematic reviews) is conducted by the AHA Office of Science Operations. For more on AHA statements and guidelines development, visit <https://professional.heart.org/statements>. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Permissions: Multiple copies, modification, alteration, enhancement, and/or distribution of this document are not permitted without the express permission of the American Heart Association. Instructions for obtaining permission are located at <https://www.heart.org/permissions>. A link to the "Copyright Permissions Request Form" appears in the second paragraph (<https://www.heart.org/en/about-us/statements-and-policies/copyright-request-form>).

© 2019 American Heart Association, Inc.

Stroke is available at <https://www.ahajournals.org/journal/str>

DOI: 10.1161/STR.0000000000000211

Results—These guidelines detail prehospital care, urgent and emergency evaluation and treatment with intravenous and intra-arterial therapies, and in-hospital management, including secondary prevention measures that are appropriately instituted within the first 2 weeks. The guidelines support the overarching concept of stroke systems of care in both the prehospital and hospital settings.

Conclusions—These guidelines provide general recommendations based on the currently available evidence to guide clinicians caring for adult patients with acute arterial ischemic stroke. In many instances, however, only limited data exist demonstrating the urgent need for continued research on treatment of acute ischemic stroke. (*Stroke*. 2019;50:e•••–e•••. DOI: 10.1161/STR.000000000000211.)

Key Words: AHA Scientific Statements ■ critical care ■ disease management ■ emergency medical services ■ secondary prevention ■ stroke ■ therapeutics

New high-quality evidence has produced major changes in the evidence-based treatment of acute ischemic stroke (AIS) since the publication of the guidelines for the early management of patients with acute ischemic stroke in 2013.¹ Much of this new evidence has been incorporated into American Heart Association (AHA) focused updates, guidelines, or scientific statements on specific topics relating to the management of patients with AIS since 2013. The purpose of these guidelines is to provide an up-to-date comprehensive set of recommendations for clinicians caring for adult patients with acute arterial ischemic stroke in a single document. These guidelines address prehospital care, urgent and emergency evaluation and treatment with intravenous (IV) and intra-arterial therapies, and in-hospital management, including secondary prevention measures that are often begun during the initial hospitalization. We have restricted our recommendations to adults and to secondary prevention measures that are appropriately instituted within the first 2 weeks. We have not included recommendations for cerebral venous sinus thrombosis because these were covered in a 2011 scientific statement and there is no new evidence that would change those conclusions.²

An independent Evidence Review Committee was commissioned to perform a systematic review of a limited number of clinical questions identified in conjunction with the writing group, the results of which were considered by the writing group for incorporation into the “2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke” (2018 AIS Guidelines)^{2a} and this 2019 update. The systematic reviews for the 2018 AIS Guidelines have been previously published.^{3,4}

These guidelines use the American College of Cardiology (ACC)/AHA Class of Recommendations (COR) and Level of Evidence (LOE) format shown in Table 1. New or revised recommendations that supersede previous guideline recommendations are accompanied by 250-word knowledge bytes and data supplement tables summarizing the key studies supporting the recommendations in place of extensive text. These data supplement tables can be found in [Data Supplement 1](#) and literature search information for all data supplement tables can be found in [Data Supplement 2](#). Because this guideline represents an update of the 2018 AIS Guidelines, the term “New Recommendation” refers to recommendations that are new to either the 2018 AIS Guidelines or to this 2019 update. Existing recommendations that are unchanged are reiterated with reference to the previous publication. These previous publications and their abbreviations used in this document are listed in Table 2. When there is no new pertinent evidence

for these unchanged recommendations, no knowledge byte or data supplement is provided. For some unchanged recommendations, there are new pertinent data that support the existing recommendation, and these are provided. Additional abbreviations used in this guideline are listed in Table 3.

Members of the writing committee were appointed by the AHA Stroke Council’s Scientific Statements Oversight Committee, representing various areas of medical expertise. Strict adherence to the AHA conflict-of-interest policy was maintained throughout the writing and consensus process. Members were not allowed to participate in discussions or to vote on topics relevant to their relations with industry. Writing group members accepted topics relevant to their areas of expertise, reviewed the stroke literature with emphasis on publications since the prior guidelines, and drafted recommendations. Draft recommendations and supporting evidence were discussed by the writing group, and the revised recommendations for each topic were reviewed by a designated writing group member. The full writing group then evaluated the complete guidelines. The members of the writing group unanimously approved all recommendations except when relations with industry precluded members voting. Prerelease review of the draft 2018 guidelines was performed by 4 expert peer reviewers and by the members of the Stroke Council’s Scientific Statements Oversight Committee and Stroke Council Leadership Committee. The 2018 AIS Guidelines were approved by the AHA Science Advisory and Coordinating Committee on November 29, 2017, and by the AHA Executive Committee on December 11, 2017. It was published online January 24, 2018. On April 18, 2018, the AHA published a revision to the AIS Guidelines online, deleting 7 specific recommendations and all of Section 6, In-Hospital Institution of Secondary Prevention. The writing group was asked to review the entire guideline, including the deleted recommendations. In June 2018, the writing group submitted a document with minor changes and with inclusion of important newly published randomized controlled trials (RCTs) with >100 participants and clinical outcomes at least 90 days after AIS. The document was sent out to 14 peer reviewers. The writing group evaluated the peer reviewers’ comments and revised when appropriate. This revised document was reviewed by Stroke Council’s Scientific Statements Oversight Committee and the AHA Science Advisory and Coordinating Committee. To allow these guidelines to be as timely as possible, RCTs addressing AIS published between November 2018 and April 2019 were reviewed by the writing group. Modifications of Section 3.5.6., Recommendation 1, Section 3.6., Recommendation 4, and Section 3.7.4., Recommendation 5 resulted. To allow these

Table 1. Applying ACC/AHA Class of Recommendation and Level of Evidence to Clinical Strategies, Interventions, Treatments, or Diagnostic Testing in Patient Care* (Updated August 2015)

| CLASS (STRENGTH) OF RECOMMENDATION | LEVEL (QUALITY) OF EVIDENCE†‡ |
|---|--|
| <p>CLASS I (STRONG) Benefit >>> Risk</p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> Is recommended Is indicated/useful/effective/beneficial Should be performed/administered/other Comparative-Effectiveness Phrases†: <ul style="list-style-type: none"> Treatment/strategy A is recommended/indicated in preference to treatment B Treatment A should be chosen over treatment B | <p>LEVEL A</p> <ul style="list-style-type: none"> High-quality evidence‡ from more than 1 RCT Meta-analyses of high-quality RCTs One or more RCTs corroborated by high-quality registry studies |
| <p>CLASS IIa (MODERATE) Benefit >> Risk</p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> Is reasonable Can be useful/effective/beneficial Comparative-Effectiveness Phrases†: <ul style="list-style-type: none"> Treatment/strategy A is probably recommended/indicated in preference to treatment B It is reasonable to choose treatment A over treatment B | <p>LEVEL B-R (Randomized)</p> <ul style="list-style-type: none"> Moderate-quality evidence‡ from 1 or more RCTs Meta-analyses of moderate-quality RCTs |
| <p>CLASS IIb (WEAK) Benefit ≥ Risk</p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> May/might be reasonable May/might be considered Usefulness/effectiveness is unknown/unclear/uncertain or not well established | <p>LEVEL B-NR (Nonrandomized)</p> <ul style="list-style-type: none"> Moderate-quality evidence‡ from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies Meta-analyses of such studies |
| <p>CLASS III: No Benefit (MODERATE) Benefit = Risk <i>(Generally, LOE A or B use only)</i></p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> Is not recommended Is not indicated/useful/effective/beneficial Should not be performed/administered/other | <p>LEVEL C-LD (Limited Data)</p> <ul style="list-style-type: none"> 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 |
| <p>CLASS III: Harm (STRONG) Risk > Benefit</p> <p>Suggested phrases for writing recommendations:</p> <ul style="list-style-type: none"> Potentially harmful Causes harm Associated with excess morbidity/mortality Should not be performed/administered/other | <p>LEVEL C-EO (Expert Opinion)</p> <p>Consensus of expert opinion based on clinical experience</p> |

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 consensus 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 I and IIa; 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.

Downloaded from <http://ahajournals.org> by on October 31, 2019

modifications to be incorporated, the standard peer review process was abbreviated, with review provided by the members of the Stroke Council’s Scientific Statements Oversight Committee and by liaisons from the endorsing organizations listed on the masthead. The list of these reviewers is provided at the end of the guideline. The final document was approved by the AHA Science Advisory and Coordinating Committee and Executive Committee.

These guidelines provide general recommendations based on the currently available evidence to guide clinicians caring

for adult patients with acute arterial ischemic stroke. They will not be applicable to all patients. Local resources and expertise, specific clinical circumstances and patient preferences, and evidence published since the issuance of these guidelines are some of the additional factors that should be considered when making individual patient care decisions. In many instances, only limited data exist demonstrating the urgent need for continued research on treatment of AIS.

A focused update addressing data from additional relevant recent RCTs is in process.

Table 2. Guidelines, Policies, and Statements Relevant to the Management of AIS

| Document Title | Year Published | Abbreviation Used in This Document |
|--|----------------|------------------------------------|
| "Recommendations for the Implementation of Telemedicine Within Stroke Systems of Care: A Policy Statement From the American Heart Association" ⁵ | 2009 | N/A |
| "Diagnosis and Management of Cerebral Venous Thrombosis: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" ² | 2011 | N/A |
| "Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹ | 2013 | 2013 AIS Guidelines |
| "Interactions Within Stroke Systems of Care: A Policy Statement From the American Heart Association/American Stroke Association" ⁶ | 2013 | 2013 Stroke Systems of Care |
| "2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society" ⁷ | 2014 | N/A |
| "Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" ⁸ | 2014 | 2014 Brain Swelling |
| "Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" ⁹ | 2014 | 2014 Palliative Care |
| "Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹⁰ | 2014 | 2014 Secondary Prevention |
| "Clinical Performance Measures for Adults Hospitalized With Acute Ischemic Stroke: Performance Measures for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹¹ | 2014 | N/A |
| "Part 15: First Aid: 2015 American Heart Association and American Red Cross Guidelines Update for First Aid" ¹² | 2015 | 2015 CPR/ECC |
| "2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹³ | 2015 | 2015 Endovascular |
| "Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹⁴ | 2015 | 2015 IV Alteplase |
| "Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹⁵ | 2016 | 2016 Rehab Guidelines |
| "Poststroke Depression: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹⁶ | 2017 | N/A |
| "Treatment and Outcome of Hemorrhagic Transformation After Intravenous Alteplase in Acute Ischemic Stroke: A Scientific Statement for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹⁷ | 2017 | N/A |
| "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines" ¹⁸ | 2018 | N/A |
| "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines" ¹⁹ | 2018 | 2018 Cholesterol Guidelines |

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; AIS, acute ischemic stroke; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; CPR, cardiopulmonary resuscitation; ECC, emergency cardiovascular care; HRS, Heart Rhythm Society; IV, intravenous; N/A, not applicable; NLA, National Lipid Association; NMA, National Medical Association; and PCNA, Preventive Cardiovascular Nurses Association.

Table 3. Abbreviations in This Guideline

| | |
|---------|--|
| ACC | American College of Cardiology |
| AHA | American Heart Association |
| AIS | Acute ischemic stroke |
| ARD | Absolute risk difference |
| ASA | American Stroke Association |
| ASCVD | Atherosclerotic cardiovascular disease |
| ASPECTS | Alberta Stroke Program Early Computed Tomography Score |
| BP | Blood pressure |
| CEA | Carotid endarterectomy |
| CeAD | Cervical artery dissection |
| CMB | Cerebral microbleed |
| COR | Class of recommendation |
| CPAP | Continuous positive airway pressure |
| CS | Conscious sedation |
| CT | Computed tomography |
| CTA | Computed tomographic angiography |
| CTP | Computed tomographic perfusion |
| DTN | Door-to-needle |
| DVT | Deep vein thrombosis |
| DW-MRI | Diffusion-weighted magnetic resonance imaging |
| ED | Emergency department |
| EMS | Emergency medical services |
| EVT | Endovascular therapy |
| GA | General anesthesia |
| GWTG | Get With The Guidelines |
| HBO | Hyperbaric oxygen |
| HR | Hazard ratio |
| HT | Hemorrhagic transformation |
| ICH | Intracerebral hemorrhage |


(Continued)

Table 3. Continued

| | |
|-------|---|
| IPC | Intermittent pneumatic compression |
| IV | Intravenous |
| LDL-C | Low-density lipoprotein cholesterol |
| LMWH | Low-molecular-weight heparin |
| LOE | Level of evidence |
| LVO | Large vessel occlusion |
| M1 | Middle cerebral artery segment 1 |
| M2 | Middle cerebral artery segment 2 |
| M3 | Middle cerebral artery segment 3 |
| MCA | Middle cerebral artery |
| MI | Myocardial infarction |
| MR | Magnetic resonance |
| MRA | Magnetic resonance angiography |
| MRI | Magnetic resonance imaging |
| mRS | Modified Rankin Scale |
| mTICI | Modified Thrombolysis in Cerebral Infarction |
| NCCT | Noncontrast computed tomography |
| NIHSS | National Institutes of Health Stroke Scale |
| NINDS | National Institute of Neurological Disorders and Stroke |
| OR | Odds ratio |
| OSA | Obstructive sleep apnea |
| PFO | Patent foramen ovale |
| RCT | Randomized clinical trial |
| RR | Relative risk |
| rt-PA | Recombinant tissue-type plasminogen activator |
| SBP | Systolic blood pressure |
| sICH | Symptomatic intracerebral hemorrhage |
| TIA | Transient ischemic attack |
| UFH | Unfractionated heparin |

1. Prehospital Stroke Management and Systems of Care

1.1. Prehospital Systems

| 1.1. Prehospital Systems | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. Public health leaders, along with medical professionals and others, should design and implement public education programs focused on stroke systems and the need to seek emergency care (by calling 9-1-1) in a rapid manner. These programs should be sustained over time and designed to reach racially/ethnically, age, and sex diverse populations. | I | B-NR | Recommendation revised from 2013 Stroke Systems of Care. COR and LOE added. |
| 2. Such educational programs should be designed to specifically target the public, physicians, hospital personnel, and emergency medical services (EMS) personnel to increase use of the 9-1-1 EMS system, to decrease stroke onset to emergency department (ED) arrival times, and to increase timely use of thrombolysis and thrombectomy. | I | C-EO | New recommendation. |
| Early stroke symptom recognition is essential for seeking timely care. Unfortunately, knowledge of stroke warning signs and risk factors in the United States remains poor. Blacks and Hispanics particularly have lower stroke awareness than the general population and are at increased risk of prehospital delays in seeking care. ²⁰ These factors may contribute to the disparities in stroke outcomes. Available evidence suggests that public awareness interventions are variably effective by age, sex, and racial/ethnic minority status. ²¹ Thus, stroke education campaigns should be designed in a targeted manner to optimize their effectiveness. ²¹ | | | See Tables I and II in online Data Supplement 1 . |
| 3. Activation of the 9-1-1 system by patients or other members of the public is strongly recommended. 9-1-1 dispatchers should make stroke a priority dispatch, and transport times should be minimized. | I | B-NR | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| EMS use by stroke patients has been independently associated with earlier ED arrival (onset-to-door time ≤ 3 hours; adjusted odds ratio [OR], 2.00 [95% CI, 1.93–2.08]), quicker ED evaluation (more patients with door-to-imaging time ≤ 25 minutes; OR, 1.89 [95% CI, 1.78–2.00]), more rapid treatment (more patients with door-to-needle [DTN] time ≤ 60 minutes; OR, 1.44 [95% CI, 1.28–1.63]), and more eligible patients being treated with alteplase if onset is ≤ 2 hours (67% versus 44%; OR, 1.47 [95% CI, 1.33–1.64]), ²¹ yet only $\approx 60\%$ of all stroke patients use EMS. ²² Men, blacks, and Hispanics are less likely to use EMS. ^{20,22} Thus, persistent efforts to ensure activation of the 9-1-1 or similar emergency system by patients or other members of the public in the case of a suspected stroke are warranted. | | | See Table I in online Data Supplement 1 .  |

1.2. EMS Assessment and Management

| 1.2. EMS Assessment and Management | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. The use of a stroke assessment tool by first aid providers, including EMS dispatch personnel, is recommended. | I | B-NR | Recommendation reworded for clarity from 2015 CPR/ECC. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| In 1 study, the positive predictive value for a hospital discharge diagnosis of stroke/transient ischemic attack (TIA) among 900 cases for which EMS dispatch suspected stroke was 51% (95% CI, 47–54), and the positive predictive value for ambulance personnel impression of stroke was 58% (95% CI, 52–64). ²³ In another study of 21 760 dispatches for stroke, the positive predictive value of the dispatch stroke/TIA symptoms identification was 34.3% (95% CI, 33.7–35.0), and the sensitivity was 64.0% (95% CI, 63.0–64.9). ²⁴ In both cases, use of a prehospital tool for stroke screening improved stroke identification, but better stroke identification tools are needed in the prehospital setting. | | | See Table I in online Data Supplement 1 . |
| 2. EMS personnel should provide prehospital notification to the receiving hospital that a suspected stroke patient is en route so that the appropriate hospital resources may be mobilized before patient arrival. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| In the AHA Get With The Guidelines (GWTG) registry, EMS personnel provided prearrival notification to the destination ED for 67% of transported stroke patients. EMS prenotification was associated with increased likelihood of alteplase treatment within 3 hours (82.8% versus 79.2%), shorter door-to-imaging times (26 minutes versus 31 minutes), shorter DTN times (78 minutes versus 80 minutes), and shorter symptom onset-to-needle times (141 minutes versus 145 minutes). ²⁵ | | | See Table I in online Data Supplement 1 . |

1.3. EMS Systems

| 1.3. EMS Systems | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Regional systems of stroke care should be developed. These should consist of the following: (a) healthcare facilities that provide initial emergency care, including administration of IV alteplase, and (b) centers capable of performing endovascular stroke treatment with comprehensive periprocedural care to which rapid transport can be arranged when appropriate. | I | A | Recommendation reworded for clarity from 2015 Endovascular. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| 2. EMS leaders, in coordination with local, regional, and state agencies and in consultation with medical authorities and local experts, should develop triage paradigms and protocols to ensure that patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized tool for stroke screening. | I | B-NR | Recommendation reworded for clarity from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Multiple stroke screening tools have been developed for prehospital evaluation of suspected stroke. A 2016 systematic review assessed the performance of 7 tools. ²⁶ Those with the highest number of subjects in whom the tool had been applied included Cincinnati Prehospital Stroke Scale (CPSS), ²⁷ Los Angeles Prehospital Stroke Screen (LAPSS), ²⁸ Recognition of Stroke in the Emergency Room (ROSIER), ²⁹ and FAST (Face, Arm, Speech, Time). ³⁰ CPSS and FAST performed similarly with regard to sensitivity (range, 44%–95% for CPSS, 79%–97% for FAST) but both had poor specificity (range, 24%–79% for CPSS, 13%–88% for FAST). More complex tools such as LAPSS had improved specificity (range, 48%–97%) but at the cost of sensitivity (range, 59%–91%). All tools inadequately accounted for false-negative cases, thereby likely artificially boosting performance. The review concluded that no strong recommendation could be made for use of one tool over another. | | | See Tables III and IV in online Data Supplement 1 . |
| 3. Patients with a positive stroke screen or who are strongly suspected to have a stroke should be transported rapidly to the closest healthcare facilities that are able to administer IV alteplase. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. See Table XCV in online Data Supplement 1 for original wording. |
| The 2013 recommendation referred to initial emergency care as described elsewhere in the guidelines, which specified administration of IV alteplase as part of this care. The current recommendation is unchanged in intent but reworded to make this clear. | | | |
| 4. When several IV alteplase–capable hospital options exist within a defined geographic region, the benefit of bypassing the closest to bring the patient to one that offers a higher level of stroke care, including mechanical thrombectomy, is uncertain. | IIb | B-NR | New recommendation. |
| 5. Effective prehospital procedures to identify patients who are ineligible for IV thrombolysis and have a strong probability of large vessel occlusion (LVO) stroke should be developed to facilitate rapid transport of patients potentially eligible for thrombectomy to the closest healthcare facilities that are able to perform mechanical thrombectomy. | IIb | C-EO | New recommendation. |
| At least 6 stroke severity scales targeted at recognition of LVO in the prehospital setting to facilitate transfer to endovascular centers have been published. ^{31–36} The 2018 AHA systematic review on the accuracy of prediction instruments for diagnosing LVO in patients with suspected stroke concluded that “No scale predicted LVO with both high sensitivity and high specificity.” ⁴ Specifically, the probability of LVO with a positive LVO prediction test was thought to be only 50% to 60%, whereas >10% of those with a negative test may have an LVO. Thus, more effective tools are needed to identify suspected stroke patients with a strong probability of LVO. All the scales were initially derived from data sets of confirmed stroke cases or selected prehospital cases, and there has been only limited study of their performance in the prehospital setting. ^{37–39} For prehospital patients with suspected LVO by a stroke severity scale, the Mission: Lifeline Severity–based Stroke Triage Algorithm for EMS ⁴⁰ recommends direct transport to a comprehensive stroke center if the travel time to the comprehensive stroke center is <15 additional minutes compared with the travel time to the closest primary stroke center or acute stroke-ready hospital. However, at this time, there is insufficient evidence to recommend 1 scale over the other or a specific threshold of additional travel time for which bypass of a primary stroke center or acute stroke-ready hospital is justifiable. Given the known impact of delays to IV alteplase on outcomes, ⁴¹ the known impact of delays to mechanical thrombectomy on outcome, ⁴² and the anticipated delays in transport for mechanical thrombectomy in eligible patients originally triaged to a nonendovascular center, the Mission: Lifeline algorithm may be a reasonable guideline in some circumstances. Customization of the guideline to optimize patient outcomes will be needed to account for local and regional factors, including the availability of endovascular centers, door in–door out times for nonendovascular stroke centers, interhospital transport times, and DTN and door-to-puncture times. Rapid, protected, collaborative, regional quality review, including EMS agencies and hospitals, is recommended for operationalized bypass algorithms. Further research is needed. | | | See Table III in online Data Supplement 1 . |

1.4. Hospital Stroke Capabilities

| 1.4. Hospital Stroke Capabilities | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| <p>1. Certification of stroke centers by an independent external body, such as Center for Improvement in Healthcare Quality, Det Norske Veritas, Healthcare Facilities Accreditation Program, and The Joint Commission (TJC),* or designation by a state health department, is recommended.</p> <p><small>*AHA has a cobranded, revenue-generating stroke certification with TJC.</small></p> | I | B-NR | <p>Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.</p> <p>See Table XCV in online Data Supplement 1 for original wording.</p> |
| <p>Data support the development of stroke centers to improve patient care and outcomes.⁴³ Differences in stroke quality of care are associated with differences in certifying organization. Between 2010 and 2012, an analysis of 477 297 AIS admissions from 977 certified primary stroke centers (73.8% TJC, 3.7% Det Norske Veritas, 1.2% Healthcare Facilities Accreditation Program, and 21.3% state based) participating in AHA GWTC-Stroke was conducted. Composite care quality was generally similar among the 4 groups of hospitals, although state-certified primary stroke centers underperformed TJC-certified primary stroke centers in a few key measures. The rates of alteplase use were higher in TJC- and Det Norske Veritas (9.0% and 9.8%) and lower in state- and Healthcare Facilities Accreditation Program-certified hospitals (7.1% and 5.9%; $P<0.0001$). DTN times were significantly longer in Healthcare Facilities Accreditation Program hospitals. State primary stroke centers had higher in-hospital risk-adjusted mortality (OR, 1.23 [95% CI, 1.07–1.41]) compared with TJC-certified primary stroke centers.⁴⁴</p> | | | <p>See Table V in online Data Supplement 1.</p> |

1.5. Hospital Stroke Teams

| 1.5. Hospital Stroke Teams | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| <p>1. An organized protocol for the emergency evaluation of patients with suspected stroke is recommended.</p> | I | B-NR | <p>Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.</p> |
| <p>2. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is recommended. Patients with stroke should have a careful clinical assessment, including neurological examination.</p> | I | B-NR | <p>Recommendation wording modified from 2013 AIS Guidelines to match COR I stratifications. COR unchanged. LOE added to conform with ACC/AHA 2015 Recommendation Classification System.</p> |
| <p>3. Multicomponent quality improvement initiatives, which include ED education and multidisciplinary teams with access to neurological expertise, are recommended to safely increase IV fibrinolytic treatment.</p> | I | A | <p>New recommendation.</p> |
| <p>Multicomponent quality improvement programs to improve stroke care demonstrate clear utility in safely increasing alteplase use in the community hospital setting in multiple settings. The US cluster-randomized INSTINCT trial (Increasing Stroke Treatment Through Interventional Change Tactics) demonstrated increased rates of alteplase use among all stroke patients. In the intervention group hospitals, alteplase use increased from 59 of 5882 (1.00%) before intervention to 191 of 7288 (2.62%) after intervention. This compared favorably with the change in the control group hospitals from 65 of 5957 (1.09%) to 120 of 6989 (1.72%), with a relative risk (RR) of 1.68 (95% CI, 1.09–2.57; $P=0.02$). Safety was also demonstrated with symptomatic intracranial hemorrhage (within 36 hours) in 24 of 404 (5.9%) treated strokes.⁴⁵ In the PRACTISE trial (Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation), a multilevel intervention was conducted in a sample of 12 Dutch hospitals. After implementation of an intensive stroke treatment strategy, intervention hospitals treated 393 patients with IV alteplase (13.1% of all patients with acute stroke) versus 308 (12.2%) at control hospitals (adjusted OR, 1.25 [95% CI, 0.93–1.68]).⁴⁶ The AVC (Impact of a Training Program and Organization on the Management of Stroke in the Acute Phase) II trial identified a similar magnitude of improvement (adjusted OR, 1.39 [95% CI, 1.01–2.02]) for overall fibrinolytic delivery between intervention and control groups) among 18 emergency units in France using a train-the-trainer approach.⁴⁷</p> | | | <p>See Tables VI and VII in online Data Supplement 1.</p> |

| 1.5. Hospital Stroke Teams (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 4. It is recommended that stroke systems of care be developed so that fibrinolytic-eligible patients and mechanical thrombectomy-eligible patients receive treatment in the fastest achievable onset-to-treatment time. | I | A | Recommendation revised from 2013 AIS Guidelines. |
| <p>Treatment of AIS with IV tissue-type plasminogen activator is of proven benefit for select patients given up to 4.5 hours after symptom onset.^{48,49} Pooled data from RCTs indicate the benefit is greatest when treatment occurs early after stroke onset and declines with time.⁵⁰ Registry data from AHA GWTG-Stroke hospitals confirm this temporal relationship. In an analysis of 58 353 alteplase-treated patients, treatment started more rapidly (evaluated in 15-minute increments) was associated with reduced in-hospital mortality (OR, 0.96 [95% CI, 0.95–0.98]; $P<0.001$), reduced symptomatic intracerebral hemorrhage (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 increased discharge to home (OR, 1.03 [95% CI, 1.02–1.04]; $P<0.001$). Patient factors most strongly associated with shorter onset-to-treatment times include greater stroke severity, arrival by ambulance, and arrival during regular hours.⁴¹ With respect to endovascular treatment, a pooled analysis of 5 randomized trials comparing endovascular therapy (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 modified Rankin Scale [mRS] distribution) declined with longer time from symptom onset to arterial puncture.⁴² The 6- to 16- and 6- to 24-hour treatment windows 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.^{51,52} The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure that the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible.</p> | | | See Table VIII in online Data Supplement 1 . |
| 5. Establishing and monitoring target time goals for ED door-to-treatment IV fibrinolysis time can be beneficial to monitor and enhance system performance. | I | B-NR | New recommendation. |
| <p>In AHA GWTG-Stroke hospitals, median DTN time for IV alteplase administration decreased from 77 minutes (interquartile range, 60–98 minutes) during the 2003 to 2009 preintervention period to 67 minutes (interquartile range, 51–87 minutes) during the 2010 to 2013 postintervention period ($P<0.001$). The percentage of alteplase-treated patients having DTN times of ≤ 60 minutes increased from 26.5% (95% CI, 26.0–27.1) to 41.3% (95% CI, 40.8–41.7; $P<0.001$). Comparing the quarter immediately before the intervention (quarter 4 of 2009) and the final postintervention quarter (quarter 3 of 2013) showed that DTN times of ≤ 60 minutes increased from 29.6% (95% CI, 27.8–31.5) to 53.3% (95% CI, 51.5–55.2; $P<0.001$).⁵³ In a subsequent study evaluating a cohort of hospitals from 2014 to 2015, 59.3% of patients received IV alteplase within a DTN time of 60 minutes.⁵⁴</p> | | | See Table IX in online Data Supplement 1 . American Stroke Association. A Division of the American Heart Association. |

1.6. Telemedicine

| 1.6. Telemedicine | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. For sites without in-house imaging interpretation expertise, teleradiology systems approved by the US Food and Drug Administration are recommended for timely review of brain imaging in patients with suspected acute stroke. | I | A | Recommendation revised from 2013 AIS Guidelines. |
| 2. When implemented within a telestroke network, teleradiology systems approved by the US Food and Drug Administration are effective in supporting rapid imaging interpretation in time for IV alteplase administration decision making. | I | A | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE revised. See Table XCV in online Data Supplement 1 for original wording. |
| <p>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. Further support for this unchanged recommendation from the 2013 AIS Guidelines with LOE upgraded to A is provided by 3 additional studies published since the 2013 Guidelines.^{55–57}</p> | | | See Table X in online Data Supplement 1 . |
| 3. The use of telemedicine/telestroke resources and systems should be supported by healthcare institutions, governments, payers, and vendors as one method to ensure adequate 24/7 coverage and care of acute stroke patients in a variety of settings. | I | C-EO | Recommendation reworded for clarity from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 4. Telestroke/teleradiology evaluations of AIS patients can be effective for correct IV alteplase eligibility decision making. | Ila | B-R | New recommendation. |
| <p>The STRoKEDOC (Stroke Team Remote Evaluation Using a Digital Observation Camera) pooled analysis supported the hypothesis that telemedicine consultations, which included teleradiology, compared with telephone-only resulted in statistically significantly more accurate IV alteplase eligibility decision-making for patients exhibiting symptoms and signs of an acute stroke syndrome in EDs.⁵⁸</p> | | | See Table XI in online Data Supplement 1 . |

| 1.6. Telemedicine (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 5. Administration of IV alteplase guided by telestroke consultation for patients with AIS can be beneficial. | Ila | B-NR | New recommendation. |
| A systematic review and meta-analysis was performed to evaluate the safety and efficacy of IV alteplase delivered through telestroke networks in patients with AIS. sICH rates were similar between patients subjected to telemedicine-guided IV alteplase and those receiving IV alteplase at stroke centers. There was no difference in mortality or in functional independence at 3 months between telestroke-guided and stroke center–managed patients. The findings indicate that IV alteplase delivery through telestroke networks is safe and effective in the 3-hour time window. ⁵⁹ | | | See Table XII in online Data Supplement 1 . |
| 6. Telestroke networks may be reasonable for triaging patients with AIS who may be eligible for interfacility transfer in order to be considered for emergency mechanical thrombectomy. | Ilb | B-NR | New recommendation. |
| An observational study compared clinical outcomes of EVT between patients with anterior circulation stroke transferred after teleconsultation and those directly admitted to a tertiary stroke center. The study evaluated 151 patients who underwent emergency EVT for anterior circulation stroke. Of these, 48 patients (31.8%) were transferred after teleconsultation, and 103 (68.2%) were admitted primarily through an ED. Transferred patients were younger, received IV alteplase more frequently, had prolonged time from stroke onset to EVT initiation, and tended to have lower rates of symptomatic intracranial hemorrhage and mortality than directly admitted patients. Similar rates of reperfusion and favorable functional outcomes were observed in patients treated by telestroke and those who were directly admitted. Telestroke networks may enable the triage and the delivery of EVT to selected ischemic stroke patients transferred from remote hospitals. ⁶⁰ | | | See Table XII in online Data Supplement 1 . |
| 7. Providing alteplase decision-making support via telephone consultation to community physicians is feasible and safe and may be considered when a hospital has access to neither an in-person stroke team nor a telestroke system. | Ilb | C-LD | New recommendation. |
| The advantages of telephone consultations for patients with acute stroke syndromes are feasibility, history of use, simplicity, availability, portability, short consultation time, and facile implementation. ⁶¹ | | | See Table XIII in online Data Supplement 1 . |

1.7. Organization and Integration of Components



| 1.7. Organization and Integration of Components | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. All hospitals caring for stroke patients within a stroke system of care should develop, adopt, and adhere to care protocols that reflect current care guidelines as established by national and international professional organizations and state and federal agencies and laws. | I | C-EO | Recommendation unchanged from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. Different services within a hospital that may be transferring patients through a continuum of care, as well as different hospitals that may be transferring patients to other facilities, should establish hand-off and transfer protocols and procedures that ensure safe and efficient patient care within and between facilities. Protocols for interhospital transfer of patients should be established and approved beforehand so that efficient patient transfers can be accomplished at all hours of the day and night. | I | C-EO | Recommendation unchanged from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. Mechanical thrombectomy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography, qualified neurointerventionalists, and a comprehensive periprocedural care team. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures. | I | C-EO | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 4. It may be useful for primary stroke centers and other healthcare facilities that provide initial emergency care, including administration of IV alteplase, to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for mechanical thrombectomy and to reduce the time to mechanical thrombectomy. | Ilb | C-LD | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Between 2006 and 2010, the proportion of ischemic strokes undergoing computed tomographic angiography (CTA) increased from 3.8% to 9.1% ($P<0.0001$). Computed tomography perfusion (CTP) increased from 0.05% to 2.9% over the same period ($P<0.0001$). Reperfusion treatment was more common among those who were imaged with CTA (13.0%) and CTP (17.6%) compared with those with computed tomography (CT) of the head alone (4.0%; $P<0.0001$). ⁶² However, when considering implementation of multimodal CT imaging at small or remote-access hospitals, resource availability and realistic expectations for gains in efficiency should be taken into account. | | | |

| 1.7. Organization and Integration of Components (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 5. It may be useful for government agencies and third-party payers to develop and implement reimbursement schedules for patients with acute stroke that reflect the demanding care and expertise that such patients require to achieve an optimal outcome, regardless of whether they receive a specific medication or procedure. | IIb | C-EO | Recommendation revised from 2013 Stroke Systems of Care. |
| <p>Multiple studies evaluating fibrinolytic therapy and mechanical thrombectomy, alone or in combination, have demonstrated substantial societal economic value for acute stroke treatment across multiple countries. Pre-mechanical thrombectomy era data demonstrate that, in the United States, cost savings of approximately US \$30 million would be realized if the proportion of all ischemic stroke patients receiving IV alteplase was increased to 8%. This excludes any gain from increased quality-adjusted life-years gained, a source of tremendous additional economic and patient value. Before the implementation of Centers for Medicare & Medicaid Services Diagnosis-Related Group 559 payment in 2005, treatment of acute stroke was economically discouraged at a hospital level because of a high hospital cost-reimbursement ratio. Diagnosis-Related Group 559 favorably altered the cost-reimbursement ratio for stroke care. In a single-hospital study, this ratio decreased from 1.41 (95% CI, 0.98–2.28) before Diagnosis-Related Group 559 to 0.82 (95% CI, 0.66–0.97) after Diagnosis-Related Group 559. The subsequent years corresponded to a period of rapid growth in the number of primary stroke centers and increasing total stroke treatment cases. Addressing economic barriers to treatment is important as acute stroke care complexity evolves.^{63–68}</p> | | | |

1.8. Establishment of Data Repositories

| 1.8. Establishment of Data Repositories | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. Participation in a stroke data repository is recommended to promote consistent adherence to current treatment guidelines, to allow continuous quality improvement, and to improve patient outcomes. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| <p>Participation in a stroke data repository as one part of a quality improvement process was associated with improved IV alteplase administration after AIS,^{68a,68b} lower in-hospital mortality^{68b,68c} and intracranial hemorrhage rates, and an increase in the percentage of patients discharged home.^{53,69,69a}</p> | | | See Table XIV in online Data Supplement 1 . |

1.9. Stroke System Care Quality Improvement Process

| 1.9. Stroke System Care Quality Improvement Process | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. Healthcare institutions should organize a multidisciplinary quality improvement committee to review and monitor stroke care quality benchmarks, indicators, evidence-based practices, and outcomes. The formation of a clinical process improvement team and the use of a stroke care registry are helpful for such quality of care assurances. The data repository can be used to identify the gaps or disparities in quality stroke care. Once the gaps have been identified, specific interventions can be initiated to address these gaps or disparities. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE added where missing in part of recommendation. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| <p>A multidisciplinary quality improvement committee, as 1 part of a quality improvement process, was associated with improved timeliness of IV alteplase administration after AIS, lower in-hospital mortality and intracranial hemorrhage rates, and an increase in the percentage of patients discharged home.^{53,69} Identification of stroke treatment barriers with targeted interventions has demonstrated benefit in improving stroke treatment in community hospitals.⁴⁵</p> | | | See Tables VI, VII, and XIV in online Data Supplement 1 . |
| 2. Stroke outcome measures should include adjustments for baseline severity. | I | B-NR | Recommendation revised from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. Continuous quality improvement processes, implemented by each major element of a stroke system of care and the system as a whole, can be useful in improving patient care or outcomes. | IIa | B-NR | Recommendation revised from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. |
| <p>Data indicate that continuous quality improvement efforts along the stroke spectrum of care, from initial patient identification to EMS activation, ED evaluation, stroke team activation, and poststroke care, can be useful in improving outcomes.^{45,53,69} Stroke outcome measures are strongly influenced by baseline stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS).^{70–73} Other identified predictors of poor outcomes include age, blood glucose, and infarct on imaging.⁷³ Quality improvement efforts should recognize these predictors in order to have meaningful comparisons between stroke care systems.</p> | | | See Tables VI, VII, XIV, and XV in online Data Supplement 1 . |

2. Emergency Evaluation and Treatment

2.1. Stroke Scales

| 2.1. Stroke Scales | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. The use of a stroke severity rating scale, preferably the NIHSS, is recommended. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Formal stroke scores or scales such as the NIHSS (Table 4) may be performed rapidly, have demonstrated utility, and may be administered by a broad spectrum of healthcare providers with accuracy and reliability. ^{75,76} Use of a standardized scale quantifies the degree of neurological deficit, facilitates communication, helps identify patients for fibrinolytic or mechanical intervention, allows objective measurement of changing clinical status, and identifies those at higher risk for complications such as intracerebral hemorrhage (ICH). ^{71–73,77} | | | See Table XV in online Data Supplement 1 . |

Table 4. National Institutes of Health Stroke Scale

| Tested Item | Title | Responses and Scores |
|-------------|---------------------------|---------------------------------|
| 1A | Level of consciousness | 0—Alert |
| | | 1—Drowsy |
| | | 2—Obtunded |
| | | 3—Coma/unresponsive |
| 1B | Orientation questions (2) | 0—Answers both correctly |
| | | 1—Answers 1 correctly |
| | | 2—Answers neither correctly |
| 1C | Response to commands (2) | 0—Performs both tasks correctly |
| | | 1—Performs 1 task correctly |
| | | 2—Performs neither |
| 2 | Gaze | 0—Normal horizontal movements |
| | | 1—Partial gaze palsy |
| | | 2—Complete gaze palsy |
| 3 | Visual fields | 0—No visual field defect |
| | | 1—Partial hemianopia |
| | | 2—Complete hemianopia |
| | | 3—Bilateral hemianopia |
| 4 | Facial movement | 0—Normal |
| | | 1—Minor facial weakness |
| | | 2—Partial facial weakness |
| | | 3—Complete unilateral palsy |
| 5 | Motor function (arm) | 0—No drift |
| | | a. Left |
| | | 1—Drift before 10 s |
| | | b. Right |
| | | 2—Falls before 10 s |
| | | 3—No effort against gravity |
| | | 4—No movement |

Table 4. Continued

| Tested Item | Title | Responses and Scores |
|-------------|---------------------------|---------------------------------------|
| 6 | Motor function (leg) | 0—No drift |
| | | a. Left |
| | | 1—Drift before 5 s |
| | | b. Right |
| | | 2—Falls before 5 s |
| | | 3—No effort against gravity |
| | | 4—No movement |
| 7 | Limb ataxia | 0—No ataxia |
| | | 1—Ataxia in 1 limb |
| | | 2—Ataxia in 2 limbs |
| 8 | Sensory | 0—No sensory loss |
| | | 1—Mild sensory loss |
| | | 2—Severe sensory loss |
| 9 | Language | 0—Normal |
| | | 1—Mild aphasia |
| | | 2—Severe aphasia |
| | | 3—Mute or global aphasia |
| 10 | Articulation | 0—Normal |
| | | 1—Mild dysarthria |
| | | 2—Severe dysarthria |
| 11 | Extinction or inattention | 0—Absent |
| | | 1—Mild loss (1 sensory modality lost) |
| | | 2—Severe loss (2 modalities lost) |

Adapted from Lyden et al.⁷⁴ Copyright © 1994, American Heart Association, Inc.

2.2. Head and Neck Imaging

| 2.2.1. Initial Imaging | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. All patients with suspected acute stroke should receive emergency brain imaging evaluation on first arrival to a hospital before initiating any specific therapy to treat AIS. | I | A | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| 2. Systems should be established so that brain imaging studies can be performed as quickly as possible in patients who may be candidates for IV fibrinolysis or mechanical thrombectomy or both. | I | B-NR | New recommendation. |
| The benefit of IV alteplase is time dependent, with earlier treatment within the therapeutic window leading to bigger proportional benefits. ^{42,78} A brain imaging study to exclude ICH is recommended as part of the initial evaluation of patients who are potentially eligible for these therapies. 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) declined with longer time from symptom onset to arterial puncture. ⁴² The 6- to 16- and 6- to 24-hour treatment windows 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. ^{51,52} The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure that the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible. Reducing the time interval from ED presentation to initial brain imaging can help to reduce the time to treatment initiation. Studies have shown that median or mean door-to-imaging times of ≤20 minutes can be achieved in a variety of different hospital settings. ^{79–81} | | | See Tables XVI and XVII in online Data Supplement 1 . |
| 3. Noncontrast CT (NCCT) is effective to exclude ICH before IV alteplase administration. | I | A | Recommendation revised from 2013 AIS Guidelines. |
| 4. Magnetic resonance (MR) imaging (MRI) is effective to exclude ICH before IV alteplase administration. | I | B-NR | Recommendation revised from 2013 AIS Guidelines. |
| 5. CTA with CTP or MR angiography (MRA) with diffusion-weighted magnetic resonance imaging (DW-MRI) with or without MR perfusion is recommended for certain patients. | I | A | New recommendation. |
| In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention. ^{82,83} NCCT scanning 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 IV alteplase in most patients. ^{48,49} Immediate CT scanning provides high value for patients with acute stroke. ^{84,85} 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. ^{86,87} In patients who awake with stroke or have unclear time of onset >4.5 hours from baseline or last known well, MRI to identify diffusion-positive fluid-attenuated inversion recovery (FLAIR)-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition. ⁸⁸ CTA with CTP or MRA with DW-MRI with or without MR perfusion is useful for selecting candidates for mechanical thrombectomy between 6 and 24 hours after last known well. ^{51,52} See specific recommendations below. | | | See Tables XVII through XX in online Data Supplement 1 . |

| 2.2.2. IV Alteplase Eligibility | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Administration of IV alteplase in eligible patients without first obtaining MRI to exclude cerebral microbleeds (CMBs) is recommended. | I | B-NR | New recommendation. |
| CMBs are common in patients receiving IV alteplase, occurring in 15% to 27%. ^{89–94} Such patients were undoubtedly included in the pivotal NINDS and ECASS III trials that established the benefits of IV alteplase treatment. ^{48,49} Two meta-analyses of the association of baseline CMBs and the risk of sICH after IV alteplase reported that sICH is more common in patients with baseline CMBs, whereas 2 other meta-analyses and 1 multicenter study did not. ^{89–93} In 2 studies using ECASS II sICH criteria, the rates in patients with CMBs were 5.8% and 6.5% compared with 5.3% in ECASS III. ^{49,90,91} One study analyzing the risk of sICH in patients with CMBs detected after IV alteplase treatment reported sICH of 5% using the NINDS criteria compared with 6.4% in the NINDS tPA trials. ^{48,94} The risk of sICH in patients with >10 CMBs (30%–47%) is consistently reported as significantly greater than in those with no CMBs (1%–4.4%). However, these data are based on <50 patients, constituting <2% of these series. ^{90,91,93,94} No RCTs of IV alteplase in AIS with baseline MRI to identify CMBs have been conducted, so no determination of the effect of baseline CMB on the treatment effect of alteplase with CMB is available. In the absence of direct evidence that IV alteplase provides no benefit or produces harm in eligible patients with CMBs, withholding treatment on the basis of the presence of CMBs could lead to the exclusion of patients who would benefit from treatment. | | | See Table XXI in online Data Supplement 1 . |

| 2.2.2. IV Alteplase Eligibility (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 2. In patients eligible for IV alteplase, because benefit of therapy is time dependent, treatment should be initiated as quickly as possible and not delayed for additional multimodal neuroimaging, such as CT and MRI perfusion imaging. | I | B-NR | New recommendation. |
| 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 IV alteplase in most patients. ^{48,49} 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 IV alteplase. In some cases, particularly when there is substantial diagnostic uncertainty, advanced imaging may be beneficial. | | | See Table XX in online Data Supplement 1 . |
| 3. In patients with AIS who awake with stroke symptoms or have unclear time of onset > 4.5 hours from last known well or at baseline state, MRI to identify diffusion-positive FLAIR-negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition. | Ia | B-R | New recommendation. |
| The WAKE-UP trial (Efficacy and Safety of MRI-based Thrombolysis in Wake-Up Stroke) randomized 503 patients with AIS who awoke with stroke or had unclear time of onset >4.5 hours from last known well and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the middle cerebral artery (MCA), NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. The trial was terminated early for lack of funding before the designated 800 patients were randomized. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well was slightly over 10 hours. At baseline, one-third of the patients had vessel occlusion on time-of-flight MRA, and three-quarters of the FLAIR lesions were <9 mL. The end point of an mRS score of 0 to 1 at 90 days was achieved in 53.3% of the IV alteplase group and in 41.8% of the placebo group ($P=0.02$). ⁸⁸ | | | See Table XIX in online Data Supplement 1 |

| 2.2.3. Mechanical Thrombectomy Eligibility—Vessel Imaging | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. For patients who otherwise meet criteria for mechanical thrombectomy, noninvasive vessel imaging of the intracranial arteries is recommended during the initial imaging evaluation. | I | A | <small>Association.</small> Recommendation reworded for clarity from 2015 Endovascular. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| 2. For patients with suspected LVO who have not had noninvasive vessel imaging as part of their initial imaging assessment for stroke, noninvasive vessel imaging should then be obtained as quickly as possible (eg, during alteplase infusion if feasible). | I | A | Recommendation revised from 2015 Endovascular. COR and LOE unchanged. |
| A recent systematic review evaluated the accuracy of prediction instruments for diagnosing LVO. ⁴ In the setting where confirmed ischemic stroke patients would be assessed by a neurologist or emergency physician in the ED, the authors suggested that the NIHSS score is the best of the LVO prediction instruments. According to their meta-analysis, a threshold of ≥ 10 would provide the optimal balance between sensitivity (73%) and specificity (74%). To maximize sensitivity (at the cost of lower specificity), a threshold of ≥ 6 would have 87% sensitivity and 52% specificity. However, even this low threshold misses some cases with LVO, whereas the low specificity indicates that false-positives will be common. The sensitivity of CTA and MRA compared with the gold standard of catheter angiography ranges from 87% to 100%, with CTA having greater accuracy than MRA. ^{95,96} Pivotal trials of mechanical thrombectomy all required noninvasive CTA or MRA diagnosis of LVO as an inclusion criterion. | | | See Tables XVII and XXII in online Data Supplement 1 . |
| 3. In patients with suspected intracranial LVO and no history of renal impairment, who otherwise meet criteria for mechanical thrombectomy, it is reasonable to proceed with CTA if indicated before obtaining a serum creatinine concentration. | Ia | B-NR | New recommendation. |
| Analyses from a number of observational studies suggest that the risk of contrast-induced nephropathy secondary to CTA imaging is relatively low, particularly in patients without a history of renal impairment. Moreover, waiting for these laboratory results may lead to delays in mechanical thrombectomy. ^{97–102} | | | See Table XXIII in online Data Supplement 1 . |
| 4. In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, may be reasonable to provide useful information on patient eligibility and endovascular procedural planning. | Ib | C-EO | New recommendation. |
| Knowledge of vessel anatomy and presence of extracranial vessel dissections, stenoses, and occlusions may assist in planning endovascular procedures or identifying patients ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature. | | | |

| 2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 5. It may be reasonable to incorporate collateral flow status into clinical decision-making in some candidates to determine eligibility for mechanical thrombectomy. | IIb | C-LD | Recommendation revised from 2015 Endovascular. |
| <p>Several studies, including secondary analyses from MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands) and IMS (Interventional Management of Stroke) III, provide data supporting the role of collateral assessments in identifying patients likely or unlikely to benefit from mechanical thrombectomy.^{103,104} The ESCAPE trial (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times), using multiphase CTA to select patients with moderate to good collateral circulation for mechanical thrombectomy up to 12 hours from onset, was stopped early for efficacy.¹⁰⁵ Acquisition of advanced imaging should not delay door-to-groin puncture times.</p> | | | See Tables XXIV and XXV in online Data Supplement 1 . |

| 2.2.4. Mechanical Thrombectomy Eligibility–Multimodal Imaging | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window. | I | A | New recommendation. |
| <p>The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical-core mismatch (a combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority >0.999).⁵¹ The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; <i>P</i><0.0001).⁵² Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice.^{51,52}</p> | | | See Table XVII in online Data Supplement 1 . |
| 2. When evaluating patients with AIS within 6 hours of last known normal with LVO and an Alberta Stroke Program Early Computed Tomography Score (ASPECTS) of ≥6, selection for mechanical thrombectomy based on CT and CTA or MRI and MRA is recommended in preference to performance of additional imaging such as perfusion studies. | I | B-NR | New recommendation. |
| <p>Of the 6 RCTs that independently demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed <6 hours from stroke onset, 4 trials (REVASCAT [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 Eight Hours of Symptom Onset], SWIFT PRIME [Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment], EXTEND-IA [Extending the Time for Thrombolysis in Emergency Neurological Deficits–Intra-Arterial], and ESCAPE)^{105–108} used some form of advanced imaging to determine eligibility, whereas 2 (THRACE [Trial and Cost Effectiveness Evaluation of Intra-Arterial Thrombectomy in Acute Ischemic Stroke] and MR CLEAN)^{109,110} required only NCCT and demonstration of LVO. Because the last 2 studies independently demonstrated benefit in the treated group, the role of additional imaging-based eligibility criteria is not well established and could lead to the exclusion of patients who would benefit from treatment and are therefore not indicated at this time. Further RCTs may be helpful to determine whether advanced imaging paradigms using CTP, CTA, and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, are beneficial for selecting patients for reperfusion therapy who are within 6 hours of symptom onset and have an ASPECTS <6.</p> | | | See Table XVII in online Data Supplement 1 . |



2.3. Other Diagnostic Tests

| 2.3. Other Diagnostic Tests | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. Only the assessment of blood glucose must precede the initiation of IV alteplase in all patients. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Recommendation was modified to clarify that it is only blood glucose that must be measured in all patients. Other tests, for example, international normalized ratio, activated partial thromboplastin time, and platelet count, may be necessary in some circumstances if there is suspicion of coagulopathy. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, IV alteplase treatment should not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test. | | | |
| 2. Baseline electrocardiographic assessment is recommended in patients presenting with AIS but should not delay initiation of IV alteplase. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 3. Baseline troponin assessment is recommended in patients presenting with AIS but should not delay initiation of IV alteplase or mechanical thrombectomy. | I | C-LD | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 4. Usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac, or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of IV alteplase. | IIb | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Additional support for this reworded recommendation from the 2013 AIS Guidelines comes from a cohort study of 615 patients, 243 of whom had chest x-ray done before IV alteplase. Cardiopulmonary adverse events in the first 24 hours of admission, endotracheal intubation in the first 7 hours, and in-hospital mortality were not different between the 2 groups. Patients with chest x-ray done before treatment had longer mean DTN times than those who did not (75.8 minutes versus 58.3 minutes; $P=0.0001$). ¹¹¹ | | | See Table XXVI in online Data Supplement 1 . |

3. General Supportive Care and Emergency Treatment

3.1. Airway, Breathing, and Oxygenation

| 3.1. Airway, Breathing, and Oxygenation | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|------|---|
| 1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway. | I | C-EO | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. Supplemental oxygen should be provided to maintain oxygen saturation >94%. | I | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. Supplemental oxygen is not recommended in nonhypoxic patients with AIS. | III: No Benefit | B-R | Recommendation unchanged from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of oxygen by nasal cannula at 2 L/min (baseline O ₂ saturation >93%) or 3 L/min (baseline O ₂ saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights. ¹¹² | | | See Table XXVII in online Data Supplement 1 . |

| 3.1. Airway, Breathing, and Oxygenation (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|--|
| 4. Hyperbaric oxygen (HBO) is not recommended for patients with AIS except when caused by air embolization. | III: No Benefit | B-NR | Recommendation revised from 2013 AIS Guidelines. |
| The limited data available on the utility of HBO therapy for AIS (not related to cerebral air embolism) show no benefit. ¹¹³ HBO therapy is associated with claustrophobia and middle ear barotrauma, ¹¹⁴ as well as an increased risk of seizures. ¹¹⁵ Given the confines of HBO chambers, the ability to closely/adequately monitor patients may also be compromised. HBO thus should be offered only in the context of a clinical trial or to individuals with cerebral air embolism. | | | See Table XXVIII in online Data Supplement 1 . |

3.2. Blood Pressure

| 3.2. Blood Pressure | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function. | I | C-EO | New recommendation. |
| The blood pressure (BP) level that should be maintained in patients with AIS to ensure the best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others have not. ^{116–123} 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. ¹²⁴ No studies have compared different isotonic fluids. | | | See Table XXIX in online Data Supplement 1 . |
| 2. Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their SBP is <185 mm Hg and their diastolic BP is <110 mm Hg before IV fibrinolytic therapy is initiated. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| The RCTs of IV alteplase required the BP to be <185 mm Hg systolic and <110 mm Hg diastolic before treatment and <180/105 mm Hg for the first 24 hours after treatment. Options to treat arterial hypertension in patients with AIS who are candidates for immediate reperfusion therapy are given in Table 5. Some observational studies suggest that the risk of hemorrhage after administration of alteplase is greater in patients with higher BPs ^{125–181} and in patients with more BP variability. ¹³² The exact BP at which the risk of hemorrhage after IV alteplase increases is unknown. It is thus reasonable to target the BPs used in the RCTs of IV alteplase. | | | See Tables XX and XXX in online Data Supplement 1 . |
| 3. In patients for whom mechanical thrombectomy is planned and who have not received IV fibrinolytic therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure. | IIa | B-NR | Recommendation revised from 2013 AIS Guidelines. |
| Of the 6 RCTs that each independently demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed <6 hours from stroke onset, 5 (REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, and MR CLEAN) ^{106–110} had eligibility exclusions for BP >185/110 mm Hg. The sixth, ESCAPE, ¹⁰⁵ had no BP eligibility exclusion. DAWN also used an exclusion for BP >185/110 mm Hg. ⁵¹ RCT data for optimal BP management approaches in this setting are not available. Because the vast majority of patients enrolled in these RCTs had preprocedural BP managed below 185/110 mm Hg, it is reasonable to use this level as a guideline until additional data become available. | | | See Table XVII in online Data Supplement 1 . |
| 4. The usefulness of drug-induced hypertension in patients with AIS is not well established. | IIb | B-R | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

Table 5. Options to Treat Arterial Hypertension in Patients With AIS Who Are Candidates for Emergency Reperfusion Therapy*

| COR IIb | LOE C-EO |
|---|----------|
| Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg: | |
| Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or | |
| Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or | |
| Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h | |
| Other agents (eg, hydralazine, enalaprilat) may also be considered | |
| If BP is not maintained \leq 185/110 mm Hg, do not administer alteplase | |
| Management of BP during and after alteplase or other emergency reperfusion therapy to maintain BP \leq 180/105 mm Hg: | |
| Monitor BP every 15 min for 2 h from the start of alteplase therapy, then every 30 min for 6 h, and then every hour for 16 h | |
| If systolic BP >180–230 mm Hg or diastolic BP >105–120 mm Hg: | |
| Labetalol 10 mg IV followed by continuous IV infusion 2–8 mg/min; or | |
| Nicardipine 5 mg/h IV, titrate up to desired effect by 2.5 mg/h every 5–15 min, maximum 15 mg/h; or | |
| Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h | |
| If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside | |

AIS indicates acute ischemic stroke; BP, blood pressure; COR, class of recommendation; IV, intravenous; and LOE, Level of Evidence.

*Different treatment options may be appropriate in patients who have comorbid conditions that may benefit from rapid reductions in BP such as acute coronary event, acute heart failure, aortic dissection, or preeclampsia/eclampsia.

Data derived from Jauch et al.¹

3.3. Temperature

| 3.3. Temperature | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|---|
| 1. Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke. | I | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| Additional support for this recommendation unchanged from the 2013 AIS Guidelines is provided by a large retrospective cohort study conducted from 2005 to 2013 of patients admitted to intensive care units in Australia, New Zealand, and the United Kingdom. Peak temperature in the first 24 hours <37°C and >39°C was associated with an increased risk of in-hospital death compared with normothermia in 9366 patients with AIS. ¹³³ | | | See Tables XXXI and XXXII in online Data Supplement 1 . |
| 2. In patients with AIS, the benefit of treatment with induced hypothermia is uncertain. | IIb | B-R | Recommendation revised from 2013 AIS Guidelines. |
| To date, studies of hypothermia in AIS show no benefit in functional outcome and suggest that induction of hypothermia increases the risk of infection, including pneumonia. ^{134–137} These studies use a variety of methods to induce hypothermia and are small/underpowered, meaning that a benefit for hypothermia in AIS cannot be definitively excluded. A large phase III trial of hypothermia in AIS is ongoing. | | | See Tables XXXIII and XXXIV in online Data Supplement 1 . |

3.4. Blood Glucose

| 3.4. Blood Glucose | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|---|
| 1. Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS. | I | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after AIS is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in patients with AIS. | IIa | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

3.5. IV Alteplase

| 3.5.1. General Principles | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|------|---|
| 1. In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. | I | A | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| 2. In patients undergoing fibrinolytic therapy, physicians should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction. | I | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| See Table 6 for options for management of symptomatic intracranial bleeding occurring within 24 hours after administration of IV alteplase for treatment of AIS and Table 7 for options for management of orolingual angioedema associated with IV alteplase administration for AIS. | | | |
| 3. The potential risks should be discussed during IV alteplase eligibility deliberation and weighed against the anticipated benefits during decision-making. | I | C-EO | Recommendation and COR unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 4. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and determine blood glucose levels before IV alteplase initiation. IV alteplase is not indicated for nonvascular conditions. | III: No Benefit | B-NR | Recommendation reworded for clarity from 2015 IV Alteplase. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 5. Because time from onset of symptoms to treatment has such a powerful impact on outcomes, treatment with IV alteplase should not be delayed to monitor for further improvement. | III: Harm | C-EO | Recommendation wording modified from 2015 IV Alteplase to match COR III stratifications and reworded for clarity. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

| 3.5.2. Time Windows | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|---|
| 1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility. | I | A | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| The safety and efficacy of this treatment when administered within the first 3 hours after stroke onset are solidly supported by combined data from multiple RCTs ^{155–157} and confirmed by extensive community experience in many countries. ¹⁵⁸ The eligibility criteria for IV alteplase have evolved over time as its usefulness and true risks have become clearer. A recent AHA statement provides a detailed discussion of this topic. ¹⁴ Eligibility recommendations for IV alteplase in patients with AIS are summarized in Table 8. The benefit of IV alteplase is well established for adult patients with disabling stroke symptoms regardless of age and stroke severity. ^{78,159} Because of this 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 IV alteplase in an otherwise eligible adult patient with a disabling AIS. In a recent trial, a lower dose of IV alteplase (0.6 mg/kg) was not shown to be noninferior to standard-dose IV alteplase for the reduction of death and disability at 90 days. ¹⁶⁰ | | | |
| | | | See Table XX in online Data Supplement 1 . |

| 3.5.2. Time Windows (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----|-----|--|
| 2. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 8 to determine patient eligibility. | I | B-R | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| One trial (ECASS III) specifically evaluating the efficacy of IV alteplase within 3 and 4.5 hours after symptom onset ⁴⁹ and pooled analysis of multiple trials testing IV alteplase within various time windows ¹⁵⁵⁻¹⁵⁷ support the efficacy of IV alteplase up to 4.5 hours after symptom onset. ECASS III excluded octogenarians, patients taking warfarin regardless of international normalized ratio, patients with combined history of diabetes mellitus and previous ischemic stroke, and patients with very severe strokes (NIHSS score >25) because of a perceived excessive risk of intracranial hemorrhage in those cases. However, careful analysis of available published data summarized in an AHA/American Stroke Association (ASA) scientific statement indicates that these exclusion criteria from the trial may not be justified in practice (Table 8). ¹⁴ | | | See Table XX in online Data Supplement 1 . |
| 3. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) administered within 4.5 hours of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 hours from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. | IIa | B-R | New recommendation. |
| The WAKE-UP RCT randomized 503 patients with AIS who awoke with stroke or had unclear time of onset and could be treated with IV alteplase within 4.5 hours of stroke symptom recognition. Eligibility required MRI mismatch between abnormal signal on DW-MRI and no visible signal change on FLAIR. DW-MRI lesions larger than one-third of the territory of the MCA, NIHSS score >25, contraindication to treatment with alteplase, or planned thrombectomy were all exclusions. Ninety-four percent were wake-up strokes. Median NIHSS score was 6. Median time from last known well to symptom recognition was ≈7 hours and to alteplase administration slightly over 10 hours. The primary end point of an mRS score 0 to 1 at 90 days was achieved in 53.3% of the alteplase group and in 41.8% of the placebo group (P=0.02). Only 20% had LVO of the intracranial internal carotid or proximal middle cerebral arteries. ⁸⁸ | | | See Table XIX in online Data Supplement 1 . <small>American Stroke Association Division of the American Heart Association</small> |

| 3.5.3. Mild Stroke | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|------|---|
| 1. For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. | I | B-R | Recommendation revised from 2015 IV Alteplase. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. For otherwise eligible patients with mild disabling stroke symptoms, IV alteplase may be reasonable for patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. | IIb | B-NR | New recommendation. |
| 3. For otherwise eligible patients with mild nondisabling stroke symptoms (NIHSS score 0-5), IV alteplase is not recommended for patients who could be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. | III: No Benefit | B-R | New recommendation. |
| 4. For otherwise eligible patients with mild non-disabling stroke symptoms (NIHSS 0-5), IV alteplase is not recommended for patients who could be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state. | III: No Benefit | C-LD | New recommendation. |
| Subgroup analyses of the NINDS rt-PA Trial and IST (International Stroke Trial)-3 with mild stroke defined in various ways have inconsistently shown a benefit for IV alteplase. ¹⁶¹⁻¹⁶³ A meta-analysis of 9 trials of IV alteplase in AIS including subjects from the NINDS rt-PA trial and IST-3 showed benefit for patients with mild stroke defined as NIHSS score 0 to 4. ¹⁶⁴ In ECASS III, there was no significant interaction of benefit (mRS score 0-1 at 90 days) or safety (sICH or death) with stroke severity when patients were categorized by baseline NIHSS score of 0 to 9, 10 to 19, and >20. ¹⁶⁵ In SITS-ISTR (Safe Implementation of Treatments in Stroke-International Stroke Thrombolysis Registry), good functional outcomes (mRS score 0-1 at 90 days) and risk of sICH were similar or the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours. ¹⁶⁶ Similarly, in the AHA GWTG registry, good functional outcomes, mortality, and risk of sICH were the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours. ¹⁶⁷ These patients were not further categorized by whether their acute neurological deficits were disabling. The PRISMS RCT (A Study of the Safety and Efficacy of Activase [Alteplase] in Patients With Mild Stroke) evaluated IV alteplase in patients with mild (NIHSS score 0-5) AIS whose acute neurological deficits were judged to not interfere with activities of daily living or prevent return to work. There was no benefit of treatment within 3 hours of onset. ¹⁶⁸ | | | See Tables XXXV and XXXVI in online Data Supplement 1 . |

| 3.5.4. Other Specific Circumstances | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial. | IIa | B-NR | New recommendation. |
| A case-control analysis using the population from the AHA GWTG-Stroke registry, including 832 cases with sickle cell disease (all adults) 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 did not have a significant impact on the safety or the outcome at discharge of treatment with IV alteplase. ¹⁶⁹ | | | See Table XXXVII in online Data Supplement 1 . |
| 2. In patients with a hyperdense MCA sign, IV alteplase can be beneficial. | IIa | B-NR | New recommendation. |
| Analyses of data from RCTs of IV alteplase for AIS have shown no statistically significant deleterious interaction on clinical outcomes between alteplase treatment and the hyperdense MCA sign on baseline CT. In the NINDS rt-PA trial, there was no interaction between hyperdense MCA sign and treatment for outcomes at 3 months measured by any of the 4 clinical scales (mRS score 0–1, NIHSS score 0–1, Barthel Index score ≥95, Glasgow Outcome Scale score 0–1) or for death. ¹⁷⁰ In IST-3, no significant interaction of the hyperdense MCA sign with benefit of alteplase measured by the Oxford Handicap Score at 6 months was observed. ^{171,172} | | | See Table XXXVIII in online Data Supplement 1 . |

| 3.5.5. Bleeding Risk | COR | LOE | New, Revised, or Unchanged |
|--|-----------|------|--|
| 1. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test. | IIa | B-NR | Recommendation and COR unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. In otherwise eligible patients who have previously had a small number (1–10) of CMBs demonstrated on MRI, administration of IV alteplase is reasonable. | IIa | B-NR | New recommendation. |
| 3. In otherwise eligible patients who have previously had a high burden of CMBs (>10) demonstrated on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit. | IIb | B-NR | New recommendation. |
| CMBs are common in patients receiving IV alteplase, occurring in 15% to 27%. ^{89–94} No RCTs of IV alteplase in AIS with baseline MRI to identify CMBs have been conducted, so no determination of the effect of baseline CMB on the treatment effect of alteplase with CMB is available. Two meta-analyses of the association of baseline CMBs on the risk of sICH after IV alteplase reported that sICH is more common in patients with baseline CMBs, whereas 2 other meta-analyses and 1 multicenter study did not. ^{89–93} In 2 studies using ECASS II sICH criteria, the rates in patients with CMBs were 5.8% and 6.5% compared with 5.3% in ECASS III. ^{49,90,91} One study analyzing the risk of sICH in patients with CMBs detected after IV alteplase treatment reported sICH of 5% using the NINDS criteria compared with 6.4% in the NINDS rt-PA trials. ^{48,94} The risk of sICH in patients with >10 CMBs (30%–47%) is consistently reported as significantly greater than in those with no CMBs (1%–4.4%). However, these data are based on <50 patients, constituting < 2% of these series. ^{90,91,93,94} Meta-analysis of 4 studies that provide information on 3- to 6-month functional outcomes showed that the presence of CMBs was associated with worse outcomes after IV alteplase compared with patients without CMBs (OR, 1.58 [95% CI, 1.18–2.14]; <i>P</i> =0.002). ⁸⁹ Thus, the presence of CMBs increases the risk of ICH and the chances of poor outcomes after IV alteplase, but it is unclear whether these negative effects fully negate the benefit of IV alteplase. It is also unknown whether the location and number of CMBs may differentially influence outcomes. These questions deserve further investigation. | | | See Table XXI in online Data Supplement 1 . |
| 4. The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatid coadministered with IV alteplase is not well established. | IIb | B-R | Recommendation revised from 2013 AIS Guidelines. |
| Single-arm studies of eptifibatid as adjunctive therapy to IV alteplase support ongoing RCTs to establish safety and efficacy. ^{173,174} Further clinical trials are needed. | | | See Table XXXIX in online Data Supplement 1 . |
| 5. Abciximab should not be administered concurrently with IV alteplase. | III: Harm | B-R | Recommendation reworded for clarity from 2015 IV Alteplase. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 6. IV aspirin should not be administered within 90 minutes after the start of IV alteplase. | III: Harm | B-R | New recommendation. |
| The ARTIS trial (Antiplatelet Therapy in Combination with rt-PA Thrombolysis in Ischemic Stroke) compared the effects of very early addition (within 90 minutes) of 300 mg IV aspirin to alteplase with standard treatment with alteplase without IV aspirin. ¹⁷⁵ The trial was terminated after 642 of the 800 targeted patients had been enrolled because IV aspirin was associated with an increased risk of symptomatic intracranial hemorrhage (4.3% versus 1.6% in the standard treatment group; RR, 2.78 [95% CI, 1.01–7.63]; <i>P</i> =0.04) and no difference in the rate of favorable functional outcome (mRS score 0–2) at 3 months (54.0% of patients in the aspirin group versus 57.2% of patients in the standard treatment group; RR, 0.94 [95% CI, 0.82–1.09]; <i>P</i> =0.42). | | | See Table XL in online Data Supplement 1 . |

| 3.5.5. Bleeding Risk (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|------------------|-------------|---|
| 7. IV alteplase should not be administered to patients who have received a full treatment dose of low-molecular-weight heparin (LMWH) within the previous 24 hours. | III: Harm | B-NR | Recommendation reworded for clarity from 2015 IV Alteplase. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| The recommendation refers to full treatment doses and not to prophylactic doses. The 2015 “Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke” stated, “Intravenous alteplase in patients who have received a dose of LMWH within the previous 24 hours is not recommended. This applies to both prophylactic doses and treatment doses (COR III; Level of Evidence B).” ¹⁴ This statement was updated in a subsequently published erratum to specify that the contraindication does not apply to prophylactic doses. | | | |

| 3.5.6. Post-alteplase Treatment | COR | LOE | New, Revised, or Unchanged |
|---|-----------|-------------|--|
| 1. BP should be maintained at <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment. | I | B-R | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Main elements of postthrombolysis care are listed in Table 9. ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) randomized 2196 alteplase-eligible patients with AIS and systolic BP (SBP) ≥ 150 mm Hg to receive intensive target SBP of 130 to 140 mm Hg within 1 hour versus guideline target SBP < 180 mm Hg; 1081 were in the intensive group, and 1115 were in the guideline group. ¹⁷⁶ Median time from stroke onset to randomization was 3.3 hours. Mean SBP in the intensive group was 144.3 mm Hg, and mean SBP in the guideline group was 149.8 mm Hg. Primary outcome mRS score at 90 days did not differ between the 2 groups. Although fewer patients in the intensive group had ICH, the number of patients with serious adverse events did not differ between the 2 groups. Although intensive BP lowering was observed to be safe, the observed reduction in ICH did not lead to improved clinical outcome compared with guideline treatment. | | | See Table XLJ in online Data Supplement 1 . <small>American Stroke Association. A Division of the American Heart Association.</small> |
| 2. The risk of antithrombotic therapy (other than IV aspirin) within the first 24 hours after treatment with IV alteplase (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 IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk. | Ib | B-NR | New recommendation. |
| A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (< 24 hours) after IV alteplase or EVT compared with initiation > 24 hours. However, this study may have been subject to selection bias, and the timing of the initiation of antiplatelet therapy or anticoagulation should be based on an individual level, balancing risk and benefit. ¹⁷⁷ | | | See Table XLII in online Data Supplement 1 . |

Table 6. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of AIS

| COR I/b | LOE C-E/O |
|---|-----------|
| Stop alteplase infusion | |
| CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match | |
| Emergent nonenhanced head CT | |
| Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL | |
| Tranexamic acid 1000 mg IV infused over 10 min OR ε-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 or declined by patient/family or if cryoprecipitate is not available in a timely manner.) | |
| Hematology and neurosurgery consultations | |
| Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control | |

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.
Sources: Sloan et al,¹³⁸ Mahaffey et al,¹³⁹ Goldstein et al,¹⁴⁰ French et al,¹⁴¹ Yaghi et al,^{142–144} Stone et al,¹⁴⁵ and Frontera et al.¹⁴⁶

Table 7. Management of Orolingual Angioedema Associated With IV Alteplase Administration for AIS

| COR I/b | LOE C-E/O |
|--|-----------|
| Maintain airway | |
| Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips. | |
| Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation. | |
| Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis after IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase. | |
| Discontinue IV alteplase infusion 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 epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL | |
| Icatibant, a selective bradykinin B ₂ 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 | |
| Supportive care | |

ACE indicates angiotensin-converting enzyme; AIS, acute ischemic stroke; COR, class of recommendation; IV, intravenous; and LOE, Level of Evidence.
Sources: Foster-Goldman and McCarthy,¹⁴⁷ Gorski and Schmidt,¹⁴⁸ Lewis,¹⁴⁹ Lin et al,¹⁵⁰ Correia et al,¹⁵¹ O'Carroll and Aguilar,¹⁵² Myslimi et al,¹⁵³ and Pahn et al.¹⁵⁴

Table 8. Eligibility Recommendations for IV Alteplase in Patients With AIS

| Indications (COR I) | |
|----------------------------------|---|
| Within 3 h* | IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility.† (COR I; LOE A) |
| Within 3 h–Age | For otherwise medically eligible patients ≥18 y of age, IV alteplase administration within 3 h is equally recommended for patients ≤80 and >80 y of age.† (COR I; LOE A) |
| Within 3 h–Severe stroke | For severe stroke, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms.† (COR I; LOE A) |
| Within 3 h–Mild disabling stroke | For otherwise eligible patients with mild but disabling stroke symptoms, IV alteplase is recommended for patients who can be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state (COR I; LOE B–R)‡ |
| 3–4.5 h* | IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility.† (COR I; LOE B–R)§ |
| 3–4.5 h–Age | IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one-third of the MCA territory.† (COR I; LOE B–R)§ |
| Urgency | Treatment should be initiated as quickly as possible within the above-listed time frames because time to treatment is strongly associated with outcomes.† (COR I; LOE A) |
| BP | IV alteplase is recommended in patients with BP <185/110 mmHg and in those patients whose BP can be lowered safely to this level with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase.† (COR I; LOE B–R)§ |
| Blood glucose | IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.† (COR I; LOE A) |
| CT | IV alteplase administration is recommended in the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity).† (COR I; LOE A) |

(Continued)

Table 8. Continued

| | |
|--|---|
| Prior antiplatelet therapy | IV alteplase is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH.† (COR I; LOE A) |
| | IV alteplase is recommended for patients taking antiplatelet drug combination therapy (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH.† (COR I; LOE B-NR)§ |
| End-stage renal disease | In patients with end-stage renal disease on hemodialysis and normal aPTT, IV alteplase is recommended.† (COR I; LOE C-LD)§ However, those with elevated aPTT may have elevated risk for hemorrhagic complications. |
| Additional recommendations for treatment with IV alteplase for patients with AIS (COR IIa) | |
| 3 to 4.5 h—Age | For patients >80 y of age presenting in the 3- to 4.5-h window, IV alteplase is safe and can be as effective as in younger patients.† (COR IIa; LOE B-NR)§ |
| 3 to 4.5 h—Diabetes mellitus and prior stroke | In AIS patients with prior stroke and diabetes mellitus presenting in the 3- to 4.5-h window, IV alteplase may be as effective as treatment in the 0- to 3-h window and may be a reasonable option.† (COR IIb; LOE B-NR)§ |
| 3 to 4.5 h—Severe stroke | The benefit of IV alteplase between 3 and 4.5 h from symptom onset for patients with very severe stroke symptoms (NIHSS score >25) is uncertain.† (COR IIb; LOE C-LD)§ |
| 3 to 4.5 h—Mild disabling stroke | For otherwise eligible patients with mild disabling stroke, IV alteplase may be reasonable for patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well or at baseline state. (COR IIb; LOE B-NR)‡ |
| Wake-up and unknown time of onset | IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) administered within 4.5 h of stroke symptom recognition can be beneficial in patients with AIS who awake with stroke symptoms or have unclear time of onset >4.5 h from last known well or at baseline state and who have a DW-MRI lesion smaller than one-third of the MCA territory and no visible signal change on FLAIR. (COR IIa; LOE B-R)‡ |
| Preexisting disability | Preexisting disability does not seem to independently increase the risk of sICH after IV alteplase, but it may be associated with less neurological improvement and higher mortality. Therapy with IV alteplase for acute stroke patients with preexisting disability (mRS score ≥2) may be reasonable, but decisions should take into account relevant factors, including quality of life, social support, place of residence, need for a caregiver, patients' and families' preferences, and goals of care.† (COR IIb; LOE B-NR)§ |
| | Patients with preexisting dementia may benefit from IV alteplase. Individual considerations such as life expectancy and premorbid level of function are important to determine whether alteplase may offer a clinically meaningful benefit.† (COR IIb; LOE B-NR)§ |
| Early improvement | IV alteplase treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner.† (COR IIa; LOE A) |
| Seizure at onset | IV alteplase is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon.† (COR IIa; LOE C-LD)§ |
| Blood glucose | Treatment with IV alteplase in patients with AIS who present with initial glucose levels <50 or >400 mg/dL that are subsequently normalized and who are otherwise eligible may be reasonable. (Recommendation modified from 2015 IV Alteplase to conform to text of 2015 IV Alteplase. [COR IIb; LOE C-LD)§ |
| Coagulopathy | IV alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤1.7 or a PT <15 s.† (COR IIb; LOE B-NR)§ |
| | The safety and efficacy of IV alteplase for acute stroke patients with a clinical history of potential bleeding diathesis or coagulopathy are unknown. IV alteplase may be considered on a case-by-case basis.† (COR IIb; LOE C-EO)§ |
| Dural puncture | IV alteplase may be considered for patients who present with AIS, even in instances when they may have undergone a lumbar dural puncture in the preceding 7 d.† (COR IIb; LOE C-EO)§ |
| Arterial puncture | The safety and efficacy of administering IV alteplase to acute stroke patients who have had an arterial puncture of a noncompressible blood vessel in the 7 d preceding stroke symptoms are uncertain.† (COR IIb; LOE C-LD)§ |
| Recent major trauma | In AIS patients with recent major trauma (within 14 d) not involving the head, IV alteplase may be carefully considered, with the risks of bleeding from injuries related to the trauma weighed against the severity and potential disability from the ischemic stroke. (Recommendation modified from 2015 IV Alteplase to specify that it does not apply to head trauma. [COR IIb; LOE C-LD)§ |
| Recent major surgery | Use of IV alteplase in carefully selected patients presenting with AIS who have undergone a major surgery in the preceding 14 d may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits.† (COR IIb; LOE C-LD)§ |
| GI and genitourinary bleeding | Reported literature details a low bleeding risk with IV alteplase administration in the setting of past GI/genitourinary bleeding. Administration of IV alteplase in this patient population may be reasonable.† (COR IIb; LOE C-LD)§ (Note: Alteplase administration within 21 d of a GI bleeding event is not recommended; see Contraindications.) |

(Continued)

Table 8. Continued

| | |
|-------------------------------------|--|
| Menstruation | IV alteplase is probably indicated in women who are menstruating who present with AIS and do not have a history of menorrhagia. However, women should be warned that alteplase treatment could increase the degree of menstrual flow.† (COR IIa; LOE C-EO)§ |
| | When there is a history of recent or active vaginal bleeding causing clinically significant anemia, then emergency consultation with a gynecologist is probably indicated before a decision about IV alteplase is made.† (COR IIa; LOE C-EO)§ |
| | Because the potential benefits of IV alteplase probably outweigh the risks of serious bleeding in patients with recent or active history of menorrhagia without clinically significant anemia or hypotension, IV alteplase administration may be considered.† (COR IIb; LOE C-LD)§ |
| Extracranial cervical dissections | IV alteplase in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 h and probably recommended.† (COR IIa; LOE C-LD)§ |
| Intracranial arterial dissection | IV alteplase usefulness and hemorrhagic risk in AIS known or suspected to be associated with intracranial arterial dissection remain unknown, uncertain and not well established.† (COR IIb; LOE C-LD)§ |
| Unruptured intracranial aneurysm | For patients presenting with AIS who are known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of IV alteplase is reasonable and probably recommended.† (COR IIa; LOE C-LD)§ |
| | Usefulness and risk of IV alteplase in patients with AIS who harbor a giant unruptured and unsecured intracranial aneurysm are not well established.† (COR IIb; LOE C-LD)§ |
| Intracranial vascular malformations | For patients presenting with AIS who are known to harbor an unruptured and untreated intracranial vascular malformation the usefulness and risks of administration of IV alteplase are not well established.† (COR IIb; LOE C-LD)§ |
| | Because of the increased risk of ICH in this population of patients, IV alteplase may be considered in patients with stroke with severe neurological deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH.† (COR IIb; LOE C-LD)§ |
| CMBs | In otherwise eligible patients who have previously had a small number (1–10) of CMBs demonstrated on MRI, administration of IV alteplase is reasonable. (COR IIa; Level B-NR)‡ |
| | In otherwise eligible patients who have previously had a high burden of CMBs (>10) demonstrated on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit. (COR IIb; Level B-NR)‡ |
| Concomitant tirofiban, eptifibatide | The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide coadministered with IV alteplase is not well established. (COR IIb; Level B-NR)‡ |
| Extra-axial intracranial neoplasms | IV alteplase treatment is probably recommended for patients with AIS who harbor an extra-axial intracranial neoplasm.† (COR IIa; LOE C-EO)§ |
| Acute MI | For patients presenting with concurrent AIS and acute MI, treatment with IV alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated, is reasonable.† (COR IIa; LOE C-EO)§ |
| Recent MI | For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase is reasonable if the recent MI was non-STEMI.† (COR IIa; LOE C-LD)§ |
| | For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase is reasonable if the recent MI was a STEMI involving the right or inferior myocardium.† (COR IIa; LOE C-LD)§ |
| | For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase may reasonable if the recent MI was a STEMI involving the left anterior myocardium.† (COR IIb; LOE C-LD)§ |
| Acute pericarditis | For patients with major AIS likely to produce severe disability and acute pericarditis, treatment with IV alteplase may be reasonable.† (COR IIb; LOE C-EO)§; urgent consultation with a cardiologist is recommended in this situation. |
| | For patients presenting with moderate AIS likely to produce mild disability and acute pericarditis, treatment with IV alteplase is of uncertain net benefit.† (COR IIb; LOE C-EO)§ |
| Left atrial or ventricular thrombus | For patients with major AIS likely to produce severe disability and known left atrial or ventricular thrombus, treatment with IV alteplase may be reasonable.† (COR IIb; LOE C-LD)§ |
| | For patients presenting with moderate AIS likely to produce mild disability and known left atrial or ventricular thrombus, treatment with IV alteplase is of uncertain net benefit.† (COR IIb; LOE C-LD)§ |
| Other cardiac diseases | For patients with major AIS likely to produce severe disability and cardiac myxoma, treatment with IV alteplase may be reasonable.† (COR IIb; LOE C-LD)§ |
| | For patients presenting with major AIS likely to produce severe disability and papillary fibroelastoma, treatment with IV alteplase may be reasonable.† (COR IIb; LOE C-LD)§ |
| Procedural stroke | IV alteplase is reasonable for the treatment of AIS complications of cardiac or cerebral angiographic procedures, depending on the usual eligibility criteria.† (COR IIa; LOE A)§ |

(Continued)

Table 8. Continued

| | |
|--|---|
| Systemic malignancy | The safety and efficacy of IV alteplase in patients with current malignancy are not well established.† (COR IIb; LOE C-LD)§ Patients with systemic malignancy and reasonable (>6 mo) life expectancy may benefit from IV alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist. |
| Pregnancy | IV alteplase administration may be considered in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding.† (COR IIb; LOE C-LD)§ |
| | The safety and efficacy of IV alteplase in the early postpartum period (<14 d after delivery) have not been well established.† (COR IIb; LOE C-LD)§ |
| Ophthalmological conditions | Use of IV alteplase in patients presenting with AIS who have a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable to recommend, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurological deficits.† (COR IIa; LOE B-NR)§ |
| Sickle cell disease | IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial. (COR IIa; LOE B-NR)‡ |
| Hyperdense MCA sign | In patients with a hyperdense MCA sign, IV alteplase can be beneficial. (COR IIa; LOE B-NR)‡ |
| Illicit drug use | Treating clinicians should be aware that illicit drug use may be a contributing factor to incident stroke. IV alteplase is reasonable in instances of illicit drug use–associated AIS in patients with no other exclusions.† (COR IIa; LOE C-LD)§ |
| Stroke mimics | The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies.† (COR IIa; LOE B-NR)§ |
| Contraindications (COR III: No Benefit) And (COR III: Harm) | |
| 0- to 3-h window—Mild nondisabling stroke | For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. (COR III: No Benefit, LOE B-R)‡ |
| 3- to 4.5-h window—Mild nondisabling stroke | For otherwise eligible patients with mild nondisabling stroke (NIHSS score 0–5), IV alteplase is not recommended for patients who could be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well or at baseline state. (COR III: No Benefit, LOE C-LD)‡ |
| CT | There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering IV alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury.† (COR III: No Benefit; LOE A)¶ |
| ICH | IV alteplase should not be administered to a patient whose CT reveals an acute intracranial hemorrhage.† (COR III: Harm; LOE C-EO)§¶ |
| Ischemic stroke within 3 mo | Use of IV alteplase in patients presenting with AIS who have had a prior ischemic stroke within 3 mo may be harmful.† (COR III: Harm; LOE B-NR)§¶ |
| Severe head trauma within 3 mo | In AIS patients with recent severe head trauma (within 3 mo), IV alteplase is contraindicated.† (COR III: Harm; LOE C-EO)§¶ |
| Acute head trauma | Given the possibility of bleeding complications from the underlying severe head trauma, IV alteplase should not be administered in posttraumatic infarction that occurs during the acute in-hospital phase.† (COR III: Harm; LOE C-EO)§¶ (Recommendation wording modified to match COR III stratifications.) |
| Intracranial/intraspinal surgery within 3 mo | For patients with AIS and a history of intracranial/spinal surgery within the prior 3 mo, IV alteplase is potentially harmful.† (COR III: Harm; LOE C-EO)§¶ |
| History of intracranial hemorrhage | IV alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful.† (COR III: Harm; LOE C-EO)§¶ |
| Subarachnoid hemorrhage | IV alteplase is contraindicated in patients presenting with symptoms and signs most consistent with an SAH.† (COR III: Harm; LOE C-EO)§¶ |
| GI malignancy or GI bleed within 21 d | Patients with a structural GI malignancy or recent bleeding event within 21 d of their stroke event should be considered high risk, and IV alteplase administration is potentially harmful.† (COR III: Harm; LOE C-EO)§¶ |
| Coagulopathy | The safety and efficacy of IV alteplase for acute stroke patients with platelets <100 000/mm ³ , INR >1.7, aPTT >40 s, or PT >15 s are unknown, and IV alteplase should not be administered.† (COR III: Harm; LOE C-EO)§¶ (In patients without history of thrombocytopenia, treatment with IV alteplase can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm ³ . In patients without recent use of OACs or heparin, treatment with IV alteplase can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.) (Recommendation wording modified to match COR III stratifications.) |
| LMWH | IV alteplase should not be administered to patients who have received a full treatment dose of LMWH within the previous 24 h.† (COR III: Harm; LOE B-NR)§‡ (Recommendation wording modified to match COR III stratifications.) |

(Continued)

Table 8. Continued

| | |
|---|---|
| Thrombin inhibitors or factor Xa inhibitors | The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful.† (COR III: Harm; LOE C-EO)§ IV alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 h (assuming normal renal metabolizing function). (Alteplase could be considered when appropriate laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these ACs for >48 h and renal function is normal.) (Recommendation wording modified to match COR III stratifications.) |
| Concomitant Abciximab | Abciximab should not be administered concurrently with IV alteplase. (COR III: Harm; LOE B-R)‡ |
| Concomitant IV aspirin | IV aspirin should not be administered within 90 min after the start of IV alteplase. (COR III: Harm; LOE B-R)‡ |
| Infective endocarditis | For patients with AIS and symptoms consistent with infective endocarditis, treatment with IV alteplase should not be administered because of the increased risk of intracranial hemorrhage.† (COR III: Harm; LOE C-LD)§ (Recommendation wording modified to match COR III stratifications.) |
| Aortic arch dissection | IV alteplase in AIS known or suspected to be associated with aortic arch dissection is potentially harmful and should not be administered.† (COR III: Harm; LOE C-EO)§ (Recommendation wording modified to match COR III stratifications.) |
| Intra-axial intracranial neoplasm | IV alteplase treatment for patients with AIS who harbor an intra-axial intracranial neoplasm is potentially harmful.† (COR III: Harm; LOE C-EO)§ |

Unless otherwise specified, these eligibility recommendations apply to patients who can be treated within 0 to 4.5 hours of ischemic stroke symptom onset or patient last known well or at baseline state.

Clinicians should also be informed of the indications and contraindications from local regulatory agencies (for current information from the US Food and Drug Administration refer to http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/103172s5203lbl.pdf).

For a detailed discussion of this topic and evidence supporting these recommendations, refer to the American Heart Association (AHA) scientific statement on the rationale for inclusion and exclusion criteria for IV alteplase in AIS.¹⁴

AC indicates anticoagulants; AIS, acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CMB, cerebral microbleed; COR, class of recommendation; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; LOE, level of evidence; MCA, middle cerebral artery; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; PT, prothrombin time; sICH, symptomatic intracerebral hemorrhage; and STEMI, ST-segment–elevation myocardial infarction.

*When uncertain, the time of onset time should be considered the time when the patient was last known to be normal or at baseline neurological condition.

†Recommendation unchanged or reworded for clarity from 2015 IV Alteplase. See Table XCV in [online Data Supplement 1](#) for original wording.

‡See also the text of these guidelines for additional information on these recommendations.

§LOE amended to conform with American College of Cardiology/AHA 2015 Recommendation Classification System.

||COR amended to conform with American College of Cardiology/AHA 2015 Recommendation Classification System.


Table 9. Treatment of AIS: IV Administration of 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. |
| 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 emergency head CT scan. |
| Measure BP and perform neurological assessments every 15 min during and after IV alteplase infusion 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 (Table 5). |
| Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them. |
| Obtain a follow-up CT or MRI scan at 24 h after IV alteplase before starting anticoagulants or antiplatelet agents. |

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

Reprinted from Jauch et al.¹ Copyright © 2013, American Heart Association, Inc.

3.6. Other IV Fibrinolytics and Sonothrombolysis

| 3.6. Other IV Fibrinolytics and Sonothrombolysis | COR | LOE | New, Revised, or Unchanged |
|---|------------------------|------------|--|
| 1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy. | IIb | B-R | New recommendation. |
| IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke). ¹⁷⁸ This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase ($P=0.002$ for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; $P=0.04$) but less robustly for the proportion who achieved an mRS score of 0 to 1 ($P=0.23$) or 0 to 2 ($P=0.06$). sICH rates were 1% in both groups. | | | See Table XLIII in online Data Supplement 1 . |
| 2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion. | IIb | B-R | New recommendation. |
| IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase. ^{179–182} In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion. ¹⁸² Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase. | | | See Table XLIII in online Data Supplement 1 .  |
| 3. The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended. | III: No Benefit | B-R | Recommendation revised from 2013 AIS Guidelines. |
| Randomized placebo-controlled trials have not shown benefit from the administration of IV streptokinase within 6 hours or desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra, large intracranial artery occlusion, or severe stenosis. ^{155,183–186} | | | See Table XLIII in online Data Supplement 1 . |
| 4. The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended. | III: No Benefit | A | New recommendation. |
| Since the publication of the 2013 AIS Guidelines, 2 RCTs of sonothrombolysis as adjuvant therapy for IV thrombolysis 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 (93 patients) or sham (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. ¹⁸⁷ CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke) 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 (335) or sham ultrasound (341). ¹⁸⁸ Compared with the control arm, the neurological improvement, death, and serious adverse events 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. | | | See Table XLIV in online Data Supplement 1 . |


3.7. Mechanical Thrombectomy

| 3.7.1. Concomitant With IV Alteplase | COR | LOE | New, Revised, or Unchanged |
|---|----------|----------|--|
| 1. Patients eligible for IV alteplase should receive IV alteplase even if mechanical thrombectomy is being considered. | I | A | Recommendation reworded for clarity from 2015 Endovascular. See Table XCV in online Data Supplement 1 for original wording. |

| 3.7.1. Concomitant With IV Alteplase (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----------|-----|---|
| 2. In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed. | III: Harm | B-R | Recommendation revised from 2015 Endovascular. |
| <p>In pooled patient-level data from 5 trials (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials], which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS score distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; and cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes.⁴² Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, 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]).⁴² The REVASCAT trial included a 30-minute period of observation before undertaking EVT. Available data do not directly address the question of whether patients should be observed after IV alteplase to assess for clinical response before pursuing mechanical thrombectomy. However, one can infer that because disability outcomes at 90 days were directly associated with time from symptom onset to arterial puncture, any cause for delay to mechanical thrombectomy, including observing for a clinical response after IV alteplase, should be avoided. Therefore, the recommendation is slightly modified from the 2015 Endovascular Update.</p> | | | See Tables XVII and XLV in online Data Supplement 1 . |

| 3.7.2. 0 to 6 Hours From Onset | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|--|
| 1. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset. | I | A | Recommendation revised from 2015 Endovascular. |
| <p>Results from 6 recent randomized trials of mechanical thrombectomy using predominantly stent retriever devices (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE) support COR I, LOE A recommendations for a defined group of patients as described in the 2015 Guidelines.^{105–110} A pooled, patient-level analysis from 5 of these studies reported by the HERMES Collaboration showed treatment effect in the subgroup of 188 patients not treated with IV alteplase (cOR, 2.43 [95% CI, 1.30–4.55]); therefore, pretreatment with IV alteplase has been removed from the prior recommendation. The HERMES pooled patient-level data also showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years of age (cOR, 3.68 [95% CI, 1.95–6.92]).¹⁸⁹ In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration [Safety and Efficacy of Solitaire Stent Thrombectomy—Individual Patient Data Meta-Analysis of Randomized Trials]: SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT) showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years of age (3.46 [95% CI, 1.58–7.60]).¹⁹⁰ In a meta-analysis of 5 RCTs (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT), there was favorable effect with mechanical thrombectomy over standard care without heterogeneity of effect across patient age subgroups (for patients <70 and ≥70 years of age: OR, 2.41 [95% CI, 1.51–3.84] and 2.26 [95% CI, 1.20–4.26], respectively).¹⁹¹ However, the number of patients in these trials who were ≥90 years of age was very small, and the benefit of mechanical thrombectomy over standard care in patients ≥90 years of age is not clear. As with any treatment decision in an elderly patient, consideration of comorbidities and risks should factor into the decision-making for mechanical thrombectomy.</p> | | | See Tables XVII and XLV in online Data Supplement 1 . |
| 2. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs. | IIb | B-R | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE revised. See Table XCV in online Data Supplement 1 for original wording. |
| <p>In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the direction of treatment effect for mechanical thrombectomy over standard care was favorable in M2 occlusions, but the adjusted cOR was not significant (1.28 [95% CI, 0.51–3.21]).¹⁸⁹ In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration: SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT) showed that the direction of treatment effect was favorable for mechanical thrombectomy over standard care in M2 occlusions, but the OR and 95% CI were not significant.¹⁹⁰ In an analysis of pooled data from SWIFT (Solitaire With the Intention for Thrombectomy), STAR (Solitaire Flow Restoration Thrombectomy for Acute Revascularization), DEFUSE 2, and IMS III, among patients with M2 occlusions, reperfusion was associated with excellent functional outcomes (mRS score 0–1; OR, 2.2 [95% CI, 1.0–4.7]).¹⁹² Therefore, the recommendation for mechanical thrombectomy for M2/M3 occlusions does not change substantively from the 2015 AHA/ASA focused update.</p> | | | See Tables XVII and XLV in online Data Supplement 1 . |

| 3.7.2. 0 to 6 Hours From Onset (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-------------|------|--|
| 3. Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). | I lb | B-R | Recommendation unchanged from 2015 Endovascular. |
| 4. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries. | I lb | C-LD | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

| 3.7.3. 6 to 24 Hours From Onset | COR | LOE | New, Revised, or Unchanged |
|--|-------------|-----|---|
| 1. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended. | I | A | New recommendation. |
| 2. In selected patients with AIS within 16 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable. | I la | B-R | New recommendation. |
| The DAWN trial used clinical-core mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in function outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority >0.999). ⁵¹ In DAWN, there were few strokes with witnessed onset (12%). The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; $P<0.0001$). ⁵² Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice. ^{51,52} | | | See Table XVII in online Data Supplement 1 .  |

| 3.7.4. Technique | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|--|
| 1. Use of stent retrievers is indicated in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERC) device. | I | A | Recommendation unchanged from 2015 Endovascular. |
| 2. The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome. | I | A | Recommendation reworded for clarity from 2015 Endovascular. See Table XCV in online Data Supplement 1 for original wording. |
| Mechanical thrombectomy aims to achieve reperfusion, not simply recanalization. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes. ^{193,194} All recent endovascular trials used the mTICI grade 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to mTICI grade 2b/3. ¹⁸⁹ Earlier trials with less efficient devices showed lower recanalization rates, a factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%). The additional benefit of pursuing mTICI of grade 3 rather than grade 2b deserves further investigation. | | | |

| 3.7.4. Technique (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|---|
| 3. To ensure benefit, reperfusion to mTICI grade 2b/3 should be achieved as early as possible within the therapeutic window. | I | A | Recommendation revised from 2015 Endovascular. |
| 4. In the 6- to 24-hour thrombectomy window evaluation and treatment should proceed as rapidly as possible to ensure access to treatment for the greatest proportion of patients. | I | B-R | New recommendation. |
| <p>In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), ARD for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), and ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes.⁴² Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, 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]).⁴² The 6- to 16- and 6- to 24-hour treatment windows trials, which utilized advanced imaging to identify a relatively uniform patient group, showed limited variability of treatment effect with time in these highly selected patients.^{51,52} The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.^{128,129} All recent endovascular trials used the mTICI 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to TICI 2b/3.¹⁸⁹ Earlier trials with less efficient devices showed lower recanalization rates, 1 factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%).</p> | | | See Tables XVII and XLV in online Data Supplement 1 . |
| 5. Direct aspiration thrombectomy as first-pass mechanical thrombectomy is recommended as noninferior to stent retriever for patients who meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS ≥6; and (6) treatment initiation (groin puncture) within 6 hours of symptom onset. | I | B-R | Recommendation revised from 2015 Endovascular. <small>American Stroke Association A Division of the American Heart Association</small> |
| <p>Comparative available randomized data has assessed patients primarily in the therapeutic window within 6 hours of onset. The COMPASS (Comparison of Direct Aspiration Versus Stent Retriever as a First Approach) trial randomized patients with (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age ≥18 years; (4) NIHSS score of ≥5; (5) ASPECTS ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset to aspiration thrombectomy or stentriever thrombectomy as first-line technique. Primary outcome was noninferiority of mRS score at 90 days. An mRS score of 0 to 2 was achieved in 69 of 134 (52%) of patients in the aspiration group and 67 of 136 (50%) in the stentriever group, demonstrating noninferiority of aspiration thrombectomy compared with stentriever thrombectomy ($P_{\text{noninferiority}}=0.0014$). The aspiration thrombectomy group had a 21% rate of stentriever rescue. No difference in recanalization rates or intracranial hemorrhage was found.¹⁹⁵ The ASTER trial (Contact Aspiration vs Stent Retriever for Successful Revascularization) compared the contact aspiration technique and the standard stent retriever technique as first-line mechanical thrombectomy for successful revascularization within 6 hours among patients with acute anterior circulation ischemic stroke and LVO. Eligibility criteria were different from COMPASS, lacking specification of NIHSS or ASPECTS. Primary outcome was successful revascularization. The proportion of patients with successful revascularization at the end of all interventions was 85.4% (n=164) in the contact aspiration group versus 83.1% (n=157) in the stent retriever group (OR, 1.20 [95% CI, 0.68–2.10]; $P=0.53$; difference, 2.4% [95% CI, –5.4 to 9.7]). The secondary clinical end point of mRS score of 0 to 2 at 90 days was achieved by 82 of 181 (45.3%) in the contact aspiration group versus 91 of 182 (50.0%) in the stent retriever group (OR, 0.83 [95% CI, 0.54–1.26]; $P=0.38$). Given its superiority design to detect a 15% difference in the primary end point, this trial was not designed to establish noninferiority.¹⁹⁶ The Penumbra Separator 3D Trial compared a 3-D stent retriever combined with aspiration to aspiration alone as first-line intracranial mechanical thrombectomy for successful revascularization within 8 hours among patients with AIS (NIHSS score of at least 8) and LVO refractory to or ineligible for IV alteplase in a 1:1 randomized, noninferiority trial with a 15% noninferiority margin. The primary end point of mTICI grade 2 to 3 occurred in 87.2% of the combination group versus 82.3% in the aspiration alone group, meeting the noninferiority criterion of lower 90% confidence bound less than –15%. A 90-day mRS score of 0 to 2 was achieved in 45.3% of the combination group and 45.8%, difference –0.5% (95% CI, –15% to 14%) of the aspiration alone group.¹⁹⁷ The trial demonstrated noninferiority of 3-D stent retriever with aspiration versus aspiration alone, using older-generation aspiration technology. The trial was not powered to demonstrate noninferiority in the secondary outcome of 90-day functional independence.</p> | | | See Table XVII in online Data Supplement 1 . |

| 3.7.4. Technique (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 6. It is reasonable to select an anesthetic technique during EVT for AIS on the basis of individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics. | Ila | B-R | Recommendation revised from 2015 Endovascular. |
| Conscious sedation (CS) was the anesthetic modality widely used during endovascular procedures for acute stroke in the recent endovascular trials (90.9% of ESCAPE, 63% of SWIFT PRIME) with no clear positive or negative impact on outcome. In MR CLEAN, post hoc analysis showed a 51% (95% CI, 31–86) decrease in treatment effect with general anesthesia (GA) compared with CS. ¹⁹⁸ In THRACE, 51 of 67 patients receiving GA and 43 of 69 patients receiving CS during acute stroke endovascular procedures achieved mTICI grade 2b/3 ($P=0.059$) with no impact on functional outcomes (35 of 67 patients with GA and 36 of 74 with CS had an mRS score of 0–2 at 90 days). ¹⁰⁹ Thirty-five of 67 patients with GA and 36 of 74 with CS during acute stroke endovascular procedures had mRS scores of 0 to 2 at 90 days. ¹⁰⁹ Although several retrospective studies suggest that GA for acute stroke endovascular procedures produces worsening of functional outcomes, the limited available prospective randomized data do not support this. Three small (≤ 150 participants each) single-center RCTs have compared GA with CS during acute stroke endovascular procedures. All failed to show superiority of GA for the primary end point (2 clinical, 1 DW-MRI infarct growth), whereas 2 of the 3 showed better outcomes for GA for some of the many secondary clinical end points. ^{199–201} Until further data are available, either method of procedural sedation for acute stroke endovascular procedures is reasonable. | | | See Tables XLVI and XLVII in online Data Supplement 1 . |
| 7. The use of a proximal balloon guide catheter or a large-bore distal-access catheter, rather than a cervical guide catheter alone, in conjunction with stent retrievers may be beneficial. | Ila | C-LD | Recommendation and COR unchanged from 2015 Endovascular. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 8. Treatment of tandem occlusions (both extracranial and intracranial occlusions) when performing mechanical thrombectomy may be reasonable. | Ilb | B-R | Recommendation revised from 2015 Endovascular. |
| Tandem occlusions were included in recent endovascular trials that showed benefit of mechanical thrombectomy over medical management alone. In the HERMES meta-analysis, 122 of 1254 tandem occlusions (RR, 1.81 [95% CI, 0.96–3.4]) and 1132 of 1254 nontandem occlusions (RR, 1.71 [95% CI, 1.40–2.09]) were reported compared with medical management. ¹⁸⁹ In THRACE, 24 of 196 tandem occlusions (RR, 1.82 [95% CI, 0.55–6.07]) and 172 of 196 nontandem occlusions (RR, 1.34 [95% CI, 0.87–2.07]) were treated compared with IV alteplase alone. ¹⁰⁹ In HERMES, there is heterogeneity of treatment methods directed to the proximal extracranial carotid occlusion (no revascularization of the proximal lesion versus angioplasty versus stenting). A retrospective analysis of pooled data from 18 centers examined 395 patients with AIS caused by tandem lesion of the anterior circulation who underwent mechanical thrombectomy (TITAN [Thrombectomy in Tandem Lesions]). mTICI grade 2b/3 was achieved in 76.7% of patients. At 90 days, 52.2% achieved an mRS score of 0 to 2, 13.8% had parenchymal hematoma, and 13.2% were dead. ²⁰² Multiple retrospective reports detail the technical success of mechanical thrombectomy for tandem occlusions but do not provide specifics on comparative approaches. No conclusions about the optimum treatment approach for patients with tandem occlusions are therefore possible. | | | See Tables XVII and XLV in online Data Supplement 1 . |
| 9. The safety and efficacy of IV glycoprotein IIb/IIIa inhibitors administered during endovascular stroke treatment are uncertain. | Ilb | C-LD | New recommendation. |
| Uncertainty remains about the safety and efficacy of IV glycoprotein IIb/IIIa inhibitors, including abciximab, administered in the setting of endovascular stroke treatment. The published literature is limited primarily to case series and retrospective reviews of single-center databases and focuses largely on administration of IV glycoprotein IIb/IIIa inhibitors to prevent thrombus formation during emergent carotid and vertebrobasilar artery stenting and mechanical thrombectomy. ^{203–205} Further research is needed comprising multicenter analyses of endovascular stroke therapy necessitating adjunctive antiplatelet therapy for emergent angioplasty and stenting. | | | See Table XXXIX in online Data Supplement 1 . |
| 10. Use of salvage technical adjuncts, including intra-arterial fibrinolysis, may be reasonable to achieve mTICI grade 2b/3 angiographic results. | Ilb | C-LD | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Intra-arterial fibrinolytic therapy played a limited role in the recent endovascular trials but was used as rescue therapy, not initial treatment. In MR CLEAN, the EVT method was at the discretion of operator, with 40 of 233 treated with alternative stent retrievers to Trevo and Solitaire or intra-arterial alteplase. Details are not available, but no patients were treated with intra-arterial alteplase alone. Twenty-four of 233 (10.3%) had treatment with a second modality. Treatment method had no impact on outcomes in this trial. ²⁰⁶ In THRACE, an intra-arterial lytic was used to a maximum dose of 0.3 mg/kg and allowed to establish goal reperfusion, only after mechanical thrombectomy was attempted. A mean dose of 8.8 mg was administered in 15 of 141 patients receiving mechanical thrombectomy (11%). There was no effect on outcomes compared with mechanical thrombectomy alone. | | | |

American Stroke Association
A Division of the American Heart Association

| 3.7.5. Blood Pressure Management | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. In patients who undergo mechanical thrombectomy, it is reasonable to maintain the BP at ≤180/105 mm Hg during and for 24 hours after the procedure. | IIa | B-NR | New recommendation. |
| 2. In patients who undergo mechanical thrombectomy with successful reperfusion, it might be reasonable to maintain BP at a level <180/105 mm Hg. | IIb | B-NR | New recommendation. |
| <p>There are very limited data to guide BP management during and after the procedure in patients who undergo mechanical thrombectomy. RCT data on optimal BP management approaches in this setting are not available. The vast majority of patients enrolled in <6-hour RCTs received IV alteplase, and the trial protocols stipulated management according to local guidelines with BP ≤180/105 during and for 24 hours after the procedure for these participants. Two trial protocols provided additional recommendations. The ESCAPE protocol states that SBP ≥150 mm Hg is probably useful in promoting and keeping collateral flow adequate while the artery remains occluded and that controlling BP once reperfusion has been achieved and aiming for a normal BP for that individual is sensible. Labetalol or an IV β-blocker such as metoprolol in low doses is recommended.¹⁰⁵ The DAWN protocol recommends maintaining SBP <140 mm Hg in the first 24 hours in subjects who are reperfused after mechanical thrombectomy (defined as achieving more than two-thirds MCA territory reperfusion).⁵¹ Further studies are needed to determine the optimal BP target during and after mechanical thrombectomy.</p> | | | See Table XVII in online Data Supplement 1 . |

3.8. Other Endovascular Therapies

| 3.8. Other EVTs | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. Mechanical thrombectomy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy. | I | C-EO | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 2. Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of IV alteplase might be considered, but the consequences are unknown. | IIb | C-EO | Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

3.9. Antiplatelet Treatment

| 3.9. Antiplatelet Treatment | COR | LOE | New, Revised, or Unchanged |
|---|-----|-----|--|
| 1. Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk. | I | A | Recommendation revised from 2013 AIS Guidelines. |
| <p>The safety and benefit of aspirin in the treatment of patients with AIS were established by 2 large clinical trials administering doses between 160 and 300 mg.^{207,208} This has recently been confirmed by a large Cochrane review of aspirin trials.²⁰⁹ In patients unsafe or unable to swallow, rectal or nasogastric administration is appropriate. Limited data exist on the use of alternative antiplatelet agents in the treatment of AIS. However, in patients with a contraindication to aspirin, administering alternative antiplatelet agents may be reasonable. A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or EVT compared with initiation >24 hours.¹⁷⁷ However, this study may have been subject to selection bias, and the timing of initiation of antiplatelet therapy or anticoagulation should be made on an individual level, balancing risk and benefit. The recommendation was modified from the previous guideline to remove the specific dosing recommendation “initial dose is 325 mg” because previous clinical trials supporting its use for AIS included doses of 160 to 300 mg.</p> | | | See Tables XLII and XLVIII in online Data Supplement 1 . |

| 3.9. Antiplatelet Treatment (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|-----|---|
| 2. In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤ 3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset. | I | A | New recommendation. |
| <p>Two independent multicenter, randomized, double-blind, placebo-controlled trials have established the efficacy of short-term dual antiplatelet therapy to prevent recurrent ischemic stroke in patients with minor stroke or high-risk TIA. The CHANCE trial (Clopidogrel in High Risk Patients With Acute Nondisabling Cerebrovascular Events; N=5170) conducted in China studied the efficacy of short-term dual antiplatelet therapy begun within 24 hours in patients with minor stroke (NIHSS score ≤ 3) or high-risk TIA (ABCD2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥ 4). The dosing regimen was clopidogrel at an initial dose of 300 mg followed by 75 mg/d for 90 days plus aspirin at a dose of 75 mg/d for the first 21 days or placebo plus aspirin (75 mg/d for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone: hazard ratio (HR), 0.68 [95% CI, 0.57–0.81; $P < 0.001$].²¹⁰ Post hoc analysis found a small but measurable reduction in poor functional outcome (mRS score 2–6) on dual antiplatelet therapy compared with aspirin alone (absolute RR, 1.7% [95% CI, 0.03%–3.42%]; $P = 0.046$).²¹¹ However, a post hoc time-course analysis showed that the benefit in reducing recurrent ischemic stroke compared with the risk of bleeding on dual antiplatelet therapy dissipated after ≈ 10 days of treatment.²¹² A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days.²¹³ In addition, subgroup analyses found no benefit of clopidogrel plus aspirin in carriers of a CYP2C19 loss-of-function allele²¹⁴ or those with a single acute infarction or no infarction compared with those with multiple acute infarctions,²¹⁵ although these subgroup analyses were likely underpowered.</p> <p>The POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; N=4881) was conducted in North America, Europe, Australia, and New Zealand, with the majority (83%) enrolled in the United States (75% white, 20% black).²¹⁶ Similar to CHANCE, the target enrollment population included minor stroke (NIHSS score ≤ 3) or high-risk TIA (ABCD2 score ≥ 4) within 12 hours of symptom onset. Patients were randomized to either clopidogrel plus aspirin (600-mg loading dose of clopidogrel followed by 75 mg/d from day 2–90) plus open-label aspirin (50–325 mg/d) versus aspirin alone (50–325 mg/d) for 90 days. The primary outcome was a composite of ischemic stroke, myocardial infarction (MI), or death resulting from an ischemic vascular event up to 90 days, with a secondary safety end point of major hemorrhage during the same time period. Compared with aspirin alone, aspirin plus clopidogrel 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]; $P = 0.02$). Overall, the beneficial effect of aspirin plus clopidogrel was driven by a reduction in ischemic stroke (HR, 0.72 [95% CI, 0.56–0.92]; $P = 0.01$) and greatest in the first 30 days of treatment from symptom onset (HR, 0.73 [95% CI, 0.56–0.95]; $P = 0.02$). However, the risk of major hemorrhage was greatest after the first 7 days of treatment (HR, 2.69 [95% CI, 1.05–6.86]; $P = 0.04$). There was no significant added benefit of aspirin plus clopidogrel after 30 days of treatment. In addition, in a prespecified analysis of functional outcomes determined by 90-day mRS score ≥ 2 for new disability, there was no difference between groups (HR, 0.97 [95% CI, 0.82–1.14]; $P = 0.71$).</p> | | | See Table XLVIII in online Data Supplement 1 . |
| 3. The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide in the treatment of AIS is not well established. | IIb | B-R | Recommendation revised from 2013 AIS Guidelines. |
| Prospective, randomized, open-label phase II trials of tirofiban ²¹⁷ and eptifibatide ²¹⁸ have suggested safety for treatment in patients with AIS. Single-arm studies of eptifibatide as adjunctive therapy to IV alteplase support ongoing RCTs to establish safety and efficacy. ^{173,174} Further trials are necessary to clarify the safety and efficacy of this intervention. | | | See Tables XXXIX and XLVIII in online Data Supplement 1 . |
| 4. Ticagrelor is not recommended over aspirin for treatment of patients with minor acute stroke. | III: No Benefit | B-R | New recommendation. |
| The recently completed SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤ 5) or TIA (ABCD2 score ≥ 4). With a primary outcome of time to the composite end point of stroke, MI, or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89 [95% CI, 0.78–1.01]; $P = 0.07$). ²¹⁹ However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin. | | | See Table XLVIII in online Data Supplement 1 . |
| 5. The administration of the IV glycoprotein IIb/IIIa inhibitor abciximab as medical treatment for AIS is potentially harmful and should not be performed. | III: Harm | B-R | Recommendation revised from 2013 AIS Guidelines. |
| A recent Cochrane review of IV glycoprotein IIb/IIIa receptor antagonists in the treatment of AIS found that these agents are associated with a significant risk of ICH without a measurable improvement in death or disability. ²²⁰ The majority of trial data apply to abciximab, which was studied in the AbESTT trial (A Study of Effectiveness and Safety of Abciximab in Patients With Acute Ischemic Stroke). The phase III trial was terminated early because of an unfavorable risk-benefit analysis. ²²¹ | | | See Table XLVIII in online Data Supplement 1 . |
| 6. Aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy. | III: Harm | B-R | Recommendation revised from 2013 AIS Guidelines. |
| Recommendation was modified to eliminate wording about “acute interventions,” which are broadly defined, and to specify that aspirin is a less effective substitute for the treatment of AIS in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy. | | | |



American Stroke Association.
A member of the American Heart Association.

3.10. Anticoagulants


| 3.10. Anticoagulants | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|---|
| 1. The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established. | IIb | B-NR | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. The safety and usefulness of short-term anticoagulation for nonocclusive, extracranial intraluminal thrombus in the setting of AIS are not well established. | IIb | C-LD | New recommendation. |
| The optimal medical management of patients with AIS and radiologic evidence of nonocclusive, intraluminal thrombus (eg, cervical carotid, vertebralbasilar arteries) remains uncertain. Several small observational studies have suggested the safety of short-term IV heparin or LMWH in this setting, ^{222,223} but further research is required to establish safety and efficacy. | | | See Table XLIX in online Data Supplement 1 . |
| 3. At present, the usefulness of argatroban, dabigatran, or other thrombin inhibitors for the treatment of patients with AIS is not well established. | IIb | B-R | Recommendation revised from 2013 AIS Guidelines. |
| Several observational studies have demonstrated the safety and feasibility of treating AIS with thrombin inhibitors as either a single or an adjunct therapy to alteplase. The oral direct thrombin inhibitor dabigatran was studied in 53 patients with TIA or minor stroke (NIHSS score ≤3) with no occurrences of sICH up to 30 days. ²²⁴ ARTSS (Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke)-1 was an open-label, pilot safety study of argatroban infusion plus IV alteplase in 65 patients with complete or partially occlusive thrombus diagnosed by transcranial Doppler. ²²⁵ In the ARTSS-2 phase II study, patients with AIS treated with alteplase (N=90) were randomized to receive placebo or argatroban (100-μg/kg bolus), followed by infusion of either 1 (low dose) or 3 (high dose) μg/kg per minute for 48 hours. Rates of sICH were similar among the control, low-dose, and high-dose arms: 3 of 29 (10%), 4 of 30 (13%), and 2 of 31 (7%), respectively. ²²⁶ Further trials are necessary to clarify the safety and efficacy of this intervention. | | | See Tables XLIX and L in online Data Supplement 1 . |
| 4. The safety and usefulness of oral factor Xa inhibitors in the treatment of AIS are not well established. | IIb | C-LD | New recommendation. |
| Limited data exist on the use of factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban) for treatment of patients with AIS. ²²⁷ Several prospective observational studies and early-phase trials are ongoing (NCT02279940, NCT02042534, NCT02283294). Further clinical trials are needed. | | | See Table LI in online Data Supplement 1 . |
| 5. Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after AIS, is not recommended for treatment of patients with AIS. | III: No Benefit | A | Recommendation and LOE unchanged from 2013 AIS Guidelines. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| Further support for this unchanged recommendation from the 2013 AIS Guidelines is provided by 2 updated meta-analyses that confirm the lack of benefit of urgent anticoagulation. ^{228,229} An additional study, not included in these meta-analyses, investigated the efficacy of LMWH compared with aspirin in preventing early neurological deterioration in an unblinded RCT. Although there was a statistically significant difference in early neurological deterioration at 10 days after admission (LMWH, 27 [3.95%] versus aspirin, 81 [11.82%]; $P<0.001$), there was no difference in 6-month mRS score of 0 to 2 (LMWH, 64.2% versus aspirin, 62.5%; $P=0.33$). ²³⁰ | | | See Table L in online Data Supplement 1 . |

3.11. Volume Expansion/Hemodilution, Vasodilators, and Hemodynamic Augmentation

| 3.11. Volume Expansion/Hemodilution, Vasodilators, and Hemodynamic Augmentation | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|-----|---|
| 1. Hemodilution by volume expansion is not recommended for treatment of patients with AIS. | III: No Benefit | A | Recommendation and LOE unchanged from 2013 AIS Guidelines. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| A recent Cochrane review of 4174 participants from multiple RCTs confirmed the previous guideline recommendation that hemodilution therapy, including varying methods of volume expansion with or without venesection, demonstrates no significant benefit in patients with AIS. ²³¹ | | | See Table LII in online Data Supplement 1 . |
| 2. The administration of high-dose albumin is not recommended for the treatment of patients with AIS. | III: No Benefit | A | Recommendation revised from 2013 AIS Guidelines. |
| The ALIAS (Albumin in Acute Ischemic Stroke) part II trial of high-dose albumin infusion versus placebo in patients with AIS was terminated early for futility. ²³² Combined analysis of the ALIAS parts I and II trials demonstrated no difference between groups in 90-day disability. ²³³ | | | See Table LII in online Data Supplement 1 . |

| 3.11. Volume Expansion/Hemodilution, Vasodilators, and Hemodynamic Augmentation (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|-----|---|
| 3. The administration of vasodilatory agents, such as pentoxifylline, is not recommended for treatment of patients with AIS. | III: No Benefit | A | Recommendation and LOE unchanged from 2013 AIS Guidelines. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 4. Devices to mechanically augment cerebral blood flow for the treatment of patients with AIS are not useful. | III: No Benefit | B-R | New recommendation. |
| Since the 2013 AHA/ASA Guideline, a safety and feasibility RCT of external counterpulsation in AIS has been published. ²³⁴ External counterpulsation was safe and feasible to use in patients with AIS but was associated with unexpected effects on MCA flow velocity. At 30 days, there were no statistically significant differences in clinical end points between the 2 groups, but the study was not powered for this purpose. | | | See Table LIII in online Data Supplement 1 . |

3.12. Neuroprotective Agents

| 3.12. Neuroprotective Agents | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|-----|--|
| 1. At present, pharmacological or nonpharmacological treatments with putative neuroprotective actions are not recommended. | III: No Benefit | A | Recommendation reworded for clarity from 2013 AIS Guidelines. LOE unchanged. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| There have been myriad attempts to establish the efficacy of pharmacological and nonpharmacological interventions with putative neuroprotective action in acute stroke that have failed when tested in human clinical trials. Since the 2013 AIS Guidelines, there have been several more trials testing putative neuroprotective agents that have been negative. The FAST-MAG trial (Field Administration of Stroke Therapy–Magnesium) of prehospital magnesium infusion was the first acute stroke neuroprotection drug trial to enroll participants during ambulance transport, but no differences were seen between the intervention group and placebo control subjects. ²³⁵ The ALIAS trials parts I and II failed to show the efficacy of IV albumin infusion in AIS. ^{232,233} | | | See Table LII in online Data Supplement 1 .  |

3.13. Emergency Carotid Endarterectomy Carotid Angioplasty and Stenting Without Intracranial Clot

| 3.13. Emergency Carotid Endarterectomy/Carotid Angioplasty and Stenting Without Intracranial Clot | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. The usefulness of emergent or urgent carotid endarterectomy (CEA)/carotid angioplasty and stenting when clinical indicators or brain imaging suggests a small infarct core with large territory at risk (eg, penumbra), compromised by inadequate flow from a critical carotid stenosis or occlusion, or in the case of acute neurological deficit after CEA, in which acute thrombosis of the surgical site is suspected, is not well established. | IIb | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 2. In patients with unstable neurological status (eg, stroke-in-evolution), the efficacy of emergency or urgent CEA /carotid angioplasty and stenting is not well established. | IIb | B-NR | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

3.14. Other

| 3.14. Other | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|-----|---|
| 1. Transcranial near-infrared laser therapy is not recommended for the treatment of AIS. | III: No Benefit | B-R | Recommendation revised from 2013 AIS Guidelines. |
| Previous data suggested that transcranial near-infrared laser therapy for stroke held promise as a therapeutic intervention through data published in NEST (Neurothera Effectiveness and Safety Trial)-1 and NEST-2. ^{236–238} Such basic science and preclinical data culminated in the NEST-3 trial, which was a prospective RCT. This trial investigated the use of transcranial laser therapy for the treatment of ischemic stroke between 4.5 and 24 hours of stroke onset in patients with moderate stroke (NIHSS score 7–17) who did not receive IV alteplase. ²³⁹ This study was terminated because of futility after analysis of the first 566 patients found no benefit of transcranial laser therapy over sham treatment. There is currently no evidence that transcranial laser therapy is beneficial in the treatment of ischemic stroke. | | | See Table LIV in online Data Supplement 1 . |

4. In-Hospital Management of AIS: General Supportive Care

4.1. Stroke Units

| 4.1. Stroke Units | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|---|
| 1. The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation is recommended. | I | A | Recommendation unchanged from 2013 AIS Guidelines. |
| 2. The use of standardized stroke care order sets is recommended to improve general management. | I | B-NR | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

4.2 Head Positioning

| 4.2 Head Positioning | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|--|
| 1. The benefit of flat-head positioning early after hospitalization for stroke is uncertain. | IIb | B-R | New recommendation. |
| <p>Only 1 sizable trial has evaluated the effect on functional outcomes of flat versus elevated head position after a stroke. HeadPoST (Head Positioning in Acute Stroke Trial) was a large international, cluster-randomized, crossover open-label trial that enrolled any patient hospitalized for stroke (including ICHs) admitted to the hospital to flat-head (0°) or elevated head (≥30°) maintained for 24 hours after randomization.²⁴⁰ Distribution of mRS scores at 90 days did not differ between the groups (OR, 1.01 [95% CI, 0.92–1.10]; <i>P</i>=0.84). Patients in the flat-head position group were less often able to maintain the assigned head position for 24 hours, but rates of pneumonia did not differ between the 2 groups. However, this pragmatic trial has been criticized because of various limitations.²⁴¹ HeadPoST enrolled predominantly patients with minor strokes (median NIHSS score 4) who would be less likely to benefit from increased perfusion compared with patients with more severe strokes and large artery occlusions. In addition, the initiation of the intervention was very delayed (median, 14 hours), potentially missing the window in which head positioning could have made a difference. Several small studies have shown that the lying-flat position may improve cerebral perfusion in patients with AIS caused by a large artery occlusion when the intervention is initiated early after stroke onset.^{241,242} Thus, there is a rationale for further research focused on this specific cohort of patients.</p> | | | See Table LV in online Data Supplement 1 . |

American Stroke Association
A member of the American Heart Association

4.3. Supplemental Oxygen

Note: Recommendations in this section are repeated from Section 3.1 because they apply to in-hospital management as well.

| 4.3. Supplemental Oxygen | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|---|
| 1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway. | I | C-EO | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. Supplemental oxygen should be provided to maintain oxygen saturation >94%. | I | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. Supplemental oxygen is not recommended in nonhypoxic patients hospitalized with AIS. | III: No Benefit | B-R | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| <p>Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of oxygen by nasal cannula at 2 L/min (baseline O₂ saturation >93%) or 3 L/min (baseline O₂ saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights.¹¹²</p> | | | See Table XXVII in online Data Supplement 1 . |

4.4. Blood Pressure

Note: Recommendation 1 in this section is repeated from Section 3.2 because it applies to in-hospital management as well.

| 4.4. Blood Pressure | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|--|
| 1. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function. | I | C-EO | New recommendation. |
| The BP level that should be maintained in patients with AIS to ensure that the best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others do not. ^{116–123} No studies address the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing colloids with 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. ¹²⁴ No studies have compared different isotonic fluids. | | | See Table XXIX in online Data Supplement 1 . |
| 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, postfibrinolysis sICH, or preeclampsia/eclampsia). | I | C-EO | New recommendation. |
| Patients with AIS can present with severe acute comorbidities that demand emergency BP reduction to prevent serious complications. However, it is important to keep in mind that excessive BP lowering can sometimes worsen cerebral ischemia. ²⁴³ Ideal management in these situations should be individualized, but in general, initial BP reduction by 15% is a reasonable goal. There are no data to show that one strategy to lower BP is better than another after AIS. The medications and doses in Table 5 are all reasonable options. | | | |
| 3. In patients with BP \geq220/120 mm Hg who did not receive IV alteplase or mechanical thrombectomy 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. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke. | IIb | C-EO | New recommendation. |
| Patients with severe hypertension (most commonly $>$ 220/120 mm Hg) were excluded from clinical trials evaluating BP lowering after AIS. ^{244–249} Rapid BP reduction has traditionally been advised for these cases, but the benefit of such treatment in the absence of comorbid conditions that may be acutely exacerbated by severe hypertension has not been formally studied. Ideal management in these situations should be individualized, but in general, initial BP reduction by 15% is a reasonable goal. Excessive drop in BP could result in complications such as stroke progression (by compromising cerebral perfusion in penumbral tissue) and acute kidney injury (from renal hypoperfusion). There are no data to show that one strategy to lower BP is better than another after AIS. The medications and doses in Table 5 are all reasonable options. | | | See Table LVI in online Data Supplement 1 . |
| 4. In patients with BP $<$220/120 mm Hg who did not receive IV alteplase or mechanical thrombectomy 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. | III: No Benefit | A | Recommendation revised from 2013 AIS Guidelines. |
| Multiple RCTs and meta-analyses of these trials ^{244–258} have consistently shown that initiating or reinitiating antihypertensive therapy within the first 48 to 72 hours after an AIS is safe, but this strategy is not associated with improved mortality or functional outcomes. However, none of these trials were designed to study BP reduction within the first 6 hours after stroke, and all excluded patients with extreme hypertension or coexistent indications for rapid BP reduction. | | | See Table LVI in online Data Supplement 1 . |

4.5. Temperature

Note: Recommendations in this section are repeated from Section 3.3 because they apply to in-hospital management as well.


| 4.5. Temperature | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|---|
| 1. Sources of hyperthermia (temperature $>$38°C) should be identified and treated. Antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke. | I | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| Additional support for this recommendation unchanged from the 2013 AIS Guidelines is provided by a large retrospective cohort study conducted from 2005 to 2013 of patients admitted to intensive care units in Australia, New Zealand, and the United Kingdom. Peak temperature in the first 24 hours $<$ 37°C and $>$ 39°C was associated with an increased risk of in-hospital death compared with normothermia in 9366 patients with AIS. ¹³³ | | | See Tables XXXI and XXXII in online Data Supplement 1 . |
| 2. In patients with AIS, the benefit of treatment with induced hypothermia is uncertain. | IIb | B-R | Recommendation revised from 2013 AIS Guidelines. |
| To date, studies of hypothermia in AIS show no benefit in functional outcome and suggest that induction of hypothermia increases the risk of infection, including pneumonia. ^{134–137} These studies use a variety of methods to induce hypothermia and are small/underpowered, meaning that a benefit for hypothermia in AIS cannot be definitively excluded. A large phase III trial of hypothermia in AIS is ongoing. | | | See Tables XXXIII and XXXIV in online Data Supplement 1 . |

4.6. Glucose

Note: Recommendations in this section are repeated from Section 3.4 because they apply to in-hospital management as well.

| 4.6. Glucose | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS. | I | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after AIS is associated with worse outcomes than normoglycemia, and thus, it is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia. | IIa | C-LD | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

4.7. Dysphagia

| 4.7. Dysphagia | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is effective to identify patients at increased risk for aspiration. | I | C-LD | New recommendation. |
| <p>Dysphagia, a common (37%–78%) complication of acute stroke, is a risk factor for aspiration pneumonia and is associated with higher mortality and worse patient outcomes. The Evidence Review Committee completed a systematic review to determine whether dysphagia screening, compared with no screening or usual care, decreased outcomes of pneumonia, death, or dependency.^{3,259–261} There were insufficient data to determine whether implementation of a dysphagia screening protocol reduces the risk of death or dependency. However, insufficient evidence does not mean that dysphagia screening is ineffective. Joundi et al²⁶² determined that patients who failed dysphagia screening were older, had a higher rate of multiple comorbidities (including prior stroke and dementia), more often came from a long-term care facility, more often presented with weakness and speech deficits, had a lower level of consciousness, and had a higher stroke severity. Patients who failed dysphagia screening were more likely to develop pneumonia (13.1% versus 1.9%), to have more severe disability (52.4% versus 18.0%), and to be discharged to a long-term care institution (14.0% versus 4.3%). Early dysphagia screening can be effective to identify patients at higher risk for aspiration, which is associated with greater risk of pneumonia, even if dysphagia screening was not associated with reduced rates of pneumonia or improvements in death or disability when tested in RCTs.^{259–261}</p> | | | <p>See Tables LVII and LVIII in online Data Supplement 1.</p>  |
| 2. An endoscopic evaluation is reasonable for those patients suspected of aspiration to verify the presence/absence of aspiration and to determine the physiological reasons for the dysphagia to guide the treatment plan. | IIa | B-NR | Recommendation wording modified from 2016 Rehab Guidelines to match COR IIa stratifications. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. It is reasonable for dysphagia screening to be performed by a speech-language pathologist or other trained healthcare provider. | IIa | C-LD | Recommendation reworded for clarity from 2016 Rehab Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 4. It is not well established which instrument to choose for evaluation of swallowing with sensory testing, but the choice may be based on instrument availability or other considerations (ie, fiberoptic endoscopic evaluation of swallowing, videofluoroscopy, fiberoptic endoscopic evaluation with sensory testing). | IIb | C-LD | Recommendation reworded for clarity from 2016 Rehab Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

| 4.7. Dysphagia (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-------------|------|---|
| 5. Implementing oral hygiene protocols to reduce the risk of pneumonia after stroke may be reasonable. | I ib | B-NR | New recommendation. |
| <p>Limited studies suggest that intensive oral hygiene protocols might reduce the risk of aspiration pneumonia. In patients with acute stroke, Sørensen et al²⁶³ showed that intervention with standardized dysphagia screening and diet and standardized oral hygiene with antibacterial mouth rinse with chlorhexidine reduced pneumonia (7% versus 28%) compared with a historical control group in which patients were unsystematically screened for dysphagia within 24 hours and received unsystematic and arbitrary oral hygiene without chlorhexidine. In this experimental design, the efficacy of the standardized oral hygiene portion in the intervention group could not be separated from the standardized dysphagia screening and diet. Furthermore, because of the historic nature of the control group, it is possible that other changes in care that could have occurred between the historical control subjects and the intervention group might have affected the risk for development of pneumonia. A Cochrane review that included 3 studies found that oral care and decontamination gel versus oral care and placebo gel reduced the incidence of pneumonia in the intervention group ($P=0.03$).²⁶⁴ Wagner et al²⁶⁵ conducted a cohort study comparing rates of pneumonia in hospitalized stroke patients before and after implementation of systematic oral hygiene care. The unadjusted incidence of hospital-acquired pneumonia was lower in the group assigned to oral hygiene care compared with control subjects (14% versus 10.33%; $P=0.022$), with an unadjusted OR of 0.68 (95% CI, 0.48–0.95; $P=0.022$). After adjustment for confounders, the OR of hospital-acquired pneumonia in the intervention group remained significantly lower at 0.71 (95% CI, 0.51–0.98; $P=0.041$).</p> | | | See Tables LIX and LX in online Data Supplement 1 . |

4.8. Nutrition

| 4.8. Nutrition | COR | LOE | New, Revised, or Unchanged |
|---|-------------|------|---|
| 1. Enteral diet should be started within 7 days of admission after an acute stroke. | I | B-R | New recommendation. |
| 2. For patients with dysphagia, it is reasonable to initially use nasogastric tubes for feeding in the early phase of stroke (starting within the first 7 days) and to place percutaneous gastrostomy tubes in patients with longer anticipated persistent inability to swallow safely (>2–3 weeks). | I la | C-EO | New recommendation. |
| <p>The FOOD RCTs (Feed or Ordinary Diet; phases I–III), completed in 131 hospitals in 18 countries,²⁶⁶ showed that supplemented diet was associated with an absolute reduction in risk of death of 0.7% and that early tube feeding (within 7 days of admission) was associated with an absolute reduction in risk of death of 5.8% and a reduction in death or poor outcomes of 1.2%. When nasogastric feeding and percutaneous endoscopic gastrostomy feeding were compared, percutaneous endoscopic gastrostomy feeding was associated with an increase in absolute risk of death of 1.0% and an increased risk of death or poor outcomes of 7.8%. The conclusion was that stroke patients should be started on enteral diet within the first 7 days of admission.²⁶⁶ In 2012, a Cochrane review analyzed 33 RCTs involving 6779 patients to assess the intervention for dysphagia treatment, feeding strategies and timing (early [within 7 days] versus later), fluid supplementation, and the effects of nutritional supplementation on acute and subacute stroke patients.²⁶⁷ The conclusion was that, although data remained insufficient to offer definitive answers, available information suggested that percutaneous endoscopic gastrostomy feeding and nasogastric tube feeding do not differ in terms of case fatality, death, or dependency, but percutaneous endoscopic gastrostomy is associated with fewer treatment failures ($P=0.007$), less gastrointestinal bleeding ($P=0.007$), and higher food delivery ($P<0.00001$).</p> | | | See Table LXI in online Data Supplement 1 . |
| 3. Nutritional supplements are reasonable to consider for patients who are malnourished or at risk of malnourishment. | I la | B-R | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

4.9. Deep Vein Thrombosis Prophylaxis

| 4.9. Deep Vein Thrombosis Prophylaxis | COR | LOE | New, Revised, or Unchanged |
|---|-----|-----|--|
| 1. In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT). | I | B-R | Recommendation revised from 2016 Rehab Guidelines. |
| <p>CLOTS (Clots in Legs or stockings After Stroke) 3 was a multicenter trial enrolling 2867 patients in 94 centers in the United Kingdom and comparing the use of IPC with routine care and no IPC with routine care in immobile stroke patients for venous thromboembolism prophylaxis. Eligible patients were enrolled within 3 days of the acute stroke and could not mobilize to the toilet without the help of another person. Routine care was defined as the use of aspirin for nonhemorrhagic stroke, hydration, and possible compression stockings. A total of 31% of the patients received prophylactic or full-dose heparin or LMWH, but these patients were evenly distributed between both groups. After the exclusion of 323 patients who died before any primary outcome and 41 who had no screening, the primary outcome of DVT occurred in 122 of 1267 participants with IPC (9.6%) compared with 174 of 1245 participants without IPC (14.0%), giving an adjusted OR of 0.65 (95% CI, 0.51–0.84; $P=0.001$). Among patients treated with IPC, there was a statistically significant improvement in survival to 6 months (HR, 0.86 [95% CI, 0.73–0.99]; $P=0.042$) but no improvement in disability. Skin breaks were more common in the IPC group (3.1% versus 1.4%; $P=0.002$). Contraindications to IPC include leg conditions such as dermatitis, gangrene, severe edema, venous stasis, severe peripheral vascular disease, postoperative vein ligation, or grafting, as well as existing swelling or other signs of an existing DVT.²⁶⁸ A meta-analysis including this trial and 2 smaller trials confirmed these results.²⁶⁹</p> | | | See Table LXII in online Data Supplement 1 . |

| 4.9. Deep Vein Thrombosis Prophylaxis (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----------|-----|---|
| 2. The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in patients with AIS is not well established. | IIb | A | New recommendation. |
| The most recent and comprehensive meta-analysis of pharmacological interventions for venous thromboembolism prophylaxis in AIS included 1 very large trial (N=14 578), 4 small trials of UFH, 8 small trials of LMWHs or heparinoids, and 1 trial of a heparinoid. ²⁶⁹ Prophylactic anticoagulants were not associated with any significant effect on mortality or functional status at final follow-up. There were statistically significant reductions in symptomatic pulmonary embolisms (OR, 0.69 [95% CI, 0.49–0.98]) and in DVTs (OR, 0.21 [95% CI, 0.15–0.29]), most of which were asymptomatic. There were statistically significant increases in symptomatic intracranial hemorrhage (OR, 1.68 [95% CI, 1.11–2.55]) and symptomatic extracranial hemorrhages (OR, 1.65 [95% CI, 1.0–2.75]). ²⁶⁹ There may be a subgroup of patients in whom the benefits of reducing the risk of venous thromboembolism are high enough to offset the increased risks of intracranial and extracranial bleeding; however, no prediction tool to identify such a subgroup has been derived. ^{228,229,269} | | | See Table LXII in online Data Supplement 1 . |
| 3. When prophylactic anticoagulation is used, the benefit of prophylactic-dose LMWH over prophylactic-dose UFH is uncertain. | IIb | B-R | New recommendation. |
| The most recent and comprehensive meta-analysis comparing LMWH or heparinoid with UFH for venous thromboembolism prophylaxis in AIS included 1 large trial (N=1762) and 2 smaller trials comparing LMWH with UFH and 4 small trials comparing heparinoids with UFH. There were no significant effects on death or disability for LMWH/heparinoids compared with UFH. ²⁶⁹ The use of LMWH/heparinoid was associated with a statistically significant reduction in DVTs (OR, 0.55 [95% CI, 0.44–0.70]), which were mostly asymptomatic, at the expense of a greater risk of major extracranial hemorrhages (OR, 3.79 [95% CI, 1.30–11.03]). LMWH can be administered once a day and thus is more convenient for nurses and comfortable for patients. Higher cost and increased bleeding risk in elderly patients with renal impairment are disadvantages of LMWH that should be kept in mind. | | | See Table LXII in online Data Supplement 1 . |
| 4. In ischemic stroke, elastic compression stockings should not be used. | III: Harm | B-R | Recommendation wording modified from 2016 Rehab Guidelines to match COR III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

4.10. Depression Screening

| 4.10. Depression Screening | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Administration of a structured depression inventory is recommended to routinely screen for poststroke depression. | I | B-NR | Recommendation revised from 2016 Rehab Guidelines. |
| A meta-analysis of studies assessing poststroke depression screening tools (24 studies, N=2907) found several inventories with high sensitivity for detecting poststroke depression. ²⁷⁰ Two of these studies evaluated patients in the acute phase 2 weeks after onset and found that depression screening tools showed good accuracy compared with the reference standard diagnosis by the American Psychiatric Association <i>Diagnostic and Statistical Manual of Mental Disorders</i> . ^{271,272} However, further studies are needed to determine the optimal timing, setting, and follow-up for screening. ¹⁶ | | | See Tables LXIII and LXIV in online Data Supplement 1 . |
| 2. Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications and closely monitored to verify effectiveness. | I | B-R | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| Clinical trials of antidepressants in individuals with poststroke depression have shown a beneficial effect on depression remission and response, but trials were limited by small samples, variable criteria for poststroke depression, and vague definitions for remission and response. ¹⁶ Several trials have indicated a benefit of psychosocial therapies for treatment. ¹⁶ In an RCT, participants who underwent screening in the early subacute period 1 to 2 months after stroke followed by treatment with counseling antidepressant medication showed significantly lower 12-week depression scores than those who received usual care. ²⁷³ | | | See Tables LXV and LXVI in online Data Supplement 1 . |

4.11. Other

| 4.11. Other | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|---|
| 1. During hospitalization and inpatient rehabilitation, regular skin assessments are recommended with objective scales of risk such as the Braden scale. | I | C-LD | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. It is recommended to minimize or eliminate skin friction, to minimize skin pressure, to provide appropriate support surfaces, to avoid excessive moisture, and to maintain adequate nutrition and hydration to prevent skin breakdown. Regular turning, good skin hygiene, and use of specialized mattresses, wheelchair cushions, and seating are recommended until mobility returns. | I | C-LD | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. It is reasonable for patients and families with stroke to be directed to palliative care resources as appropriate. | Ila | C-EO | New recommendation. |
| It is reasonable for healthcare providers to ascertain and include patient-centered preferences in decision-making, especially during prognosis formation and considering interventions or limitations in care. Healthcare providers should ascertain and include patient-centered preferences in decision-making, especially during prognosis formation and considering interventions or limitations in care. See 2014 Palliative Care for additional information. ⁹ | | | |
| 4. Routine use of prophylactic antibiotics has not been shown to be beneficial. | III: No Benefit | A | Recommendation revised from 2013 AIS Guidelines. |
| Two large RCTs demonstrated no effect of preventive antimicrobial therapy on functional outcome. PASS (Preventive Antibiotics in Stroke Study) showed no difference in the primary end point of distribution of functional outcome scores on the mRS score at 3 months (adjusted common OR, 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 urinary tract infections (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]; $P=0.385$). ²⁷⁴ In STROKE-INF (Antibiotics to Prevent Infection in Stroke), prophylactic antibiotics did not affect the incidence of the primary end point of poststroke pneumonia (adjusted OR, 1.21 [95% CI, 0.71–2.08]; $P=0.489$) or the secondary end point of mRS score of 0 to 2 at 90 days (adjusted OR, 0.87 [95% CI, 0.6–1.24]; $P=0.448$). ²⁷⁵ Three meta-analyses including these trials and other smaller RCTs all demonstrated a reduction in infection but no change in functional outcome. ^{276–278} | | | See Table LXVII in online Data Supplement 1 . |
| 5. Routine placement of indwelling bladder catheters should not be performed because of the associated risk of catheter-associated urinary tract infections. | III: Harm | C-LD | Recommendation wording modified from 2013 AIS Guidelines to match COR III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

American Stroke Association
 A Division of the American Heart Association

4.12. Rehabilitation

| 4.12. Rehabilitation | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. It is recommended that early rehabilitation for hospitalized stroke patients be provided in environments with organized, interprofessional stroke care. | I | A | Recommendation unchanged from 2016 Rehab Guidelines. |
| 2. It is recommended that stroke survivors receive rehabilitation at an intensity commensurate with anticipated benefit and tolerance. | I | B-NR | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 3. It is recommended that all individuals with stroke be provided a formal assessment of their activities of daily living and instrumental activities of daily living, communication abilities, and functional mobility before discharge from acute care hospitalization and the findings be incorporated into the care transition and the discharge planning process. | I | B-NR | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 4. A functional assessment by a clinician with expertise in rehabilitation is recommended for patients with an acute stroke with residual functional deficits. | I | C-LD | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 5. The effectiveness of fluoxetine or other selective serotonin reuptake inhibitors to enhance motor recovery is not well established. | Iib | C-LD | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE revised from 2016 Rehab Guidelines. |

| 4.12. Rehabilitation (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|------------------|------------|--|
| 6. High-dose, very early mobilization within 24 hours of stroke onset should not be performed because it can reduce the odds of a favorable outcome at 3 months. | III: Harm | B-R | Recommendation wording modified from 2016 Rehab Guidelines to match COR III stratifications. LOE revised. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| <p>The AVERT RCT (A Very Early Rehabilitation Trial) compared high-dose, very early mobilization with standard-of-care mobility.²⁷⁹ High-dose mobilization protocol interventions included the following: Mobilization was begun 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; 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%) 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.</p> | | | See Table LXVIII in online Data Supplement 1 . |

5. In-Hospital Management of AIS: Treatment of Acute Complications

5.1. Brain Swelling

| 5.1.1. General Recommendations | COR | LOE | New, Revised, or Unchanged |
|--|----------|-------------|---|
| 1. Patients with large territorial cerebral and cerebellar infarctions are at high risk for developing brain swelling and herniation. Discussion of care options and possible outcomes should take place quickly with patients (if possible) and family or next of kin. Medical professionals and caregivers should ascertain and include patient-centered preferences in shared decision-making, especially during prognosis formation and when considering interventions or limitations in care. | I | C-EO | New recommendation. See Tables LXIX and LXX in online Data Supplement 1 . |
| <p>Brain swelling can cause serious and even life-threatening complications in patients with large territorial cerebral and cerebellar infarctions. Although less severe swelling can be managed medically, surgical treatment may be the only effective option for very severe cases; in such instances, timely decompressive surgery has been shown to reduce mortality.²⁸⁰ Nevertheless, there is evidence that persistent morbidity is common, and individual preexisting decisions about end-of-life and degree of treatment performed in the face of severe neurological injury must be considered.</p> | | | American Stroke Association See Tables LXIX and LXX in online Data Supplement 1 . |
| 2. Measures to lessen the risk of swelling and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended. Early transfer of patients at risk for malignant brain swelling to an institution with appropriate neurosurgical expertise should be considered. | I | C-LD | Recommendation reworded for brevity and consistency from 2013 AIS Guidelines. LOE revised. See Table XCV in online Data Supplement 1 for original wording. |

| 5.1.2. Medical Management | COR | LOE | New, Revised, or Unchanged |
|--|------------------------|-------------|--|
| 1. Use of osmotic therapy for patients with clinical deterioration from brain swelling associated with cerebral infarction is reasonable. | IIa | C-LD | Recommendation reworded for clarity from 2014 Brain Swelling. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 2. Use of brief moderate hyperventilation (Pco₂ target, 30–34 mm Hg) is a reasonable treatment for patients with acute severe neurological decline from brain swelling as a bridge to more definitive therapy. | IIa | C-LD | New recommendation. |
| <p>A single nonrandomized study of 3 days of sustained hyperventilation in AIS designed primarily to investigate physiological changes showed no difference in mortality.²⁸¹ Data on the use of hyperventilation for the management of increased intracranial pressure from patients with traumatic brain injury show a rapid reduction in intracranial pressure with return toward baseline over the next few hours.^{282–284} The only RCT of sustained hyperventilation in traumatic brain injury demonstrated that prophylactic hyperventilation for 5 days was associated with worse outcomes.²⁸⁵</p> | | | See Tables LXXI and LXXII in online Data Supplement 1 . |
| 3. Hypothermia or barbiturates in the setting of ischemic cerebral or cerebellar swelling are not recommended. | III: No Benefit | B-R | Recommendation and LOE revised from 2014 Brain Swelling. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| <p>The data on the use of hypothermia and barbiturates for the management of AIS continue to be limited. Such data include only studies with small numbers of patients and unclear timing of intervention with respect to stroke onset. Hypothermia use has recently been shown to have no impact on stroke outcomes in a meta-analysis of 6 RCTs.²⁸⁶ Further trials are necessary to clarify the safety and efficacy of this intervention.</p> | | | See Tables LXIX and LXX in online Data Supplement 1 . |

| 5.1.2. Medical Management (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|-----------|-----|--|
| 4. Because of a lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) should not be administered for the treatment of brain swelling complicating ischemic stroke. | III: Harm | A | Recommendation wording modified from 2013 AIS Guidelines to match COR III stratifications. LOE unchanged. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. |

| 5.1.3. Surgical Management-Supratentorial Infarction | COR | LOE | New, Revised, or Unchanged |
|---|-----|-----|---|
| 1. Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness attributed to brain swelling as selection criteria. | Ia | A | Recommendation, COR, and LOE unchanged from 2014 Brain Swelling. |
| 2. In patients ≤60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion is reasonable. | Ia | A | Recommendation revised from 2014 Brain Swelling. |
| The pooled results of 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. ²⁸⁰ These findings were noted despite differences in the clinical trials in terms of inclusion and exclusion criteria, percent of MCA territory involved, and surgical timing. ^{287,288} At 12 months, moderate disability (ability to walk) or better (mRS score 2 or 3) was achieved in 43% (22 of 51) of the total surgical group and 55% (22 of 40) of survivors compared with 21% (9 of 42; <i>P</i> =0.045) of the total nonsurgical group and 75% (9 of 12; <i>P</i> =0.318) of the nonsurgical survivors. At 12 months, independence (mRS score 2) was achieved in 14% (7 of 51) of the total surgical group and 18% (7 of 40) of survivors compared with 2% (1 of 42) of the total nonsurgical group and 8% (1 of 12) of the nonsurgical survivors. ^{280,287–290} | | | See Tables LXIX and LXX in online Data Supplement 1 . |
| 3. In patients >60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion may be considered. | Ib | B-R | Recommendation revised from 2014 Brain Swelling |
| There is evidence that patients >60 years of age can have a reduction in mortality of ~50% (76% in the nonsurgical group versus 42% in the surgical group in DESTINY [Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery] II) when decompressive craniectomy for malignant MCA infarction is performed within 48 hours of stroke onset. ^{287,288,291–295} However, functional outcomes in elderly patients seem to be worse than those in patients <60 years of age. At 12 months, moderate disability (able to walk; mRS score 3) was achieved in 6% (3 of 47) of the total surgical group and 11% (3 of 27) of survivors compared with 5% (3 of 22) of the total nonsurgical group and 20% (3 of 15) of the nonsurgical survivors. At 12 months, independence (mRS score ≤2) was not achieved by any survivors in either group. | | | See Tables LXIX and LXX in online Data Supplement 1 . |

| 5.1.4. Surgical Management-Cerebellar Infarction | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. Ventriculostomy is recommended in the treatment of obstructive hydrocephalus after cerebellar infarction. 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. | I | C-LD | Recommendation revised from 2014 Brain Swelling. |
| 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. ^{289,296} 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 cerebrospinal fluid diversion by ventriculostomy fails to improve neurological function, decompressive suboccipital craniectomy should be performed. ^{289,296,297} Although a risk of upward herniation exists with ventriculostomy alone, it can be minimized with conservative cerebrospinal fluid drainage or subsequent decompression if the cerebellar infarction causes significant swelling and mass effect. ^{289,296} | | | See Table LXIX in online Data Supplement 1 . |
| 2. Decompressive suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarction causing neurological deterioration from brainstem compression despite maximal medical therapy. When deemed safe and indicated, obstructive hydrocephalus should be treated concurrently with ventriculostomy. | I | B-NR | Recommendation revised from 2014 Brain Swelling. |
| The data support decompressive cerebellar craniectomy for the management of acute ischemic cerebellar stroke with mass effect. ^{289,296,297} 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. ^{289,296} | | | See Table LXIX in online Data Supplement 1 . |

| 5.1.4. Surgical Management-Cerebellar Infarction (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|---|
| 3. When considering decompressive suboccipital craniectomy for cerebellar infarction, it may be reasonable to inform family members that the outcome after cerebellar infarct can be good after the surgery. | IIb | C-LD | Recommendation and COR unchanged from 2014 Brain Swelling. Wording revised and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |

5.2. Seizures

| 5.2. Seizures | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|------|---|
| 1. Recurrent seizures after stroke should be treated in a manner similar to when they occur with other acute neurological conditions, and antiseizure drugs should be selected on the basis of specific patient characteristics. | I | C-LD | Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 2. Prophylactic use of antiseizure drugs is not recommended. | III: No Benefit | C-LD | Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

6. In-Hospital Institution of Secondary Stroke Prevention

The recommendations in this section reference other current AHA guidelines for secondary stroke prevention where applicable (Table 10). These other guidelines should be referred to for further information on secondary stroke prevention not covered in this document. These other guidelines are updated regularly, and the most recent versions should be used.

Table 10. Guidelines Relevant to Secondary Stroke Prevention

| Document Title | Year Published | Abbreviation Used in This Document |
|--|----------------|------------------------------------|
| "Guidelines for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association" ¹⁰ | 2014 | 2014 Secondary Prevention |
| "2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines" ¹⁸ | 2017 | N/A |
| "2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines" ¹⁹ | 2018 | 2018 Cholesterol Guidelines |

AACVPR indicates American Association of Cardiovascular and Pulmonary Rehabilitation; AAPA, American Academy of Physician Assistants; ABC, Association of Black Cardiologists; ACC, American College of Cardiology; ACPM, American College of Preventive Medicine; ADA, American Diabetes Association; AGS, American Geriatrics Society; AHA, American Heart Association; APhA, American Pharmacists Association; ASH, American Society of Hypertension; ASPC, American Society for Preventive Cardiology; N/A, not applicable; NLA, National Lipid Association; NMA, National Medical Association; and PCNA, Preventive Cardiovascular Nurses Association.

6.1. Brain Imaging

| 6.1. Brain Imaging | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| <p>1. For prevention of recurrent stroke, the use of MRI is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention treatments.</p> | IIa | C-EO | New recommendation. |
| <p>NCCT scanning of patients with acute stroke is effective for the detection of acute ICH and the avoidance of antithrombotic treatment in these patients.⁸⁵ In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention.^{82,83,298} Many RCTs that provide the current best evidence for secondary stroke prevention treatments did not require MRI for patient selection.^{207,210,216,219,299–306} The benefits shown in these RCTs can be expected when the same eligibility criteria are applied without the addition of MRI. DW-MRI is more sensitive than CT for detecting AIS,^{70,71} but there are inadequate data at this time to identify which patients will benefit from brain MRI in addition to or instead of NCCT to improve effectiveness of treatment for prevention of recurrent stroke. A systematic review in 2012 identified almost no direct evidence that MRI affects outcome in patients with stroke and limited evidence that MRI affects management.³⁰⁷ A decision-analytical model of patients with TIA and minor stroke concluded that routine use of MRI did not improve outcome except for patients presenting at >1 week after symptoms to diagnose hemorrhage.³⁰⁸ Two studies from the 1990s evaluating repeat neuroimaging recommended repeat CT over additional MRI for most clinical situations in AIS with the exceptions of documenting lacunar and infratentorial infarcts, but they did not present evidence of a benefit on outcome for these situations.^{309,310} For instance, 2 situations in which MRI can be useful to select treatments that have been demonstrated by RCTs to improve outcome are (1) patients with carotid stenosis who are potential candidates for carotid revascularization in whom NCCT or neurological examination (eg, pure motor hemiparesis) does not permit accurate localization and (2) patients with patent foramen ovale (PFO) who are potential candidates for mechanical closure (see below).</p> | | | <p>See Tables XVIII and LXXIII in online Data Supplement 1.</p> |
| <p>2. Brain MRI is reasonable in selected patients as part of a comprehensive evaluation to determine if they meet the eligibility criteria of the RCTs that investigated mechanical closure of PFO for prevention of recurrent stroke.</p> | IIa | B-R | New recommendation. |
| <p>Six RCTs have evaluated mechanical closure of echocardiographically detected PFO to prevent recurrent stroke in patients without obvious cause for their index stroke.^{311–317} These trials had highly restrictive eligibility criteria that required brain MRI, imaging of the intracranial vasculature, and echocardiography. Meta-analyses of these trials show a significantly reduced risk of recurrent stroke with mechanical closure compared with medical therapy with a number needed to treat of 131.^{318–320} A network meta-analysis concluded that, in patients <60 years of age, PFO closure probably confers an important reduction in ischemic stroke recurrence compared with antiplatelet therapy alone but may make no difference compared with anticoagulation. PFO closure also incurs a risk of persistent atrial fibrillation and device-related adverse events. Compared with alternatives, anticoagulation probably increases major bleeding.³¹⁹ Each of these 6 trials had ≥1 methodological features with a high risk of bias identified, including lack of blinding of participants and personnel, lack of blinding of outcome assessments, incomplete outcome data, and selective reporting.^{318–324}</p> | | | <p>See Tables LXXV through LXXVII in online Data Supplement 1.</p> |
| <p>3. The effectiveness of routine brain MRI to guide treatment selection for prevention of recurrent stroke is uncertain. (See knowledge byte following 6.1, recommendation 1.)</p> | IIb | B-NR | New recommendation. |

6.2. Vascular Imaging

| 6.2. Vascular Imaging | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| <p>1. For patients with nondisabling (mRS score 0–2) AIS in the carotid territory who are candidates for CEA or stenting, noninvasive imaging of the cervical carotid arteries should be performed routinely within 24 hours of admission.</p> | I | B-NR | New recommendation. |
| <p>Past data have indicated that the risk of recurrent stroke caused by symptomatic carotid stenosis is highest early after the initial event.^{325–329} Although there is evidence that early or emergency revascularization via either CEA or carotid angioplasty and stenting may be safe in selected cases,^{330–332} there are no high-quality prospective data supporting early versus late carotid revascularization in all cases.³³³ In cases of nondisabling stroke, a meta-analysis by De Rango et al³²⁶ demonstrates high rates of complications when treated <48 hours after the initial event and no difference in risks when treated between 0 and 7 days and 0 and 15 days. Revascularization between 48 hours and 7 days after initial stroke is supported by the data in cases of nondisabling stroke (mRS score 0–2).³³⁴ Imaging within 24 hours of admission is feasible and recommended to facilitate CEA/carotid angioplasty and stenting in eligible patients in the 48- to 72-hour window.</p> | | | <p>See Table LXXVIII in online Data Supplement 1.</p> |

| 6.2. Vascular Imaging (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 2. For prevention of recurrent stroke, the use of intracranial vessel imaging is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention treatments. | IIa | C-EO | New recommendation. |
| <p>An extensive literature search did not yield adequate data to identify subgroups of patients with AIS for whom information obtained from intracranial vessel imaging will lead to improved outcome. There is no RCT evidence that patients with AIS and symptomatic intracranial stenosis should be treated differently from other patients with ischemic stroke of presumed atherosclerotic cause. In the WASID RCT (Warfarin-Aspirin Symptomatic Intracranial Disease), warfarin provided no benefit over aspirin 325 mg/d, even in those who were taking antithrombotics at the time of the qualifying event.³³⁵ The SAMMPRIS trial (Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis) showed no benefit of adding Wingspan stenting to aggressive medical therapy that included aspirin 325 mg/d and clopidogrel 75 mg/d for 90 days after enrollment, again even in those who were taking antithrombotics at the time of qualifying event.^{336–338} The CHANCE trial, which compared dual antiplatelet treatment with clopidogrel and aspirin and aspirin alone for 21 days in patients with high-risk TIA and minor stroke, showed no evidence of preferential benefit from dual antiplatelet treatment in patients with intracranial arterial stenosis. Compared with pooled historical control subjects in WASID, the medical treatment–only group in SAMMPRIS had an almost 2-fold lower risk of any stroke or death within 30 days or ischemic stroke in the territory of the qualifying artery after 30 days. Whether this was the result of dual antiplatelet treatment with aspirin and clopidogrel for 90 days remains to be demonstrated by an RCT.^{337–339}</p> | | | See Tables LXXIX and LXXX in online Data Supplement 1 . |
| 3. Imaging of the intracranial vasculature to detect atherosclerotic stenosis of a major intracranial artery is reasonable in selected patients as part of a comprehensive evaluation to determine if they meet the eligibility criteria of the RCTs that investigated mechanical closure of PFO for prevention of recurrent stroke. | IIa | B-R | New recommendation. |
| <p>Six RCTs have evaluated mechanical closure of echocardiographically detected PFO to prevent recurrent stroke in patients without obvious cause for their index stroke.^{311–317} These trials had highly restrictive eligibility criteria that required brain MRI, imaging of the intracranial vasculature, and echocardiography. Meta-analyses of these trials show a significantly reduced risk of recurrent stroke with mechanical closure compared with medical therapy with a number needed to treat of 131.^{318–320} A network meta-analysis concluded that, in patients <60 years of age, PFO closure probably confers an important reduction in ischemic stroke recurrence compared with antiplatelet therapy alone but may make no difference compared with anticoagulation. PFO closure also incurs a risk of persistent atrial fibrillation and device-related adverse events. Compared with alternatives, anticoagulation probably increases major bleeding.³¹⁹ Each of these 6 trials had ≥1 methodological features with a high risk of bias identified, including lack of blinding of participants and personnel, lack of blinding of outcome assessments, incomplete outcome data, and selective reporting.^{318–324}</p> | | | See Tables LXXV through LXXVII in online Data Supplement 1 . |
| 4. Routine imaging of the intracranial vasculature to detect atherosclerotic stenosis of a major intracranial artery to guide selection of antithrombotic or intracranial endovascular treatment for prevention of recurrent stroke is not well established. (See knowledge byte following 6.2, recommendation 2.) | IIb | B-NR | New recommendation. |

6.3. Cardiac Evaluation

| 6.3.1. Electrocardiographic Monitoring | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours. | I | B-NR | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| <p>Further support for this unchanged recommendation from the 2013 AIS Guidelines is provided by 2 additional studies published since the 2013 guidelines. Kallmünzer et al³⁴⁰ prospectively monitored by cardiac telemetry 501 patients with acute stroke (92% with cerebral ischemia) for a median of 73 hours after admission to a dedicated stroke unit. A total of 139 serious arrhythmias were detected in 126 patients (25.1%). Atrial fibrillation accounted for 24 of 139 (17%) of the arrhythmias. Detection of arrhythmia led to direct antiarrhythmic treatment in 77.7%. In that study, 52.2% of all detected arrhythmias occurred within 12 hours and 74.4% within 24 hours after admission. Fernández-Menéndez et al³⁴¹ prospectively monitored by cardiac telemetry for a minimum of 48 hours 332 patients admitted to the stroke unit with a diagnosis of ischemic stroke, TIA, or intraparenchymal hemorrhage (90% with cerebral ischemia) admitted within 48 hours of symptom onset. One hundred seventy-four significant cardiac arrhythmias occurred in 98 patients (29.5%). Atrial fibrillation/flutter accounted for 23 of 174 (13%) of the arrhythmias. Thirty-three of 98 (34%) patients were directly treated for the arrhythmia (excluding anticoagulation for atrial fibrillation). Thirty-seven percent of all detected arrhythmias occurred on day 1, 29% on day 2, and 15% on day 3.³⁴¹</p> | | | See Table LXXXI in online Data Supplement 1 . |

| 6.3.1. Electrocardiographic Monitoring (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 2. The effectiveness of prolonged cardiac monitoring during hospitalization after AIS to guide treatment selection for prevention of recurrent stroke is uncertain. | IIb | C-LD | New recommendation. |
| <p>In patients with TIA or ischemic stroke and atrial fibrillation detected by routine ECG at the time or within the preceding 24 months, oral anticoagulation begun within 3 months is superior to aspirin for the prevention of vascular death, stroke, MI, and systemic embolism (HR, 0.60 [95% CI, 0.41–0.87]).³⁴² With prolonged cardiac monitoring during hospitalization, atrial fibrillation is newly detected in nearly a quarter of patients with stroke or TIA.³⁴³ No RCTs have specifically evaluated the benefit of anticoagulation in patients with brief episodes of subclinical atrial fibrillation detected in hospital after AIS. In CRYSTAL AF (Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke), at 36 months, atrial fibrillation was detected in 30% of 221 patients with implantable cardiac monitors and in 3% of 220 control subjects ($P<0.001$), but the occurrence of TIA or ischemic stroke was 9% in the implantable cardiac monitor group and 11% in the control group ($P=0.64$).^{344,345} In Find-AF_{RANDOMISED} (Finding Atrial Fibrillation in Stroke—Evaluation of Enhanced and Prolonged Holter Monitoring), atrial fibrillation was detected in 14% of 200 patients with 10-day Holter monitoring at baseline, 3 months, and 6 months versus 5% of 198 patients in the standard care group who had at least 24 hours of rhythm monitoring ($P=0.002$). There was no significant difference in recurrent stroke at 12 months (3.7% versus 5.4%; $P=0.46$).³⁴⁶ Other smaller studies have also failed to show a difference in outcomes.^{347–349} All of these studies were underpowered for the secondary clinical end points. Randomized trials are ongoing to determine whether oral anticoagulation therapy compared with aspirin reduces the risk of stroke or systemic embolism in patients with permanent pacemakers, defibrillators, or insertable cardiac monitors who have subclinical atrial fibrillation or high-rate episodes and additional risk factors (NCT01938248, NCT02618577).</p> | | | See Tables LXXXII through LXXXIV in online Data Supplement 1 . |

| 6.3.2. Echocardiography | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. For prevention of recurrent stroke, the use of echocardiography is reasonable in some patients with AIS to provide additional information to guide selection of appropriate secondary stroke prevention. | IIa | C-EO | New recommendation. |
| <p>In many patients, appropriate evidence-based treatment for secondary prevention can be selected without the use of echocardiography. Many RCTs that provide the current best evidence for secondary prevention treatments did not require echocardiography for patient selection. These include NASCET (North American Symptomatic Carotid Endarterectomy Trial), ECST (European Carotid Surgery Trial), IST, SALT (Swedish Aspirin Low-dose Trial), CAPRIE (Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events), ESPS2 (European Stroke Prevention Study 2), PROFESS (Prevention Regimen for Effectively Avoiding Second Strokes), CHANCE, PROGRESS (Perindopril Protection Against Recurrent Stroke Study), SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels), SOCRATES, POINT, and TARDIS (Triple Antiplatelets for Reducing Dependency After Ischaemic Stroke).^{207,210,216,219,299–306,350} The benefits shown in these RCTs can be expected when the same eligibility criteria are applied. Those patients with known or newly discovered atrial fibrillation by routine ECG will benefit from oral anticoagulation regardless of echocardiographic findings.³⁴² Intracardiac thrombus occurs almost exclusively in patients with clinical evidence of heart disease but is rare even in them. Echocardiography for detecting intracardiac thrombus in unselected patients will produce at least as many false-positive as true-positive diagnoses.³⁵¹ In large series of patients with AIS who underwent echocardiography, the reported yield of important potentially cardioembolic sources has ranged from 0.2% to 55% (Table LXXXV in online Data Supplement 1). Much of this discrepancy is the result of differences in categorization of cardiac pathology as either pathophysiologically or therapeutically relevant. The efficacy of treatment in reducing the risk of recurrent stroke associated with many of these echocardiographic lesions is unknown, or there is not a treatment that has been shown to be better than standard medical therapy.^{352–360} Different authors have concluded that routine echocardiography is indicated or contraindicated. Various inconsistent recommendations for selecting which patients with AIS should undergo echocardiography have been made.^{358,361–363} Six RCTs have evaluated mechanical closure of echocardiographically detected PFO to prevent recurrent stroke in patients without an obvious cause for their index stroke.^{311–317} These trials had highly restrictive eligibility criteria. They do not support the routine use of echocardiography in all patients with AIS.</p> | | | See Tables LXXIV and LXXXV in online Data Supplement 1 . |
| 2. Echocardiography is reasonable in selected patients as part of a comprehensive evaluation to determine if they meet the eligibility criteria of the RCTs that investigated mechanical closure of PFO for prevention of recurrent stroke. | IIa | B-R | New recommendation. |
| <p>Six RCTs have evaluated mechanical closure of echocardiographically detected PFO to prevent recurrent stroke in patients without an obvious cause for their index stroke.^{311–317} These trials had highly restrictive eligibility criteria that required brain MRI, imaging of the intracranial vasculature, and echocardiography. Meta-analyses of these trials show a significantly reduced risk of recurrent stroke with mechanical closure compared with medical therapy with a number needed to treat of 131.^{318–320} A network meta-analysis concluded that, in patients <60 years of age, PFO closure probably confers an important reduction in ischemic stroke recurrence compared with antiplatelet therapy alone but may make no difference compared with anticoagulation. PFO closure also incurs a risk of persistent atrial fibrillation and device-related adverse events. Compared with alternatives, anticoagulation probably increases major bleeding.³¹⁹ Each of these 6 trials had ≥ 1 methodological features with a high risk of bias identified, including lack of blinding of participants and personnel, lack of blinding of outcome assessments, incomplete outcome data, and selective reporting.^{318–324}</p> | | | See Tables LXXV through LXXVII in online Data Supplement 1 . |

| 6.3.2. Echocardiography (Continued) | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|----------------------------|
| 3. The effectiveness of routine echocardiography to guide treatment selection for prevention of recurrent stroke is uncertain. (See knowledge byte following 6.3.2, recommendation 1.) | IIb | B-NR | New recommendation. |


6.4. Glucose

| 6.4. Glucose | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|--|
| 1. After AIS, it is reasonable to screen all patients for diabetes mellitus with testing of fasting plasma glucose, hemoglobin A_{1c}, or an oral glucose tolerance test. Choice of test and timing should be guided by clinical judgment and recognition that acute illness may temporarily perturb measures of plasma glucose. In general, hemoglobin A_{1c} may be more accurate than other screening tests in the immediate postevent period. | IIa | C-EO | Recommendation wording modified from 2014 Secondary Prevention to match COR IIa stratifications and reworded for clarity. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

6.5. Other Tests for Secondary Prevention

| 6.5. Other Tests for Secondary Prevention | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|--|
| 1. The usefulness of screening for thrombophilic states in patients with ischemic stroke is unknown. | IIb | C-LD | Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| Current evidence suggests that there is little, if any, contribution of the inherited thrombophilias to the development of arterial thrombotic events. Therefore, tests for inherited thrombophilia should not be ordered for the evaluation of MI, stroke, or peripheral arterial thrombosis. ^{364,365} | | | |
| 2. Routine screening of patients with recent ischemic stroke for obstructive sleep apnea (OSA) is not recommended. | III: No Benefit | B-R | New recommendation. |
| Numerous studies have established an association between OSA and stroke. OSA is highly prevalent among ischemic stroke patients and has been associated with considerable morbidity, including increased risk of cardiovascular and cerebrovascular events, worse prognosis, and higher mortality. Continuous positive airway pressure (CPAP) remains the most effective medical therapy for OSA. ³⁶⁶⁻³⁷⁰ A small RCT of CPAP in 127 patients started 4.6±2.8 days after AIS showed mixed results with no effect on disability, total cardiovascular events, cardiovascular mortality, or cardiovascular event-free survival but a reduction in time to first cardiovascular event during 24-month follow-up. This trial did not specify a primary end point and compared multiple different outcomes at multiple time points. ³⁷¹ The SAVE RCT (Continuous Positive Airway Pressure Treatment of Obstructive Sleep Apnea to Prevent Cardiovascular Disease) randomized 2717 patients with established cardiovascular or cerebrovascular disease (but not within the first 90 days after a stroke except for minor strokes) and moderate to severe OSA to CPAP versus usual care without CPAP and found no reduction of vascular events, including stroke, in patients treated with CPAP over a mean follow-up of 3.7 years. ³⁷² Thus, the routine screening for OSA of all patients with AIS for the secondary prevention of cardiovascular events or death is not recommended at this time. Several ongoing National Institutes of Health-funded RCTs are further investigating the effects of CPAP in patients with AIS and OSA (NR018335, NS099043). | | | |
| 3. Routine testing for antiphospholipid antibodies is not recommended for patients with ischemic stroke who have no other manifestations of the antiphospholipid syndrome and who have an alternative explanation for their ischemic event such as atherosclerosis, carotid stenosis, or atrial fibrillation. | III: No Benefit | C-LD | Recommendation reworded for clarity from 2014 Secondary Prevention. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 4. Routine screening for hyperhomocysteinemia among patients with a recent ischemic stroke is not indicated. | III: No Benefit | C-EO | Recommendation reworded for clarity from 2014 Secondary Prevention. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

6.6. Antithrombotic Treatment

| 6.6.1. Noncardioembolic Stroke | COR | LOE | New, Revised, or Unchanged |
|--|-----------------|------|--|
| 1. For patients with noncardioembolic AIS, the use of antiplatelet agents rather than oral anticoagulation is recommended to reduce the risk of recurrent stroke and other cardiovascular events. | I | A | Recommendation reworded for clarity from 2014 Secondary Prevention. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording. |
| 2. For early secondary prevention in patients with noncardioembolic AIS, the selection of an antiplatelet agent should be individualized on the basis of patient risk factor profiles, cost, tolerance, relative known efficacy of the agents, and other clinical characteristics. | I | C-EO | Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 3. For patients who have a noncardioembolic AIS while taking aspirin, increasing the dose of aspirin or switching to an alternative antiplatelet agent for additional benefit in secondary stroke prevention is not well established. | IIb | B-R | Recommendation revised from 2014 Secondary Prevention. |
| In patients with a noncardioembolic ischemic stroke, the therapeutic benefit of aspirin is similar across a wide range of doses, but the hemorrhagic risk increases with higher doses. In patients taking aspirin at the time of the incident stroke, the benefit of switching to an alternative antiplatelet agent or combination therapy is not well established. The SPS3 RCT (Secondary Prevention of Small Subcortical Strokes) found no benefit from adding clopidogrel to aspirin compared with placebo in patients with a recent small vessel, lacunar stroke taking aspirin at the time of their index event. However, the median time from the qualifying event to enrollment in the SPS3 trial was >40 days, so results may have underestimated benefit in the early poststroke period. ³⁷³ A recent meta-analysis of 5 studies, including 3 RCTs and 2 observational registries, of patients with noncardioembolic stroke taking aspirin at the time of the index event found a decreased risk of major cardiovascular events and recurrent stroke in patients switching to an alternative antiplatelet agent or combination antiplatelet therapy. This analysis included data from aspirin failure subgroups in the CHANCE trial of dual antiplatelet therapy in patients with minor stroke or TIA and the SOCRATES trial of aspirin versus ticagrelor. However, there was significant heterogeneity among the included studies, and results may have been driven by data from registries susceptible to unmeasured confounders and bias. ³⁷⁴ | | | See Tables LXXXVII and LXXXVIII in online Data Supplement 1 .  American Stroke Association. A Division of the American Heart Association. |
| 4. Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke, depending on the abnormality and the clinical circumstances. | IIb | C-LD | Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |
| 5. For patients who have a noncardioembolic AIS while taking antiplatelet therapy, switching to warfarin is not indicated for secondary stroke prevention. | III: No Benefit | B-NR | New recommendation. |
| In patients taking aspirin at the time of baseline stroke in WARSS (Warfarin Aspirin Recurrent Stroke Study; n=181), there was no difference in recurrence of stroke between those randomized to remain on aspirin and those who switched to warfarin (RR, 0.9 [95% CI, 0.5–1.5]; P=0.63). ³⁷⁵ In addition, post hoc analysis from the WASID trial found no difference in the primary outcome of ischemic stroke, brain hemorrhage, or vascular death in patients taking antiplatelet therapy at the time of their qualifying event who were subsequently randomized to warfarin. ^{376,377} | | | See Table LXXXIX in online Data Supplement 1 . |
| 6. In patients with noncardioembolic ischemic stroke, treatment with triple antiplatelet therapy (aspirin+clopidogrel+dipyridamole) for secondary stroke prevention is harmful and should not be administered. | III: Harm | B-R | New recommendation. |
| The TARDIS trial (N=3096) was a multicenter, prospective, randomized, open-label trial conducted in Denmark, Georgia, New Zealand, and the United Kingdom of short-term triple antiplatelet therapy for secondary stroke prevention in patients with recent noncardioembolic ischemic stroke or TIA. ³⁵⁰ The open-label treatment arms included aspirin+clopidogrel+dipyridamole versus either clopidogrel alone or aspirin and dipyridamole for 30 days from symptom onset. There was no benefit of triple therapy in prevention of stroke or TIA at 90 days (6% versus 7%; HR, 0.90 [95% CI, 0.67–1.20]; P=0.47). Moreover, there was a significant increase in risk of all hemorrhage (20% versus 9%; HR, 2.54 [95% CI, 2.05–3.16]; P<0.0001), including intracranial hemorrhage (HR, 3.14 [95% CI, 1.14–8.61]; P=0.0063), and extracranial hemorrhage (HR, 2.37; 95% CI, 1.93–2.91; P<0.0001). | | | See Table XLVIII in online Data Supplement 1 . |

| 6.6.2. Atrial Fibrillation | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation between 4 and 14 days after the onset of neurological symptoms. | IIa | B-NR | Recommendation revised from 2014 Secondary Prevention. |
| <p>A multicenter prospective cohort of 1029 patients with AIS and newly diagnosed atrial fibrillation showed a better composite outcome of stroke, TIA, systemic embolism, sICH, and major extracranial bleeding within 90 days when anticoagulant was initiated 4 to 14 days from stroke onset (HR 0.53 [95% CI, 0.30–0.93] for starting anticoagulation at 4–14 days compared with <4 days); high CHA₂DS₂-VASc score, high NIHSS score, large ischemic lesions, and type of anticoagulation were associated with poorer outcomes.³⁷⁸ In a prospective, open-label study of 60 patients with atrial fibrillation and either mild to moderate AIS with 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 hemorrhagic transformation (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.²²⁷</p> | | | See Table LI in online Data Supplement 1 . |
| 2. For patients with a history of ischemic stroke, atrial fibrillation, and coronary artery disease, the usefulness of adding antiplatelet therapy to oral anticoagulants is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet/oral anticoagulation. | IIb | C-LD | Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording. |

| 6.6.3. Arterial Dissection | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|--|
| 1. For patients with AIS and extracranial carotid or vertebral arterial dissection, treatment with either antiplatelet or anticoagulant therapy for 3 to 6 months is reasonable. | IIa | B-NR | Recommendation revised from 2014 Secondary Prevention. |
| <p>Although there has not been a randomized trial of antithrombotic therapy versus placebo in patients with acute cervical artery dissection (CeAD), numerous observational studies and expert opinion suggest that it is reasonable to initiate antithrombotic therapy in the acute setting to prevent early thromboembolic events. The CADISS (Cervical Artery Dissection in Stroke Study) group published a randomized, open-label phase II feasibility trial of anticoagulation versus antiplatelet therapy in 250 participants with extracranial carotid or vertebral artery dissection recruited from 46 centers in the United Kingdom and Australia.³⁷⁹ The primary outcome was ipsilateral stroke or all-cause mortality within 3 months of randomization in an intention-to-treat analysis, and there were no significant differences between groups. There was also no difference in rates of major bleeding. As a phase II trial, the study concluded that a definitive phase III trial would not be feasible, primarily because of the low event rates in both groups. Additional limitations included a lack of central radiological confirmation in 20% of cases and a mean time to randomization of 3.65 days that perhaps limits generalizability of the results to the hyperacute period. Nonetheless, the CADISS trial supports numerous previous observational studies that found no significant difference in clinical outcomes with the use of anticoagulation compared with antiplatelet therapy in patients with CeAD. In addition, in a follow-up CADISS analysis of dissecting aneurysms (DAs), there was no association between treatment allocation (antiplatelets versus anticoagulants) and whether DAs at baseline persisted at follow-up or whether new DAs developed. During 12 months of follow-up, stroke occurred in 1 of 48 patients with DA and in 7 of 216 patients without DA (age- and sex-adjusted OR, 0.84 [95% CI, 0.10–7.31]; <i>P</i>=0.88). A review of published studies, mainly retrospective, showed a similarly low risk of stroke and no evidence of an increased stroke rate in patients with DA.³⁸⁰ These data provide evidence that DAs may have a benign prognosis, and therefore, medical treatment should be considered.</p> | | | See Tables LI and XC in online Data Supplement 1 . |
| 2. For patients with AIS and extracranial carotid or extracranial vertebral arterial dissection who have definite recurrent cerebral ischemic events despite medical therapy, the value of extracranial EVT (stenting) is not well established. | IIb | C-LD | Recommendation revised from 2014 Secondary Prevention. |
| <p>There have been no controlled trials of EVT and stenting in patients with extracranial CeAD. The published literature reflects small case series, individual case reports, and several systematic reviews.³⁸¹ A systematic review of the literature published until 2009 found 31 published reports (N=140) with a technical success rate of 99% and procedural complication rate of 1.3%. However, these observational data are prone to selection and reporting biases. A retrospective analysis of patients with CeAD (n=161) comparing extracranial EVT (with and without stenting) with medical therapy alone found no difference in 90-day outcomes (adjusted OR, 0.62 [95% CI, 0.12–3.14]; <i>P</i>=0.56). With medical therapy alone, the overall prognosis and natural history of CeAD, including DAs, are favorable.^{379,380} Therefore, the benefit of extracranial EVT and stenting in patients with CeAD and definite recurrent cerebral ischemic events despite medical therapy is not well established.</p> | | | See Table LI in online Data Supplement 1 . |

| 6.6.4. Hemorrhagic Transformation | COR | LOE | New, Revised, or Unchanged |
|---|-----------|-------------|--|
| 1. For patients with AIS and HT, initiation or continuation of antiplatelet or anticoagulation therapy may be considered, depending on the specific clinical scenario and underlying indication. | Ib | C-LD | Recommendation revised from 2014 Secondary Prevention. |
| Several observational studies suggest that antithrombotics can be safely initiated or continued in patients with AIS and HT. In a prospective, open-label study of 60 patients with atrial fibrillation 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. ²²⁷ 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 antithrombotics 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. ³⁸² Individual assessment of the clinical indication, benefits, and associated risks is warranted. ^{10,382,383} | | | See Table LI in online Data Supplement 1 . |

6.7. Carotid Revascularization

| 6.7. Carotid Revascularization | COR | LOE | New, Revised, or Unchanged |
|---|-----------|-------------|---|
| 1. When revascularization is indicated for secondary prevention in patients with minor, nondisabling stroke (mRS score 0–2), it is reasonable to perform the procedure between 48 hours and 7 days of the index event rather than delay treatment if there are no contraindications to early revascularization. | Ia | B-NR | Recommendation revised from 2014 Secondary Prevention. |
| The risk of recurrent stroke resulting from symptomatic carotid stenosis is highest in the first few days after the initial event. ^{325–329} Although there is evidence that early or emergency revascularization via either CEA or carotid angioplasty and stenting may be safe in selected cases, ^{330–332} there are no high-quality prospective data supporting early versus late carotid revascularization in all cases. ³³³ In cases of minor, nondisabling stroke, a meta-analysis by De Rango et al ³²⁶ demonstrates favorable rates of complications when treated at least 48 hours after the initial event, and the risks are not different when treated between 0 to 7 and 0 to 15 days. Revascularization between 48 hours and 7 days after initial stroke is supported by these data in cases of nondisabling stroke (mRS score 0–2). ³³⁴ | | | See Table LXXVIII in online Data Supplement 1 . |

6.8. Treatment of Hyperlipidemia

| 6.8.1. General Principles | COR | LOE | New, Revised, or Unchanged |
|--|----------|-------------|--|
| 1. Patients with AIS should be managed according to the 2018 ACC/AHA Cholesterol Guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations. | I | A | Recommendation, COR, and LOE updated from 2014 Secondary Prevention to reference 2018 Cholesterol Guidelines |
| The 2018 Cholesterol Guidelines provide a comprehensive set of recommendations for managing hyperlipidemia. ¹⁹ Those recommendations that are most pertinent to the in-hospital management of patients with AIS are excerpted here. The full guidelines should be used for guidance in managing these disorders in patients with AIS and for supporting evidence. | | | |
| 2. In adults who are 20 years of age or older and not on lipid-lowering therapy, measurement of either a fasting or a nonfasting plasma lipid profile is effective in estimating atherosclerotic cardiovascular disease (ASCVD) risk and documenting baseline low-density lipoprotein cholesterol (LDL-C). | I | B-NR | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 3. Adherence to changes in lifestyle and effects of LDL-C-lowering medication should be assessed by measurement of fasting lipids and appropriate safety indicators 4 to 12 weeks after statin initiation or dose adjustment and every 3 to 12 months thereafter based on need to assess adherence or safety. | I | A | Recommendation unchanged from 2018 Cholesterol Guidelines. |

| 6.8.2. Choice of Lipid-lowering Drugs for Patients with Clinical ASCVD* | COR | LOE | New, Revised, or Unchanged |
|---|----------|----------|--|
| 1. In patients who are 75 years of age or younger with clinical ASCVD, high-intensity statin therapy should be initiated or continued with the aim of achieving a 50% or greater reduction in LDL-C levels. | I | A | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 2. In patients with clinical ASCVD in whom high-intensity statin therapy is contraindicated or who experience statin-associated side effects, moderate-intensity statin therapy should be initiated or continued with the aim of achieving a 30% to 49% reduction in LDL-C levels. | I | A | Recommendation unchanged from 2018 Cholesterol Guidelines. |

| 6.8.2. Choice of Lipid-lowering Drugs for Patients with Clinical ASCVD* (Continued) | COR | LOE | New, Revised, or Unchanged |
|---|--|------|--|
| 3. In patients at increased ASCVD risk with chronic, stable liver disease (including nonalcoholic fatty liver disease) when appropriately indicated, it is reasonable to use statins after obtaining baseline measurements and determining a schedule of monitoring and safety checks. | I | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 4. In patients with clinical ASCVD, who are judged to be very high-risk and considered for proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitor therapy, maximally tolerated LDL-C lowering therapy should include maximally tolerated statin therapy and ezetimibe. | I | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 5. In patients with clinical ASCVD who are judged to be very high risk and who are on maximally tolerated LDL-C lowering therapy with LDL-C 70 mg/dL or higher (≥ 1.8 mmol/L) or a non-HDL-C level of 100 mg/dL or higher (≥ 2.6 mmol/L), it is reasonable to add a PCSK9 inhibitor following a clinician-patient discussion about the net benefit, safety, and cost. | Ia | A | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 6. At mid-2018 list prices, PCSK9 inhibitors have a low cost value ($> \$150,000$ per quality-adjusted life-year) compared to good cost value ($< \$50,000$ per quality-adjusted life-year). | Value Statement: Low Value (LOE: B-NR) | | Statement unchanged from 2018 Cholesterol Guidelines. |
| 7. In patients with clinical ASCVD who are on maximally tolerated statin therapy and are judged to be at very high risk and have an LDL-C level of 70 mg/dL or higher (≥ 1.8 mmol/L), it is reasonable to add ezetimibe therapy. | Ia | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 8. In patients older than 75 years of age with clinical ASCVD, it is reasonable to initiate moderate- or high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. | Ia | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 9. In patients older than 75 years of age who are tolerating high-intensity statin therapy, it is reasonable to continue high-intensity statin therapy after evaluation of the potential for ASCVD risk reduction, adverse effects, and drug-drug interactions, as well as patient frailty and patient preferences. | Ia | C-LD | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 10. In patients with clinical ASCVD who are receiving maximally tolerated statin therapy and whose LDL-C level remains 70 mg/dL or higher (≥ 1.8 mmol/L), it may be reasonable to add ezetimibe. | Iib | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |

*Clinical ASCVD includes acute coronary syndrome, those with history of MI, stable or unstable angina, or coronary or other arterial revascularization, stroke, TIA, or peripheral artery disease, including aortic aneurysm, all of atherosclerotic origin.

For high-intensity statin therapy, the 2018 ACC/AHA Cholesterol Guidelines recommend atorvastatin 80 mg daily or rosuvastatin 20 mg daily. Please refer to these guidelines for contraindications to high-intensity statin therapy and recommendations for moderate-intensity statin therapy.

Very high risk includes a history of multiple major ASCVD events or 1 major ASCVD event and multiple high-risk conditions:

Major ASCVD Events:

- Recent acute coronary syndrome (within the past 12 months)
- History of MI (other than recent acute coronary syndrome event listed above)
- History of ischemic stroke
- Symptomatic peripheral arterial disease (history of claudication with ankle-brachial index < 0.85 , or previous revascularization or amputation).

High-Risk Conditions:

- Age ≥ 65 years
- Heterozygous familial hypercholesterolemia
- History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
- Diabetes mellitus
- Hypertension
- Chronic kidney disease (estimated glomerular filtration rate $15-59$ mL·min⁻¹·1.73 m²)
- Current smoking

| 6.8.3 Implementation | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|--|
| 1. A clinician-patient risk discussion is recommended before initiation of statin therapy to review net clinical benefit, weighing the potential for ASCVD risk reduction against the potential for statin-associated side effects, statin-drug interactions, and safety, while emphasizing that side effects can be addressed successfully. | I | A | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 2. In patients with indication for statin therapy, identification of potential predisposing factors for statin-associated side effects, including new-onset diabetes mellitus and statin-associated muscle symptoms, is recommended before initiation of treatment. | I | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 3. In patients with statin-associated side effects that are not severe, it is recommended to reassess and to rechallenge to achieve a maximal LDL-C lowering by modified dosing regimen, an alternate statin or in combination with nonstatin therapy. | I | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 4. In patients at increased ASCVD risk with severe statin-associated muscle symptoms or recurrent statin-associated muscle symptoms despite appropriate statin rechallenge, it is reasonable to use RCT-proven nonstatin therapy that is likely to provide net clinical benefit. ³⁸⁴⁻³⁸⁶ | IIa | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |

| 6.8.4. Timing | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable. | IIa | B-R | Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. |
| 2. For patients with AIS who qualify for statin treatment, in-hospital initiation of statin therapy is reasonable. | IIa | C-LD | New recommendation. <small>American Stroke Association.</small> |
| <p>Statin have an established role in secondary stroke prevention and harbor promise in improving index stroke outcomes.^{1,10} A retrospective cohort study that assessed 3-month treatment adherence rates after in-hospital initiation of statins in patients with ischemic stroke showed a high rate of adherence to statin therapy 3 months after hospital discharge.³⁸⁷ A meta-analysis of primarily observational studies found that in-hospital statin use was associated with good functional outcomes.³⁸⁸ Withdrawal of statins after ischemic stroke was associated with poor functional outcomes. There are limited published randomized trials examining the role of early statin use in AIS patients. FASTER (Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence) evaluated simvastatin 40 mg versus placebo in patients with a TIA or minor stroke within the previous 24 hours.³⁸⁹ Because of slow enrollment, this trial was terminated early. There were no significant differences in recurrent stroke or safety outcomes in the simvastatin versus placebo groups. FASTER was underpowered because of early termination, and the statin doses used in FASTER were of moderate intensity (not the high-intensity dose recommended for secondary stroke prevention). ASSORT (Administration of Statin on Acute Ischemic Stroke Patient) showed no difference in 90-day mRS score when statins were begun within 24 hours or on the seventh day.³⁹⁰</p> | | | <p>See Tables XCI and XCII in online Data Supplement 1.</p> |

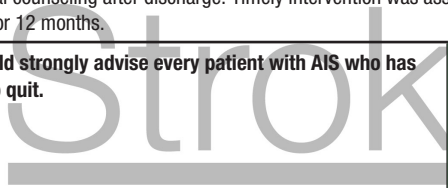
| 6.8.5 Special Patient Groups | COR | LOE | New, Revised, or Unchanged |
|---|-----------------|------|--|
| 1. Women of childbearing age who are treated with statin therapy and are sexually active should be counseled to use a reliable form of contraception. | I | C-LD | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 2. Women of childbearing age with hypercholesterolemia who plan to become pregnant should stop the statin 1 to 2 months before pregnancy is attempted or, if they become pregnant while on a statin, should have the statin stopped as soon as the pregnancy is discovered. | I | C-LD | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 3. In adults with advanced kidney disease that requires dialysis treatment who are currently on LDL-lowering therapy with a statin, it may be reasonable to continue the statin. | IIb | C-LD | Recommendation unchanged from 2018 Cholesterol Guidelines. |
| 4. In adults with advanced kidney disease who require dialysis treatment, initiation of a statin is not recommended. | III: No Benefit | B-R | Recommendation unchanged from 2018 Cholesterol Guidelines. |

6.9. Institution of Antihypertensive Medications

| 6.9. Institution of Antihypertensive Medications | COR | LOE | New, Revised, or Unchanged |
|--|-----|-----|---|
| 1. Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mm Hg who are neurologically stable is safe and is reasonable to improve long-term BP control unless contraindicated. | IIa | B-R | New recommendation. |
| <p>Starting or restarting antihypertensive medications has been shown to be associated with improved control of the BP after discharge in 2 trials.^{247,248} Therefore, it is reasonable to start or restart antihypertensive medications in the hospital when the patient remains hypertensive and is neurologically stable. Studies evaluating this question included only patients with previous diagnosis of hypertension²⁴⁷ or enrolled mostly patients with previous hypertension.²⁴⁸ However, because hypertension is not uncommonly first diagnosed during the hospitalization for stroke, it is reasonable to apply this recommendation also to patients without preexistent hypertension.</p> | | | See Table LVI in online Data Supplement 1 . |

6.10. Smoking Cessation Intervention

| 6.10. Smoking Cessation Intervention | COR | LOE | New, Revised, or Unchanged |
|---|-----|------|---|
| 1. Smokers with AIS should receive in-hospital initiation of high-intensity behavioral interventions to promote smoking cessation. | I | A | New recommendation. |
| 2. For smokers with an AIS, who receive in-hospital initiation of high-intensity behavioral interventions to promote smoking cessation, nicotine replacement therapy is recommended. | I | A | New recommendation. |
| <p>A 2012 meta-analysis by the Cochrane group indicates that high-intensity behavioral interventions that begin during an index hospitalization and include at least 1 month of supportive contact after discharge increased smoking cessation rates after discharge (RR, 1.37 [95% CI, 1.27–1.48]; 25 trials). The estimate of the effect for each level of intervention intensity among patients with a cardiovascular diagnosis was very similar (RR, 1.42 [95% CI, 1.29–1.56]). Adding nicotine replacement therapy to an intensive counselling intervention increased smoking cessation rates compared with intensive counseling alone (RR, 1.54 [95% CI, 1.34–1.79]; 6 trials).³⁹¹ A 2016 retrospective cohort study of Korean smokers with AIS assessed a timely intervention strategy versus historical controls who received conventional counseling.³⁹² Timely intervention comprised a certified nurse providing comprehensive education during admission and additional counseling after discharge. Timely intervention was associated with greater odds of sustained smoking cessation for 12 months.</p> | | | See Table XCIII and XCIV in online Data Supplement 1 . |
| 3. Healthcare providers should strongly advise every patient with AIS who has smoked in the past year to quit. | I | C-EO | <p>Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.</p> <p>See Table XCV in online Data Supplement 1 for original wording.</p> |
| 4. It is reasonable to advise patients after ischemic stroke to avoid secondhand (passive) tobacco smoke. | IIa | B-NR | <p>Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.</p> <p>See Table XCV in online Data Supplement 1 for original wording.</p> |
| 5. For smokers with an AIS, in-hospital initiation of varenicline to promote smoking cessation might be considered. | IIb | B-R | New recommendation. |
| <p>A 2012 meta-analysis by the Cochrane group indicates that high-intensity behavioral interventions that begin during an index hospitalization and include at least 1 month of supportive contact after discharge increased smoking cessation rates after discharge (RR, 1.37 [95% CI, 1.27–1.48]; 25 trials). The estimate of the effect for each level of intervention intensity among patients with a cardiovascular diagnosis was very similar (RR, 1.42 [95% CI, 1.29–1.56]). There was insufficient direct evidence to conclude that adding bupropion or varenicline to intensive counseling increases cessation rates over what is achieved by counseling alone.³⁹¹ A subsequent 2016 multicenter, double-blind, randomized, placebo-controlled trial in which 302 smokers hospitalized with an acute coronary syndrome were randomized to varenicline or placebo for 12 weeks showed that at 24 weeks abstinence rates were 47.3% in the varenicline group versus 32.5% in the placebo group. Continuous abstinence rates were 35.8% in the varenicline group versus 25.8% in the placebo group.³⁹³ Patients in both groups received low-intensity counseling.</p> | | | See Tables XCIII and XCIV in online Data Supplement 1 . |



6.11. Stroke Education

| 6.11. Stroke Education | COR | LOE | New, Revised, or Unchanged |
|--|-----|------|---|
| 1. Patient education about stroke is recommended. Patients should be provided with information, advice, and the opportunity to talk about the impact of the illness on their lives. | I | C-EO | Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE revised. |

Additional reference support for this guideline is provided in [online Data Supplement 1](#).^{394–544}

Disclosures

Writing Group Disclosures

| Writing Group Member | Employment | Research Grant | Other Research Support | Speakers' Bureau/ Honoraria | Expert Witness | Ownership Interest | Consultant/ Advisory Board | Other |
|-------------------------|---|---|------------------------|-----------------------------|--|--------------------|----------------------------|---------------------------|
| William J. Powers | University of North Carolina, Chapel Hill | None | None | None | Wake Forest University Baptist Medical Center* | None | None | None |
| Alejandro A. Rabinstein | Mayo Clinic | None | None | None | None | None | None | None |
| Teri Ackerson | Saint Luke's Health System, AHA/ASA | None | None | None | None | None | None | None |
| Opeolu M. Adeoye | University of Cincinnati | None | None | None | None | None | None | None |
| Nicholas C. Bambakidis | University Hospitals, Cleveland Medical Center | None | None | None | None | None | None | None |
| Kyra Becker | University of Washington School of Medicine, Harborview Medical Center | None | None | None | Defense and prosecution* | None | None | None |
| José Biller | Loyola University Chicago | None | None | None | None | None | None | None |
| Michael Brown | Michigan State University College of Human Medicine, Emergency Medicine | None | None | None | 2018 Defense, Sandberg, Phoenix & Von Gontard*; 2018 Defense, Kamykowski, Gavin & Smith* | None | None | Cochrane (senior editor)† |
| Bart M. Demaerschalk | Mayo Clinic, Mayo Clinic Hospital | None | None | None | None | None | None | None |
| Brian Hoh | University of Florida | None | None | None | None | None | None | None |
| Edward C. Jauch | Mission Health System Research Institute | NINDS (StrokeNet coinvestigator)*; Diffusion Pharmaceuticals (PHAST-TSC DSMB member)* | None | None | Plaintiff and defense* | None | Biogen* | None |
| Chelsea S. Kidwell | University of Arizona | None | None | None | None | None | None | None |
| Thabele M. Leslie-Mazwi | Massachusetts General Hospital | None | None | None | None | None | None | None |
| Bruce Ovbiagele | UCSF | None | None | None | None | None | None | None |

(Continued)

Writing Group Disclosures Continued

| Writing Group Member | Employment | Research Grant | Other Research Support | Speakers' Bureau/Honoraria | Expert Witness | Ownership Interest | Consultant/Advisory Board | Other |
|-----------------------|---|---|---|----------------------------|---|--|---------------------------|--|
| Phillip A. Scott | University of Michigan Department of Emergency Medicine | NIH (principal investigator)† | University of Michigan (co-medical director, Clinical Trials Support Unit)* | None | Expert testimony 2017*; 2018* | None | None | University of Michigan (associate chair, Research Department of Emergency Medicine)† |
| Kevin N. Sheth | Yale University School of Medicine | Astrocyte (advisory)*; Bard (PI, Stroke Trial)†; Biogen (PI Stroke Trial)†; Hyperfine (PI, Imaging Trial including stroke patients)†; Zoll (DSMB chair)* | None | None | None | Alva Health* | Biogen* | None |
| Andrew M. Southerland | University of Virginia | Diffusion Pharmaceuticals, Inc (Prehospital Administration of Acute Stroke Therapy with Trans-sodium Crocetinate [PHAST-TSC])†; NINDS U01 NS069498 (SHINE Trial)*; NHLBI-NINDS U01 HL088942 (Cardiothoracic Surgical Trials Network)†; Coulter Translational Research Foundation (Brain and Neurological Deficit Identification Tool [BANDIT] Study)* | None | None | Plaintiff and defense cases focused on questions related to stroke* | iTREAT Project, US Patent Application No. 14/910,890*; BANDIT Project, US Provisional Patent Application No. 62/620,096* | None | None |
| Deborah V. Summers | Saint Luke's Health System | None | None | None | None | None | None | None |
| David L. Tirschwell | Harborview Medical Center | NIH† | None | None | None | None | None | 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 \$10,000 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 \$10,000 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.

†Significant.

Reviewer Disclosures

| Reviewer | Employment | Research Grant | Other Research Support | Speakers' Bureau/Honoraria | Expert Witness | Ownership Interest | Consultant/Advisory Board | Other |
|---------------------|--------------------------|-----------------------------------|---------------------------------------|-------------------------------|----------------|--------------------|---------------------------|-------|
| Mark J. Alberts | Hartford HealthCare | None | None | Genentech (speakers' bureau)† | None | None | None | None |
| Joseph P. Broderick | University of Cincinnati | NIH (trial)†; NIH (investigator)† | Genentech (PRISMS)†; Genentech (TNK)† | None | None | None | None | None |

(Continued)

Reviewer Disclosures Continued

| Reviewer | Employment | Research Grant | Other Research Support | Speakers' Bureau/ Honoraria | Expert Witness | Ownership Interest | Consultant/ Advisory Board | Other |
|----------------------|---|-----------------|------------------------|---|---|--|---|--------------------------------------|
| Colin P. Derdeyn | University of Iowa | None | None | None | None | Pulse therapeutics* | Penumbra* | None |
| Marc Fisher | Beth Israel Deaconess Medical Center | None | None | None | None | None | None | American Heart Association† |
| Karen L. Furie | Rhode Island Hospital | None | None | None | None | None | None | None |
| Philip B. Gorelick | Michigan State University | None | None | None | Employer received compensation for expert witness work† | None | IMPACT clinical trial*; NeuroSpring* | None |
| Walter N. Kernan | Yale University | None | None | None | None | None | None | None |
| Steven J. Kittner | Veterans Affairs Maryland Health Care System; University of Maryland School of Medicine | None | None | None | None | None | None | None |
| Patrick D. Lyden | Cedars-Sinai Medical Center | NIH* | None | None | None | None | None | None |
| Philip M. Meyers | Columbia University | None | None | None | None | None | None | None |
| Jeffrey L. Saver | UCLA | None | None | None | None | Rapid Medical* | Medtronic*; Stryker*; Neuravi/ Ceronovus*; Boehringer Ingelheim*; St. Jude Medical* | University of California (employer)* |
| Steven Warach | University of Texas at Austin | State of Texas† | None | None | Private law firm* | Stock holdings in various pharma companies in a managed investment portfolio (myself)*; stock holdings in various pharma companies in a managed investment portfolio (family)* | Genentech* | None |
| Lawrence R. Wechsler | University of Pittsburgh | None | None | None | None | None | None | None |
| Babu G. Welch | UT Southwestern Medical Center | None | None | Stryker Neurovascular (speakers' bureau)*; Stryker Neurovascular (honoraria)* | None | None | Stryker Neurovascular* | 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 \$10,000 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 \$10,000 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.

†Significant.

Stroke

References

1. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, et al; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Peripheral Vascular Disease; Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. doi: 10.1161/STR.0b013e318284056a
2. Saposnik G, Barinagarrementeria F, Brown RD Jr, Bushnell CD, Cucchiara B, Cushman M, deVeber G, Ferro JM, Tsai FY; on behalf of the American Heart Association Stroke Council and the Council on Epidemiology and Prevention. Diagnosis and management of cerebral venous thrombosis: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2011;42:1158–1192. doi: 10.1161/STR.0b013e31820a8364
- 2a. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. 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 [published corrections appear in *Stroke*. 2018;49:e138 and *Stroke*. 2018;49:e233–234]. *Stroke*. 2018;49:e46–e99. doi: 10.1161/STR.0000000000000158
3. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec DB; on behalf of the American Heart Association Stroke Council. Effect of dysphagia screening strategies on clinical outcomes after stroke: a systematic review for the 2018 guidelines for the early management of patients with acute ischemic stroke [published correction appears in *Stroke*. 2018;49:e140]. *Stroke*. 2018;49:e123–e128. doi: 10.1161/STR.0000000000000159
4. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec DB; on behalf of the American Heart Association Stroke Council. Accuracy of prediction instruments for diagnosing large vessel occlusion in individuals with suspected stroke: a systematic review for the 2018 guidelines for the early management of patients with acute ischemic stroke [published correction appears in *Stroke*. 2018;49:e139]. *Stroke*. 2018;49:e111–e122. doi: 10.1161/STR.0000000000000160
5. Schwamm LH, Audebert HJ, Amarenco P, Chumbler NR, Frankel MR, George MG, Gorelick PB, Horton KB, Kaste M, Lackland DT, et al; on behalf of the American Heart Association Stroke Council; Council on Epidemiology and Prevention; Interdisciplinary Council on Peripheral Vascular Disease; Council on Cardiovascular Radiology and Intervention. Recommendations for the implementation of telemedicine within stroke systems of care: a policy statement from the American Heart Association. *Stroke*. 2009;40:2635–2660. doi: 10.1161/STROKEAHA.109.192361
6. Higashida R, Alberts MJ, Alexander DN, Crocco TJ, Demaerschalk BM, Derdeyn CP, Goldstein LB, Jauch EC, Mayer SA, Meltzer NM, et al; on behalf of the American Heart Association Advocacy Coordinating Committee. Interactions within stroke systems of care: a policy statement from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:2961–84. doi: 10.1161/STR.0b013e3182a6d2b2
7. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, et al. 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040
8. Wijdicks EF, Sheth KN, Carter BS, Greer DM, Kasner SE, Kimberly WT, Schwab S, Smith EE, Tamargo RJ, Wintermark M; on behalf of the American Heart Association Stroke Council. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1222–1238. doi: 10.1161/01.str.0000441965.15164.d6
9. Holloway RG, Arnold RM, Creutzfeldt CJ, Lewis EF, Lutz BJ, McCann RM, Rabinstein AA, Saposnik G, Sheth KN, Zahuranec DB, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, and Council on Clinical Cardiology. Palliative and end-of-life care in stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:1887–1916. doi: 10.1161/STR.0000000000000015
10. Kernan WN, Ovbiagele B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD, Fang MC, Fisher M, Furie KL, Heck DV, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024
11. Smith EE, Saver JL, Alexander DN, Furie KL, Hopkins LN, Katzan IL, Mackey JS, Miller EL, Schwamm LH, Williams LS; on behalf of the AHA/ASA Stroke Performance Oversight Committee. Clinical performance measures for adults hospitalized with acute ischemic stroke: performance measures for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:3472–3498. doi: 10.1161/STR.0000000000000045
12. Singletary EM, Charlton NP, Epstein JL, Ferguson JD, Jensen JL, MacPherson AI, Pellegrino JL, Smith WW, Swain JM, Lojero-Wheatley LF, et al. Part 15: first aid: 2015 American Heart Association and American Red Cross Guidelines Update for First Aid. *Circulation*. 2015;132(suppl 2):S574–S589. doi: 10.1161/CIR.0000000000000269
13. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, Johnston SC, Khalessi AA, Kidwell CS, et al; on behalf of the American Heart Association Stroke Council. 2015 American Heart Association/American Stroke Association focused update of the 2013 guidelines for the early management of patients with acute ischemic stroke regarding endovascular treatment: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2015;46:3020–3035. doi: 10.1161/STR.0000000000000074
14. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY, Prabhakaran S, et al; on behalf of the American Heart Association Stroke Council and Council on Epidemiology and Prevention. Scientific rationale for the inclusion and exclusion criteria for intravenous alteplase in acute ischemic stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2016;47:e262]. *Stroke*. 2016;47:581–641. doi: 10.1161/STR.0000000000000086
15. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, et al; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2017;48:e78 and *Stroke*. 2017;48:e369]. *Stroke*. 2016;47:e98–e169. doi: 10.1161/STR.0000000000000098
16. Towfighi A, Ovbiagele B, El Hussein N, Hackett ML, Jorge RE, Kissela BM, Mitchell PH, Skolarus LE, Whooley MA, Williams LS; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; and Council on Quality of Care and Outcomes Research. Poststroke depression: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e30–e43. doi: 10.1161/STR.0000000000000113
17. Yaghi S, Willey JZ, Cucchiara B, Goldstein JN, Gonzales NR, Khatri P, Kim LJ, Mayer SA, Sheth KN, Schwamm LH; on behalf of the American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; and Council on Quality of Care and Outcomes Research. Treatment and outcome of hemorrhagic transformation after intravenous alteplase in acute ischemic stroke: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2017;48:e343–e361. doi: 10.1161/STR.0000000000000152
18. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Hypertension*. 2018;71:e140–e144]. *Hypertension*. 2018;71:e13–e115. doi: 10.1161/HYP.0000000000000065

19. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, Braun LT, de Ferranti S, Faiella-Tommasino J, Forman DE, et al. 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APHA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines [published correction appears in *Circulation*. 2019;139:e1186]. *Circulation*. 2019;139:e1082–e1143. doi: 10.1161/CIR.0000000000000625
20. Ojike N, Ravenell J, Seixas A, Masters-Israilov A, Rogers A, Jean-Louis G, Ogedegbe G, McFarlane SI. Racial disparity in stroke awareness in the US: an analysis of the 2014 National Health Interview Survey. *J Neurol Neurophysiol*. 2016;7:365.
21. Ekundayo OJ, Saver JL, Fonarow GC, Schwamm LH, Xian Y, Zhao X, Hernandez AF, Peterson ED, Cheng EM. Patterns of emergency medical services use and its association with timely stroke treatment: findings from Get With The Guidelines–Stroke. *Circ Cardiovasc Qual Outcomes*. 2013;6:262–269. doi: 10.1161/CIRCOUTCOMES.113.000089
22. Mochari-Greenberger H, Xian Y, Hellkamp AS, Schulte PJ, Bhatt DL, Fonarow GC, Saver JL, Reeves MJ, Schwamm LH, Smith EE. Racial/ethnic and sex differences in emergency medical services transport among hospitalized US stroke patients: analysis of the national Get With The Guidelines–Stroke Registry. *J Am Heart Assoc*. 2015;4:e002099. doi: 10.1161/JAHA.115.002099
23. Berglund A, Svensson L, Wahlgren N, von Euler M; HASTA Collaborators. Face Arm Speech Time Test use in the prehospital setting, better in the ambulance than in the emergency medical communication center. *Cerebrovasc Dis*. 2014;37:212–216. doi: 10.1159/000358116
24. De Luca A, Giorgi Rossi P, Villa GF; Stroke Group Italian Society Pre Hospital Emergency Services. The use of Cincinnati Prehospital Stroke Scale during telephone dispatch interview increases the accuracy in identifying stroke and transient ischemic attack symptoms. *BMC Health Serv Res*. 2013;13:513. doi: 10.1186/1472-6963-13-513
25. Lin CB, Peterson ED, Smith EE, Saver JL, Liang L, Xian Y, Olson DM, Shah BR, Hernandez AF, Schwamm LH, et al. Emergency medical service hospital prenotification is associated with improved evaluation and treatment of acute ischemic stroke. *Circ Cardiovasc Qual Outcomes*. 2012;5:514–522. doi: 10.1161/CIRCOUTCOMES.112.965210
26. Rudd M, Buck D, Ford GA, Price CI. A systematic review of stroke recognition instruments in hospital and prehospital settings. *Emerg Med J*. 2016;33:818–822. doi: 10.1136/emermed-2015-205197
27. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med*. 1999;33:373–378. doi: 10.1016/s0196-0644(99)70299-4
28. Kidwell CS, Saver JL, Schubert GB, Eckstein M, Starkman S. Design and retrospective analysis of the Los Angeles Prehospital Stroke Screen (LAPSS). *Prehosp Emerg Care*. 1998;2:267–273.
29. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, Davis M, Ford GA. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. *Lancet Neurol*. 2005;4:727–734. doi: 10.1016/S1474-4422(05)70201-5
30. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. *Stroke*. 2003;34:71–76. doi: 10.1161/01.str.0000044170.46643.5e
31. Katz BS, McMullan JT, Sucharew H, Adeoye O, Broderick JP. Design and validation of a prehospital scale to predict stroke severity: Cincinnati Prehospital Stroke Severity Scale. *Stroke*. 2015;46:1508–1512. doi: 10.1161/STROKEAHA.115.008804
32. Lima FO, Silva GS, Furie KL, Frankel MR, Lev MH, Camargo EC, Haussen DC, Singhal AB, Koroshetz WJ, Smith WS, et al. Field assessment stroke triage for emergency destination: a simple and accurate prehospital scale to detect large vessel occlusion strokes. *Stroke*. 2016;47:1997–2002. doi: 10.1161/STROKEAHA.116.013301
33. Perez de la Ossa N, Carrera D, Gorchs M, Querol M, Millan M, Gomis M, Dorado L, Lopez-Cancio E, Hernandez-Perez M, Chicharro V, et al. Design and validation of a prehospital stroke scale to predict large arterial occlusion: the rapid arterial occlusion evaluation scale. *Stroke*. 2014;45:87–91.
34. Hastrup S, Damgaard D, Johnsen SP, Andersen G. Prehospital acute stroke severity scale to predict large artery occlusion: design and comparison with other scales. *Stroke*. 2016;47:1772–1776. doi: 10.1161/STROKEAHA.115.012482
35. Singer OC, Dvorak F, du Mesnil de Rochemont R, Lanfermann H, Sitzer M, Neumann-Haefelin T. A simple 3-item stroke scale: comparison with the National Institutes of Health Stroke Scale and prediction of middle cerebral artery occlusion. *Stroke*. 2005;36:773–776. doi: 10.1161/01.STR.0000157591.61322.df
36. Nazliel B, Starkman S, Liebeskind DS, Ovbiagele B, Kim D, Sanossian N, Ali L, Buck B, Villablanca P, Vinuela F, et al. A brief prehospital stroke severity scale identifies ischemic stroke patients harboring persisting large arterial occlusions. *Stroke*. 2008;39:2264–2267. doi: 10.1161/STROKEAHA.107.508127
37. Carrera D, Campbell BC, Cortés J, Gorchs M, Querol M, Jiménez X, Millán M, Dávalos A, Pérez de la Ossa N. Predictive value of modifications of the prehospital rapid arterial occlusion evaluation scale for large vessel occlusion in patients with acute stroke. *J Stroke Cerebrovasc Dis*. 2017;26:74–77. doi: 10.1016/j.jstrokecerebrovasdis.2016.08.032
38. Kim JT, Chung PW, Starkman S, Sanossian N, Stratton SJ, Eckstein M, Pratt FD, Conwit R, Liebeskind DS, Sharma L, et al; on behalf of the FAST-MAG Trial (Field Administration of Stroke Therapy–Magnesium) Nurse–Coordinators and Investigators. Field validation of the Los Angeles Motor Scale as a tool for paramedic assessment of stroke severity. *Stroke*. 2017;48:298–306. doi: 10.1161/STROKEAHA.116.015247
39. McMullan JT, Katz B, Broderick J, Schmit P, Sucharew H, Adeoye O. Prospective prehospital evaluation of the Cincinnati Stroke Triage Assessment Tool. *Prehosp Emerg Care*. 2017;21:481–488.
40. American Heart Association. Severity-based stroke triage algorithm for EMS. <https://www.heart.org/missionlifelinesstroke>. Accessed December 1, 2017.
41. Saver JL, Fonarow GC, Smith EE, Reeves MJ, Grau-Sepulveda MV, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA*. 2013;309:2480–2488.
42. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, et al; HERMES Collaborators. Time to treatment with endovascular thrombectomy and outcomes from ischemic stroke: a meta-analysis. *JAMA*. 2016;316:1279–1288. doi: 10.1001/jama.2016.13647
43. Ganesh A, Lindsay P, Fang J, Kapral MK, Côté R, Joiner I, Hakim AM, Hill MD. Integrated systems of stroke care and reduction in 30-day mortality: a retrospective analysis. *Neurology*. 2016;86:898–904. doi: 10.1212/WNL.0000000000002443
44. Man S, Cox M, Patel P, Smith EE, Reeves MJ, Saver JL, Bhatt DL, Xian Y, Schwamm LH, Fonarow GC. Differences in acute ischemic stroke quality of care and outcomes by primary stroke center certification organization. *Stroke*. 2017;48:412–419. doi: 10.1161/STROKEAHA.116.014426
45. Scott PA, Meurer WJ, Frederiksen SM, Kalbfleisch JD, Xu Z, Haan MN, Silbergleit R, Morgenstern LB; INSTINCT Investigators. A multi-level intervention to increase community hospital use of alteplase for acute stroke (INSTINCT): a cluster-randomised controlled trial. *Lancet Neurol*. 2013;12:139–148. doi: 10.1016/S1474-4422(12)70311-3
46. Dirks M, Niessen LW, van Wijngaarden JD, Koudstaal PJ, Franke CL, van Oostenbrugge RJ, Huijsman R, Lingsma HF, Minkman MM, Dippel DW; for the PROMoting ACute Thrombolysis in Ischemic Stroke (PRACTISE) Investigators. Promoting thrombolysis in acute ischemic stroke. *Stroke*. 2011;42:1325–1330. doi: 10.1161/STROKEAHA.110.596940
47. Haesebaert J, Nighoghossian N, Mercier C, Termoz A, Porthault S, Derex L, Gueugniard PY, Bravant E, Rabilloud M, Schott AM; on behalf of the AVC II Trial Group. Improving access to thrombolysis and in-hospital management times in ischemic stroke: a stepped-wedge randomized trial. *Stroke*. 2018;49:405–411. doi: 10.1161/STROKEAHA.117.018335
48. Tissue plasminogen activator for acute ischemic stroke: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333:1581–1587.
49. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, et al; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329. doi: 10.1056/NEJMoa0804656
50. Lees KR, Bluhmki E, von Kummer R, Brott TG, Toni D, Grotta JC, Albers GW, Kaste M, Marler JR, Hamilton SA, et al; ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. *Lancet*. 2010;375:1695–1703. doi: 10.1016/S0140-6736(10)60491-6
51. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, et al; DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *N Engl J Med*. 2018;378:11–21. doi: 10.1056/NEJMoa1706442

52. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart RA, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, et al; DEFUSE 3 Investigators. Thrombectomy for stroke at 6 to 16 hours with selection by perfusion imaging. *N Engl J Med*. 2018;378:708–718. doi: 10.1056/NEJMoa1713973
53. Fonarow GC, Zhao X, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Xian Y, Hernandez AF, Peterson ED, Schwamm LH. Door-to-needle times for tissue plasminogen activator administration and clinical outcomes in acute ischemic stroke before and after a quality improvement initiative. *JAMA*. 2014;311:1632–1640.
54. Xian Y, Xu H, Lytle B, Blevins J, Peterson ED, Hernandez AF, Smith EE, Saver JL, Messe SR, Paulsen M, et al. Use of strategies to improve door-to-needle times with tissue-type plasminogen activator in acute ischemic stroke in clinical practice: findings from Target: Stroke. *Circ Cardiovasc Qual Outcomes*. 2017;10:e003227.
55. Demaerschalk BM, Bobrow BJ, Raman R, Ernstrom K, Hoxworth JM, Patel AC, Kiernan TE, Aguilar MI, Ingall TJ, Dodick DW, et al; for the Stroke Team Remote Evaluation Using a Digital Observation Camera (STRoKE DOC) in Arizona—The Initial Mayo Clinic Experience (AZ TIME) Investigators. CT interpretation in a telestroke network: agreement among a spoke radiologist, hub vascular neurologist, and hub neuroradiologist. *Stroke*. 2012;43:3095–3097. doi: 10.1161/STROKEAHA.112.666255
56. Spokorny I, Raman R, Ernstrom K, Demaerschalk BM, Lyden PD, Hemmen TM, Guzik AK, Chen JY, Meyer BC. Pooled assessment of computed tomography interpretation by vascular neurologists in the STRoKE DOC telestroke network. *J Stroke Cerebrovasc Dis*. 2014;23:511–515. doi: 10.1016/j.jstrokecerebrovasdis.2013.04.023
57. Puetz V, Bodechtel U, Gerber JC, Dzialowski I, Kunz A, Wolz M, Hentschel H, Schultheiss T, Kepplinger J, Schneider H, et al. Reliability of brain CT evaluation by stroke neurologists in telemedicine. *Neurology*. 2013;80:332–338. doi: 10.1212/WNL.0b013e31827f07d0
58. Demaerschalk BM, Raman R, Ernstrom K, Meyer BC. Efficacy of telemedicine for stroke: pooled analysis of the Stroke Team Remote Evaluation Using a Digital Observation Camera (STRoKE DOC) and STRoKE DOC Arizona telestroke trials. *Telemed J E Health*. 2012;18:230–237. doi: 10.1089/tmj.2011.0116
59. Kepplinger J, Barlinn K, Deckert S, Scheibe M, Bodechtel U, Schmitt J. Safety and efficacy of thrombolysis in telestroke: a systematic review and meta-analysis. *Neurology*. 2016;87:1344–1351. doi: 10.1212/WNL.0000000000003148
60. Barlinn J, Gerber J, Barlinn K, Pallesen LP, Siepmann T, Zerna C, Wojciechowski C, Puetz V, von Kummer R, Reichmann H, et al. Acute endovascular treatment delivery to ischemic stroke patients transferred within a telestroke network: a retrospective observational study. *Int J Stroke*. 2017;12:502–509. doi: 10.1177/1747493016681018
61. Fong WC, Ismail M, Lo JW, Li JT, Wong AH, Ng YW, Chan PY, Chan AL, Chan GH, Fong KW, et al. Telephone and teleradiology-guided thrombolysis can achieve similar outcome as thrombolysis by neurologist on-site. *J Stroke Cerebrovasc Dis*. 2015;24:1223–1228. doi: 10.1016/j.jstrokecerebrovasdis.2015.01.022
62. Vagal A, Meganathan K, Kleindorfer DO, Adeoye O, Hornung R, Khatri P. Increasing use of computed tomographic perfusion and computed tomographic angiograms in acute ischemic stroke from 2006 to 2010. *Stroke*. 2014;45:1029–1034. doi: 10.1161/STROKEAHA.113.004332
63. Demaerschalk BM, Yip TR. Economic benefit of increasing utilization of intravenous tissue plasminogen activator for acute ischemic stroke in the United States. *Stroke*. 2005;36:2500–2503. doi: 10.1161/01.STR.0000185699.37843.14
64. Demaerschalk BM, Durocher DL. How diagnosis-related group 559 will change the US Medicare cost reimbursement ratio for stroke centers. *Stroke*. 2007;38:1309–1312. doi: 10.1161/01.STR.0000260185.74694.a7
65. Penaloza-Ramos MC, Sheppard J, Jowett S, Barton P, Mant J, Quinn T, Mellor RM, Sims D, Sandler D, et al; on behalf of the Birmingham and Black Country Collaborations for Leadership in Applied Health Research and Care Investigators. Cost-effectiveness of optimizing acute stroke care services for thrombolysis. *Stroke*. 2014;45:553–562. doi: 10.1161/STROKEAHA.113.003216
66. Tan Tanny SP, Busija L, Liew D, Teo S, Davis SM, Yan B. Cost-effectiveness of thrombolysis within 4.5 hours of acute ischemic stroke: experience from Australian stroke center. *Stroke*. 2013;44:2269–2274. doi: 10.1161/STROKEAHA.113.001295
67. Health Quality Ontario. Mechanical thrombectomy in patients with acute ischemic stroke: a health technology assessment. *Ont Health Technol Assess Ser*. 2016;16:1–79.
68. Ganesalingam J, Pizzo E, Morris S, Sunderland T, Ames D, Lobotesis K. Cost-utility analysis of mechanical thrombectomy using stent retrievers in acute ischemic stroke. *Stroke*. 2015;46:2591–2598. doi: 10.1161/STROKEAHA.115.009396
- 68a. Tong X, Wiltz JL, George MG, Odom EC, Coleman King SM, Chang T, Xiaoping Y, Paul Coverdell National Acute Stroke Program Team, Meritt RK. A decade of improvement in door-to-needle time among acute ischemic stroke patients, 2008 to 2017. *Circ Cardiovasc Qual Outcomes*. 2018;11:e004981. doi: 10.1161/CIRCOUTCOMES.118.004981
- 68b. Wiedmann S, Heuschmann PU, Hillmann S, Busse O, Wietholter H, Walter GM, Seidel G, Misselwitz B, Janssen A, Berger K, et al; German Stroke Registers Study Group. The quality of acute stroke care: an analysis of evidence-based indicators in 260 000 patients. *Dtsch Arztebl Int*. 2014;111:759–765. doi: 10.3238/arztebl.2014.0759
- 68c. Centers for Disease Control and Prevention. Use of a registry to improve acute stroke care: seven states, 2005–2009. *MMWR Morb Mortal Wkly Rep*. 2011;60:206–210.
69. Song S, Fonarow GC, Olson DM, Liang L, Schulte PJ, Hernandez AF, Peterson ED, Reeves MJ, Smith EE, Schwamm LH, et al. Association of Get With The Guidelines—Stroke program participation and clinical outcomes for Medicare beneficiaries with ischemic stroke. *Stroke*. 2016;47:1294–1302.
- 69a. Hills NK, Johnston SC. Duration of hospital participation in a nationwide stroke registry is associated with improved quality of care. *BMC Neurol*. 2006;6:20.
70. NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1997;28:2119–2125.
71. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, Woolson RF, Hansen MD. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53:126–131. doi: 10.1212/wnl.53.1.126
72. Frankel MR, Morgenstern LB, Kwiatkowski T, Lu M, Tilley BC, Broderick JP, Libman R, Levine SR, Brott T. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurology*. 2000;55:952–959. doi: 10.1212/wnl.55.7.952
73. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erlil T, Ford GA, Grond M, Hacke W, et al; for the Safe Implementation of Thrombolysis in Stroke-MONitoring STudy Investigators. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MONitoring Study (SITS-MOST). *Stroke*. 2008;39:3316–3322. doi: 10.1161/STROKEAHA.107.510768
74. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training: NINDS TPA Stroke Study Group. *Stroke*. 1994;25:2220–2226. doi: 10.1161/01.str.25.11.2220
75. Josephson SA, Hills NK, Johnston SC. NIH Stroke Scale reliability in ratings from a large sample of clinicians. *Cerebrovasc Dis*. 2006;22:389–395. doi: 10.1159/000094857
76. Lyden P, Raman R, Liu L, Emr M, Warren M, Marler J. National Institutes of Health Stroke Scale certification is reliable across multiple venues. *Stroke*. 2009;40:2507–2511. doi: 10.1161/STROKEAHA.108.532069
77. Fonarow GC, Saver JL, Smith EE, Broderick JP, Kleindorfer DO, Sacco RL, Pan W, Olson DM, Hernandez AF, Peterson ED, et al. Relationship of National Institutes of Health Stroke Scale to 30-day mortality in Medicare beneficiaries with acute ischemic stroke. *J Am Heart Assoc*. 2012;1:42–50.
78. Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA, Grotta JC, Kaste M, von Kummer R, Lansberg MG, et al; on behalf of the Stroke Thrombolysis Trialists' Collaborators Group. Effects of alteplase for acute stroke on the distribution of functional outcomes: a pooled analysis of 9 trials. *Stroke*. 2016;47:2373–2379. doi: 10.1161/STROKEAHA.116.013644
79. Aghaebrahim A, Streib C, Rangaraju S, Kenmuir CL, Giurgiu DV, Horev A, Saeed Y, Callaway CW, Guyette FX, Martin-Gill C, et al. Streamlining door to recanalization processes in endovascular stroke therapy. *J Neurointerv Surg*. 2017;9:340–345. doi: 10.1136/neurintsurg-2016-012324
80. Messe SR, Khatri P, Reeves MJ, Smith EE, Saver JL, Bhatt DL, Grau-Sepulveda MV, Cox M, Peterson ED, Fonarow GC, et al. Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry. *Neurology*. 2016;87:1565–1574.
81. Zaidi SF, Shawver J, Espinosa Morales A, Salahuddin H, Tietjen G, Lindstrom D, Parquette B, Adams A, Korsnack A, Jumaa MA. Stroke

- care: initial data from a county-based bypass protocol for patients with acute stroke. *J Neurointerv Surg*. 2017;9:631–635. doi: 10.1136/neurintsurg-2016-012476
82. Chalela JA, Kidwell CS, Nentwich LM, Luby M, Butman JA, Demchuk AM, Hill MD, Patronas N, Latour L, Warach S. Magnetic resonance imaging and computed tomography in emergency assessment of patients with suspected acute stroke: a prospective comparison. *Lancet*. 2007;369:293–298. doi: 10.1016/S0140-6736(07)60151-2
 83. Barber PA, Hill MD, Eliasziw M, Demchuk AM, Pexman JH, Hudon ME, Tomanek A, Frayne R, Buchan AM; ASPECTS Study Group. Imaging of the brain in acute ischaemic stroke: comparison of computed tomography and magnetic resonance diffusion-weighted imaging. *J Neurol Neurosurg Psychiatry*. 2005;76:1528–1533. doi: 10.1136/jnnp.2004.059261
 84. Anderson JL, Heidenreich PA, Barnett PG, Creager MA, Fonarow GC, Gibbons RJ, Halperin JL, Hlatky MA, Jacobs AK, Mark DB, et al. ACC/AHA statement on cost/value methodology in clinical practice guidelines and performance measures: a report of the American College of Cardiology/American Heart Association Task Force on Performance Measures and Task Force on Practice Guidelines. *Circulation*. 2014;129:2329–2345. doi: 10.1161/CIR.0000000000000042
 85. Wardlaw JM, Seymour J, Cairns J, Keir S, Lewis S, Sandercock P. Immediate computed tomography scanning of acute stroke is cost-effective and improves quality of life. *Stroke*. 2004;35:2477–2483. doi: 10.1161/01.STR.0000143453.78005.44
 86. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM, Butman JA, Patronas N, Alger JR, Latour LL, et al. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA*. 2004;292:1823–1830. doi: 10.1001/jama.292.15.1823
 87. Fiebach JB, Schellinger PG, Gass A, Kucinski T, Siebler M, Villringer A, Olkers P, Hirsch JD, Heiland S, Wilde P, et al; for the Kompetenznetzwerk Schlaganfall B5. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. *Stroke*. 2004;35:502–506. doi: 10.1161/01.STR.0000114203.75678.88
 88. Thomalla G, Simonsen CZ, Boutitie F, Andersen G, Berthezene Y, Cheng B, Cheripelli B, Cho TH, Fazekas F, Fiehler J, et al; WAKE-UP Investigators. MRI-guided thrombolysis for stroke with unknown time of onset. *N Engl J Med*. 2018;379:611–622. doi: 10.1056/NEJMoa1804355
 89. Charidimou A, Shoamaneh A; International META-MICROBLEEDS Initiative. Clinical relevance of microbleeds in acute stroke thrombolysis: comprehensive meta-analysis. *Neurology*. 2016;87:1534–1541. doi: 10.1212/WNL.0000000000003207
 90. Tsvigoulis G, Zand R, Katsanos AH, Turo G, Nolte CH, Jung S, Cordonnier C, Fiebach JB, Scheitz JF, Klinger-Gratz PP, et al. Risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden: a meta-analysis. *JAMA Neurol*. 2016;73:675–683. doi: 10.1001/jamaneurol.2016.0292
 91. Zand R, Tsvigoulis G, Singh M, McCormack M, Goyal N, Ishfaq MF, Shahripour RB, Nearing K, Elijevich L, Alexandrov AW, et al. Cerebral microbleeds and risk of intracerebral hemorrhage post intravenous thrombolysis. *J Stroke Cerebrovasc Dis*. 2017;26:538–544. doi: 10.1016/j.jstrokecerebrovasdis.2016.11.127
 92. Wang S, Lv Y, Zheng X, Qiu J, Chen HS. The impact of cerebral microbleeds on intracerebral hemorrhage and poor functional outcome of acute ischemic stroke patients treated with intravenous thrombolysis: a systematic review and meta-analysis. *J Neurol*. 2017;264:1309–1319. doi: 10.1007/s00415-016-8339-1
 93. Charidimou A, Turo G, Oppenheim C, Yan S, Scheitz JF, Erdur H, Klinger-Gratz PP, El-Koussy M, Takahashi W, Moriya Y, et al. Microbleeds, cerebral hemorrhage, and functional outcome after stroke thrombolysis: individual patient data meta-analysis. *Stroke*. 2017;48:2084–2090.
 94. Chacon-Portillo MA, Llinas RH, Marsh EB. Cerebral microbleeds shouldn't dictate treatment of acute stroke: a retrospective cohort study evaluating risk of intracerebral hemorrhage. *BMC Neurol*. 2018;18:33. doi: 10.1186/s12883-018-1029-0
 95. Hirai T, Korogi Y, Ono K, Nagano M, Maruoka K, Uemura S, Takahashi M. Prospective evaluation of suspected stenocclusive disease of the intracranial artery: combined MR angiography and CT angiography compared with digital subtraction angiography. *AJNR Am J Neuroradiol*. 2002;23:93–101.
 96. Bash S, Villablanca JP, Jahan R, Duckwiler G, Tillis M, Kidwell C, Saver J, Sayre J. Intracranial vascular stenosis and occlusive disease: evaluation with CT angiography, MR angiography, and digital subtraction angiography. *AJNR Am J Neuroradiol*. 2005;26:1012–1021.
 97. Ehrlich ME, Turner HL, Currie LJ, Wintermark M, Worrall BB, Southerland AM. Safety of computed tomographic angiography in the evaluation of patients with acute stroke: a single-center experience. *Stroke*. 2016;47:2045–2050. doi: 10.1161/STROKEAHA.116.013973
 98. Aulicky P, Mikulik R, Goldmund D, Reif M, Dufek M, Kubelka T. Safety of performing CT angiography in stroke patients treated with intravenous thrombolysis. *J Neurol Neurosurg Psychiatry*. 2010;81:783–787. doi: 10.1136/jnnp.2009.184002
 99. Lima FO, Lev MH, Levy RA, Silva GS, Ebril M, de Camargo EC, Pomerantz S, Singhal AB, Greer DM, Ay H, et al. Functional contrast-enhanced CT for evaluation of acute ischemic stroke does not increase the risk of contrast-induced nephropathy. *AJNR Am J Neuroradiol*. 2010;31:817–821. doi: 10.3174/ajnr.A1927
 100. Hopyan JJ, Gladstone DJ, Mallia G, Schiff J, Fox AJ, Symons SP, Buck BH, Black SE, Aviv RI. Renal safety of CT angiography and perfusion imaging in the emergency evaluation of acute stroke. *AJNR Am J Neuroradiol*. 2008;29:1826–1830. doi: 10.3174/ajnr.A1257
 101. Krol AL, Dzialowski I, Roy J, Puetz V, Subramaniam S, Coutts SB, Demchuk AM. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography. *Stroke*. 2007;38:2364–2366. doi: 10.1161/STROKEAHA.107.482778
 102. Josephson SA, Dillon WP, Smith WS. Incidence of contrast nephropathy from cerebral CT angiography and CT perfusion imaging. *Neurology*. 2005;64:1805–1806. doi: 10.1212/01.WNL.0000161845.69114.62
 103. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, Lingsma HF, Sprengers ME, Jenniskens SF, Lycklama À Nijeholt GJ, et al; on behalf of the MR CLEAN Investigators. Collateral status on baseline computed tomographic angiography and intra-arterial treatment effect in patients with proximal anterior circulation stroke. *Stroke*. 2016;47:768–776. doi: 10.1161/STROKEAHA.115.011788
 104. Menon BK, Qazi E, Nambiar V, Foster LD, Yeatts SD, Liebeskind D, Jovin TG, Goyal M, Hill MD, Tomsick TA, et al; for the Interventional Management of Stroke III Investigators. Differential effect of baseline computed tomographic angiography collaterals on clinical outcome in patients enrolled in the Interventional Management of Stroke III Trial. *Stroke*. 2015;46:1239–1244. doi: 10.1161/STROKEAHA.115.009009
 105. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, et al; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905
 106. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, et al; REVASCAT Trial Investigators. Thrombectomy within 8 hours after symptom onset in ischemic stroke. *N Engl J Med*. 2015;372:2296–2306. doi: 10.1056/NEJMoa1503780
 107. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, et al; SWIFT PRIME Investigators. Stent-retriever thrombectomy after intravenous t-PA vs. t-PA alone in stroke. *N Engl J Med*. 2015;372:2285–2295. doi: 10.1056/NEJMoa1415061
 108. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, et al; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792
 109. Bracard S, Ducrocq X, Mas JL, Soudant M, Oppenheim C, Moulin T, Guillemin F; THRACE Investigators. Mechanical thrombectomy after intravenous alteplase versus alteplase alone after stroke (THRACE): a randomised controlled trial. *Lancet Neurol*. 2016;15:1138–1147. doi: 10.1016/S1474-4422(16)30177-6
 110. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, et al; MR CLEAN Investigators. A randomized trial of intraarterial treatment for acute ischemic stroke. *N Engl J Med*. 2015;372:11–20. doi: 10.1056/NEJMoa1411587
 111. Saber H, Silver B, Santillan A, Azarpazhooh MR, Misra V, Behrouz R. Role of emergent chest radiography in evaluation of hyperacute stroke. *Neurology*. 2016;87:782–785. doi: 10.1212/WNL.0000000000002964
 112. Roffe C, Neveloff T, Sim J, Bishop J, Ives N, Ferdinand P, Gray R; Stroke Oxygen Study Investigators and the Stroke Oxygen Study Collaborative Group. Effect of routine low-dose oxygen supplementation on death and disability in adults with acute stroke: the Stroke Oxygen Study randomized clinical trial. *JAMA*. 2017;318:1125–1135. doi: 10.1001/jama.2017.11463

113. Bennett MH, Weibel S, Wasiaik J, Schnabel A, French C, Kranke P. Hyperbaric oxygen therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014;CD004954. doi: 10.1002/14651858.CD004954.pub3
114. Heyboer M 3rd, Sharma D, Santiago W, McCulloch N. Hyperbaric oxygen therapy: side effects defined and quantified. *Adv Wound Care (New Rochelle)*. 2017;6:210–224. doi: 10.1089/wound.2016.0718
115. Heyboer M 3rd, Jennings S, Grant WD, Ojevve C, Byrne J, Wojcik SM. Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy. *Undersea Hyperb Med*. 2014;41:379–385.
116. Wohlfahrt P, Krajcoviechova A, Jozifova M, Mayer O, Vanek J, Filipovsky J, Cifkova R. Low blood pressure during the acute period of ischemic stroke is associated with decreased survival. *J Hypertens*. 2015;33:339–345. doi: 10.1097/HJH.0000000000000414
117. Vemmos KN, Tsvigoulis G, Spengos K, Zakopoulos N, Syntetos A, Manios E, Konstantopoulou P, Mavrikakis M. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med*. 2004;255:257–265. doi: 10.1046/j.1365-2796.2003.01291.x
118. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens*. 2005;23:1217–1223. doi: 10.1097/01.hjh.0000170385.76826.4a
119. Stead LG, Gilmore RM, Decker WW, Weaver AL, Brown RD Jr. Initial emergency department blood pressure as predictor of survival after acute ischemic stroke. *Neurology*. 2005;65:1179–1183. doi: 10.1212/01.wnl.0000180939.24845.22
120. Castillo J, Leira R, García MM, Serena J, Blanco M, Dávalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke*. 2004;35:520–526. doi: 10.1161/01.STR.0000109769.22917.B0
121. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; for the IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315–1320. doi: 10.1161/01.str.0000014509.11540.66
122. Manning LS, Mistri AK, Potter J, Rothwell PM, Robinson TG. Short-term blood pressure variability in acute stroke: post hoc analysis of the Controlling Hypertension and Hypotension Immediately Post Stroke and Continue or Stop Post-Stroke Antihypertensives Collaborative Study trials. *Stroke*. 2015;46:1518–1524. doi: 10.1161/STROKEAHA.115.009078
123. Muscari A, Puddu GM, Serafini C, Fabbri E, Vizioli L, Zoli M. Predictors of short-term improvement of ischemic stroke. *Neurol Res*. 2013;35:594–601. doi: 10.1179/1743132813Y.0000000181
124. Visvanathan A, Dennis M, Whiteley W. Parenteral fluid regimens for improving functional outcome in people with acute stroke. *Cochrane Database Syst Rev*. 2015;CD011138. doi: 10.1002/14651858.CD011138.pub2
125. Butcher K, Christensen S, Parsons M, De Silva DA, Ebinger M, Levi C, Jeerakathil T, Campbell BC, Barber PA, Bladin C, et al; for the EPITHET Investigators. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. *Stroke*. 2010;41:72–77. doi: 10.1161/STROKEAHA.109.563767
126. Perini F, De Boni A, Marcon M, Bolgan I, Pellizzari M, Dionisio LD. Systolic blood pressure contributes to intracerebral haemorrhage after thrombolysis for ischemic stroke. *J Neurol Sci*. 2010;297:52–54. doi: 10.1016/j.jns.2010.06.025
127. Toni D, Ahmed N, Anzini A, Lorenzano S, Brozman M, Kaste M, Mikulik R, Putaala J, Wahlgren N; SITS Investigators. Intravenous thrombolysis in young stroke patients: results from the SITS-ISTR. *Neurology*. 2012;78:880–887. doi: 10.1212/WNL.0b013e31824d966b
128. Mazya M, Egado JA, Ford GA, Lees KR, Mikulik R, Toni D, Wahlgren N, Ahmed N; for the SITS Investigators. Predicting the risk of symptomatic intracerebral hemorrhage in ischemic stroke treated with intravenous alteplase: Safe Implementation of Treatments in Stroke (SITS) symptomatic intracerebral hemorrhage risk score. *Stroke*. 2012;43:1524–1531. doi: 10.1161/STROKEAHA.111.644815
129. Wu W, Huo X, Zhao X, Liao X, Wang C, Pan Y, Wang Y, Wang Y; TIMS-CHINA Investigators. Relationship between blood pressure and outcomes in acute ischemic stroke patients administered lytic medication in the TIMS-China Study. *PLoS One*. 2016;11:e0144260. doi: 10.1371/journal.pone.0144260
130. Endo K, Kario K, Koga M, Nakagawara J, Shiohara Y, Yamagami H, Furui E, Kimura K, Hasegawa Y, Okada Y, et al. Impact of early blood pressure variability on stroke outcomes after thrombolysis: the SAMURAI rt-PA Registry. *Stroke*. 2013;44:816–818. doi: 10.1161/STROKEAHA.112.681007
131. Waltimo T, Haapaniemi E, Surakka IL, Melkas S, Sairanen T, Sibolt G, Tatlisumak T, Strbian D. Post-thrombolytic blood pressure and symptomatic intracerebral hemorrhage. *Eur J Neurol*. 2016;23:1757–1762. doi: 10.1111/ene.13118
132. Liu K, Yan S, Zhang S, Guo Y, Lou M. Systolic blood pressure variability is associated with severe hemorrhagic transformation in the early stage after thrombolysis. *Transl Stroke Res*. 2016;7:186–191. doi: 10.1007/s12975-016-0458-6
133. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, Bellomo R, Finfer S, Beasley R, Hyam J, Menon D, et al. Early temperature and mortality in critically ill patients with acute neurological diseases: trauma and stroke differ from infection. *Intensive Care Med*. 2015;41:823–832. doi: 10.1007/s00134-015-3676-6
134. Lyden P, Hemmen T, Grotta J, Rapp K, Ernstrom K, Rzesiewicz T, Parker S, Concha M, Hussain S, Agarwal S, et al. Results of the ICTuS 2 Trial (Intravascular Cooling in the Treatment of Stroke 2). *Stroke*. 2016;47:2888–2895. doi: 10.1161/STROKEAHA.116.014200
135. Geurts M, Petersson J, Brizzi M, Olsson-Hau S, Luijckx GJ, Algra A, Dippel DW, Kappelle LJ, van der Worp HB. COOLIST (Cooling for Ischemic Stroke Trial): a multicenter, open, randomized, phase II, clinical trial. *Stroke*. 2017;48:219–221. doi: 10.1161/STROKEAHA.116.014757
136. Piironen K, Tainen M, Mustanoja S, Kaukonen KM, Meretoja A, Tatlisumak T, Kaste M. Mild hypothermia after intravenous thrombolysis in patients with acute stroke: a randomized controlled trial. *Stroke*. 2014;45:486–491. doi: 10.1161/STROKEAHA.113.003180
137. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruz-Flores S, Wijman CA, Rapp KS, Grotta JC, Lyden PD; for the ICTuS-L Investigators. Intravenous Thrombolysis Plus Hypothermia for Acute Treatment of Ischemic Stroke (ICTuS-L): final results. *Stroke*. 2010;41:2265–2270. doi: 10.1161/STROKEAHA.110.592295
138. Sloan MA, Price TR, Petito CK, Randall AM, Solomon RE, Terrin ML, Gore J, Collen D, Kleiman N, Feit F. Clinical features and pathogenesis of intracerebral hemorrhage after rt-PA and heparin therapy for acute myocardial infarction: the Thrombolysis in Myocardial Infarction (TIMI) II Pilot and Randomized Clinical Trial combined experience. *Neurology*. 1995;45:649–658. doi: 10.1212/WNL.45.4.649
139. Mahaffey KW, Granger CB, Sloan MA, Green CL, Gore JM, Weaver WD, White HD, Simoons ML, Barbash GI, Topol EJ, et al. Neurosurgical evacuation of intracranial hemorrhage after thrombolytic therapy for acute myocardial infarction: experience from the GUSTO-I trial: Global Utilization of Streptokinase and Tissue-Plasminogen Activator (tPA) for Occluded Coronary Arteries. *Am Heart J*. 1999;138(pt 1):493–499. doi: 10.1016/s0002-8703(99)70152-3
140. Goldstein JN, Marrero M, Masrur S, Pervez M, Barrocas AM, Abdullah A, Oleinik A, Rosand J, Smith EE, Dzik WH, et al. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol*. 2010;67:965–969. doi: 10.1001/archneurol.2010.175
141. French KF, White J, Hoesch RE. Treatment of intracerebral hemorrhage with tranexamic acid after thrombolysis with tissue plasminogen activator. *Neurocrit Care*. 2012;17:107–111. doi: 10.1007/s12028-012-9681-5
142. Yaghi S, Eisenberger A, Willey JZ. Symptomatic intracerebral hemorrhage in acute ischemic stroke after thrombolysis with intravenous recombinant tissue plasminogen activator: a review of natural history and treatment. *JAMA Neurol*. 2014;71:1181–1185. doi: 10.1001/jamaneurol.2014.1210
143. Yaghi S, Haggiagi A, Sherzai A, Marshall RS, Agarwal S. Use of recombinant factor VIIa in symptomatic intracerebral hemorrhage following intravenous thrombolysis. *Clin Pract*. 2015;5:756. doi: 10.4081/cp.2015.756
144. Yaghi S, Boehme AK, Dibu J, Leon Guerrero CR, Ali S, Martin-Schild S, Sands KA, Noorian AR, Blum CA, Chaudhary S, et al. Treatment and outcome of thrombolysis-related hemorrhage: a multicenter retrospective study. *JAMA Neurol*. 2015;72:1451–1457. doi: 10.1001/jamaneurol.2015.2371
145. Stone JA, Willey JZ, Keyrouz S, Butera J, McTaggart RA, Cutting S, Silver B, Thompson B, Furie KL, Yaghi S. Therapies for hemorrhagic transformation in acute ischemic stroke. *Curr Treat Options Neurol*. 2017;19:1. doi: 10.1007/s11940-017-0438-5
146. Frontera JA, Lewin JJ 3rd, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, et al. Guideline for reversal of antithrombotics in intracranial hemorrhage: a statement for healthcare professionals from the Neurocritical Care Society and Society of Critical Care Medicine. *Neurocrit Care*. 2016;24:6–46. doi: 10.1007/s12028-015-0222-x
147. Foster-Goldman A, McCarthy D. Angioedema from recombinant TPA administration: case report and pathophysiology review. *Am J Ther*. 2013;20:691–693. doi: 10.1097/MJT.0b013e3182799083

148. Gorski EM, Schmidt MJ. Orolingual angioedema with alteplase administration for treatment of acute ischemic stroke. *J Emerg Med.* 2013;45:e25–e26. doi: 10.1016/j.jemermed.2013.02.004
149. Lewis LM. Angioedema: etiology, pathophysiology, current and emerging therapies. *J Emerg Med.* 2013;45:789–796. doi: 10.1016/j.jemermed.2013.03.045
150. Lin SY, Tang SC, Tsai LK, Yeh SJ, Hsiao YJ, Chen YW, Chen KH, Yip BS, Shen LJ, Wu FL, et al. Orolingual angioedema after alteplase therapy of acute ischaemic stroke: incidence and risk of prior angiotensin-converting enzyme inhibitor use. *Eur J Neurol.* 2014;21:1285–1291. doi: 10.1111/ene.12472
151. Correia AS, Matias G, Calado S, Lourenço A, Viana-Baptista M. Orolingual angioedema associated with alteplase treatment of acute stroke: a reappraisal. *J Stroke Cerebrovasc Dis.* 2015;24:31–40. doi: 10.1016/j.jstrokecerebrovasdis.2014.07.045
152. O'Carroll CB, Aguilar MI. Management of postthrombolysis hemorrhagic and orolingual angioedema complications. *Neurohospitalist.* 2015;5:133–141. doi: 10.1177/1941874415587680
153. Myslimi F, Caparros F, Dequatre-Ponchelle N, Moulin S, Gautier S, Girardie P, Cordonnier C, Bordet R, Leys D. Orolingual angioedema during or after thrombolysis for cerebral ischemia. *Stroke.* 2016;47:1825–1830. doi: 10.1161/STROKEAHA.116.013334
154. Pahs L, Droege C, Kneale H, Pancioli A. A novel approach to the treatment of orolingual angioedema after tissue plasminogen activator administration. *Ann Emerg Med.* 2016;68:345–348. doi: 10.1016/j.annemergmed.2016.02.019
155. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2014:CD000213. doi: 10.1002/14651858.CD000213.pub3
156. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, et al; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet.* 2004;363:768–774. doi: 10.1016/S0140-6736(04)15692-4
157. Wardlaw JM, Murray V, Berge E, del Zoppo G, Sandercock P, Lindley RL, Cohen G. Recombinant tissue plasminogen activator for acute ischaemic stroke: an updated systematic review and meta-analysis. *Lancet.* 2012;379:2364–2372. doi: 10.1016/S0140-6736(12)60738-7
158. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, et al; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet.* 2007;369:275–282. doi: 10.1016/S0140-6736(07)60149-4
159. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, et al; IST-3 Collaborative Group. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the Third International Stroke Trial [IST-3]): a randomised controlled trial. *Lancet.* 2012;379:2352–2363. doi: 10.1016/S0140-6736(12)60768-5
160. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, Broderick JP, Chen X, Chen G, Sharma VK, et al; ENCHANTED Investigators and Coordinators. Low-dose versus standard-dose intravenous alteplase in acute ischemic stroke. *N Engl J Med.* 2016;374:2313–2323. doi: 10.1056/NEJMoa1515510
161. Khatri P, Tayama D, Cohen G, Lindley RI, Wardlaw JM, Yeatts SD, Broderick JP, Sandercock P; PRISMS and IST-3 Collaborative Groups. Effect of intravenous recombinant tissue-type plasminogen activator in patients with mild stroke in the Third International Stroke Trial-3: post hoc analysis. *Stroke.* 2015;46:2325–2327. doi: 10.1161/STROKEAHA.115.009951
162. National Institute of Neurological Disorders Stroke rtPA Stroke Study Group. Recombinant tissue plasminogen activator for minor strokes: the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study experience. *Ann Emerg Med.* 2005;46:243–252. doi: 10.1016/j.annemergmed.2005.02.013
163. Ingall TJ, O'Fallon WM, Asplund K, Goldfrank LR, Hertzberg VS, Louis TA, Christianson TJ. Findings from the reanalysis of the NINDS tissue plasminogen activator for acute ischemic stroke treatment trial. *Stroke.* 2004;35:2418–2424. doi: 10.1161/01.STR.0000140891.70547.56
164. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, Brott T, Cohen G, Davis S, Donnan G, et al; Stroke Thrombolysis Trialists' Collaborative Group. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet.* 2014;384:1929–1935. doi: 10.1016/S0140-6736(14)60584-5
165. Bluhmki E, Chamorro A, Dávalos A, Machnig T, Sauce C, Wahlgren N, Wardlaw J, Hacke W. Stroke treatment with alteplase given 3.0–4.5 h after onset of acute ischaemic stroke (ECASS III): additional outcomes and subgroup analysis of a randomised controlled trial. *Lancet Neurol.* 2009;8:1095–1102. doi: 10.1016/S1474-4422(09)70264-9
166. Ahmed N, Wahlgren N, Grond M, Hennerici M, Lees KR, Mikulik R, Parsons M, Roine RO, Toni D, Ringleb P; SITS Investigators. Implementation and outcome of thrombolysis with alteplase 3–4.5 h after an acute stroke: an updated analysis from SITS-ISTR. *Lancet Neurol.* 2010;9:866–874. doi: 10.1016/S1474-4422(10)70165-4
167. Romano JG, Smith EE, Liang L, Gardener H, Camp S, Shuey L, Cook A, Campo-Bustillo I, Khatri P, Bhatt DL, et al. Outcomes in mild acute ischemic stroke treated with intravenous thrombolysis: a retrospective analysis of the Get With The Guidelines-Stroke registry. *JAMA Neurol.* 2015;72:423–431. doi: 10.1001/jamaneurol.2014.4354
168. Khatri P, Kleindorfer DO, Devlin T, Sawyer RN Jr, Starr M, Mejilla J, Broderick J, Chatterjee A, Jauch EC, Levine SR, et al; PRISMS Investigators. Effect of alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor nondisabling neurologic deficits: the PRISMS randomized clinical trial. *JAMA.* 2018;320:156–166. doi: 10.1001/jama.2018.8496
169. Adams RJ, Cox M, Ozark SD, Kanter J, Schulte PJ, Xian Y, Fonarow GC, Smith EE, Schwamm LH. Coexistent sickle cell disease has no impact on the safety or outcome of lytic therapy in acute ischemic stroke: findings from Get With The Guidelines-Stroke. *Stroke.* 2017;48:686–691. doi: 10.1161/STROKEAHA.116.015412
170. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Janjua N, Divani AA. Is IV tissue plasminogen activator beneficial in patients with hyperdense artery sign? *Neurology.* 2006;66:1171–1174. doi: 10.1212/01.wnl.0000208407.69544.5a
171. IST Collaborative Group. Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): secondary analysis of a randomised controlled trial. *Lancet Neurol.* 2015;14:485–496. doi: 10.1016/S1474-4422(15)00012-5
172. Mair G, von Kummer R, Morris Z, von Heijne A, Bradey N, Cala L, Peeters A, Farrall AJ, Adami A, Potter G, et al; IST-3 Collaborative Group. Effect of alteplase on the CT hyperdense artery sign and outcome after ischaemic stroke. *Neurology.* 2016;86:118–125. doi: 10.1212/WNL.0000000000002236
173. Adeoye O, Sucharew H, Khoury J, Tomsick T, Khatri P, Palesch Y, Schmit PA, Pancioli AM, Broderick JP; for the CLEAR-ER, IMS III, and ALIAS Part 2 Investigators. Recombinant tissue-type plasminogen activator plus eptifibatid versus recombinant tissue-type plasminogen activator alone in acute ischemic stroke: propensity score-matched post hoc analysis. *Stroke.* 2015;46:461–464. doi: 10.1161/STROKEAHA.114.006743
174. Adeoye O, Sucharew H, Khoury J, Vagal A, Schmit PA, Ewing I, Levine SR, Demel S, Eckerle B, Katz B, et al. Combined approach to lysis utilizing eptifibatid and recombinant tissue-type plasminogen activator in acute ischemic stroke: Full Dose Regimen Stroke Trial. *Stroke.* 2015;46:2529–2533. doi: 10.1161/STROKEAHA.115.010260
175. Zinkstok SM, Roos YB; ARTIS Investigators. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet.* 2012;380:731–737. doi: 10.1016/S0140-6736(12)60949-0
176. Anderson CS, Huang Y, Lindley RI, Chen X, Arima H, Chen G, Li Q, Billot L, Delcourt C, Bath PM, et al; ENCHANTED Investigators and Coordinators. Intensive blood pressure reduction with intravenous thrombolysis therapy for acute ischaemic stroke (ENCHANTED): an international, randomised, open-label, blinded-endpoint, phase 3 trial. *Lancet.* 2019;393:877–888. doi: 10.1016/S0140-6736(19)30038-8
177. Jeong HG, Kim BJ, Yang MH, Han MK, Bae HJ, Lee SH. Stroke outcomes with use of antithrombotics within 24 hours after recanalization treatment. *Neurology.* 2016;87:996–1002. doi: 10.1212/WNL.0000000000003083
178. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, Yan B, Bush SJ, Dewey HM, Thijs V, et al; EXTEND-IA TNK Investigators. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med.* 2018;378:1573–1582. doi: 10.1056/NEJMoa1716405
179. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, Ford I, Muir KW. Alteplase versus tenecteplase

- for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol.* 2015;14:368–376. doi: 10.1016/S1474-4422(15)70017-7
180. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, O'Brien B, Bladin C, McElduff P, Allen C, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med.* 2012;366:1099–1107. doi: 10.1056/NEJMoa1109842
 181. Haley EC Jr, Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, Fanale C, Libman R, Kwiatkowski TG, Llinas RH, et al; for the Tenecteplase in Stroke Investigators. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke.* 2010;41:707–711. doi: 10.1161/STROKEAHA.109.572040
 182. Logallo N, Novotny V, Assmus J, Kvistad CE, Altheheld L, Rønning OM, Thommessen B, Amthor KF, Ihle-Hansen H, Kurz M, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol.* 2017;16:781–788. doi: 10.1016/S1474-4422(17)30253-3
 183. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebich JB, Gruber F, Kaste M, Lipka LJ, Pedraza S, Ringleb PA, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol.* 2009;8:141–150. doi: 10.1016/S1474-4422(08)70267-9
 184. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, et al; for the DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke.* 2005;36:66–73. doi: 10.1161/01.STR.0000149938.08731.2c
 185. von Kummer R, Mori E, Truelsen T, Jensen JS, Grønning BA, Fiebich JB, Lovblad KO, Pedraza S, Romero JM, Chabriat H, et al; for the DIAS-4 Investigators. Desmoteplase 3 to 9 hours after major artery occlusion stroke: the DIAS-4 Trial (Efficacy and Safety Study of Desmoteplase to Treat Acute Ischemic Stroke). *Stroke.* 2016;47:2880–2887. doi: 10.1161/STROKEAHA.116.013715
 186. Albers GW, von Kummer R, Truelsen T, Jensen JK, Ravn GM, Grønning BA, Chabriat H, Chang KC, Davalos AE, Ford GA, et al; DIAS-3 Investigators. Safety and efficacy of desmoteplase given 3–9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (DIAS-3): a double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Neurol.* 2015;14:575–584. doi: 10.1016/S1474-4422(15)00047-2
 187. Nacu A, Kvistad CE, Naess H, Øygarden H, Logallo N, Assmus J, Waje-Andreassen U, Kurz KD, Neckelmann G, Thomassen L. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study): randomized controlled contrast-enhanced sonothrombolysis in an unselected acute ischemic stroke population. *Stroke.* 2017;48:335–341. doi: 10.1161/STROKEAHA.116.014644
 188. Alexandrov AV, Köhrmann M, Soinne L, Tsvigoulis G, Barreto AD, Demchuk AM, Sharma VK, Mikulik R, Muir KW, Brandt G, et al; CLOBUST-ER Trial Investigators. Safety and efficacy of sonothrombolysis for acute ischaemic stroke: a multicentre, double-blind, phase 3, randomised controlled trial. *Lancet Neurol.* 2019;18:338–347. doi: 10.1016/S1474-4422(19)30026-2
 189. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, et al; HERMES Collaborators. Endovascular thrombectomy after large-vessel ischaemic stroke: a meta-analysis of individual patient data from five randomised trials. *Lancet.* 2016;387:1723–1731. doi: 10.1016/S0140-6736(16)00163-X
 190. Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, Roy D, Thornton J, Dorado L, Bonafe A, et al. Safety and efficacy of solitaire stent thrombectomy: individual patient data meta-analysis of randomized trials. *Stroke.* 2016;47:798–806. doi: 10.1161/STROKEAHA.115.012360
 191. Bush CK, Kurimella D, Cross LJ, Conner KR, Martin-Schild S, He J, Li C, Chen J, Kelly T. Endovascular treatment with stent-retriever devices for acute ischemic stroke: a meta-analysis of randomized controlled trials. *PLoS One.* 2016;11:e0147287. doi: 10.1371/journal.pone.0147287
 192. Lemmens R, Hamilton SA, Liebeskind DS, Tomsick TA, Demchuk AM, Nogueira RG, Marks MP, Jahan R, Gralla J, Yoo AJ, et al; DEFUSE 2, IMS III, STAR, and SWIFT Trialists; DEFUSE 2 IMS III STAR and SWIFT Trialists. Effect of endovascular reperfusion in relation to site of arterial occlusion. *Neurology.* 2016;86:762–770. doi: 10.1212/WNL.0000000000002399
 193. Yoo AJ, Simonsen CZ, Prabhakaran S, Chaudhry ZA, Issa MA, Fugate JE, Linfante I, Liebeskind DS, Khatri P, Jovin TG, et al; for the Cerebral Angiographic Revascularization Grading Collaborators. Refining angiographic biomarkers of revascularization: improving outcome prediction after intra-arterial therapy. *Stroke.* 2013;44:2509–2512. doi: 10.1161/STROKEAHA.113.001990
 194. Marks MP, Lansberg MG, Mlynash M, Kemp S, McTaggart R, Zaharchuk G, Bammer R, Albers GW; DEFUSE 2 Investigators. Correlation of AOL recanalization, TIMI reperfusion and TICI reperfusion with infarct growth and clinical outcome. *J Neurointerv Surg.* 2014;6:724–728. doi: 10.1136/neurintsurg-2013-010973
 195. Turk AS 3rd, Siddiqui A, Fifi JT, De Leacy RA, Fiorella DJ, Gu E, Levy EI, Snyder KV, Hanel RA, Aghaebrahim A, et al. Aspiration thrombectomy versus stent retriever thrombectomy as first-line approach for large vessel occlusion (COMPASS): a multicentre, randomised, open label, blinded outcome, non-inferiority trial. *Lancet.* 2019;393:998–1008. doi: 10.1016/S0140-6736(19)30297-1
 196. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, et al; ASTER Trial Investigators. Effect of endovascular contact aspiration vs stent retriever on revascularization in patients with acute ischemic stroke and large vessel occlusion: the ASTER randomized clinical trial. *JAMA.* 2017;318:443–452. doi: 10.1001/jama.2017.9644
 197. Nogueira RG, Frei D, Kirmani JF, Zaidat O, Lopes D, Turk AS 3rd, Heck D, Mason B, Haussen DC, Levy EI, et al; Penumbra Separator 3D Investigators. Safety and efficacy of a 3-dimensional stent retriever with aspiration-based thrombectomy vs aspiration-based thrombectomy alone in acute ischemic stroke intervention: a randomized clinical trial. *JAMA Neurol.* 2018;75:304–311. doi: 10.1001/jamaneurol.2017.3967
 198. Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF, Schonewille W, van den Berg R, Wermer MJ, Boiten J, et al; MR CLEAN Investigators. The effect of anesthetic management during intra-arterial therapy for acute stroke in MR CLEAN. *Neurology.* 2016;87:656–664. doi: 10.1212/WNL.0000000000002976
 199. Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Sundeman H, Reinsfelt B, Ricksten SE. Hypotension during endovascular treatment of ischemic stroke is a risk factor for poor neurological outcome. *Stroke.* 2015;46:2678–2680. doi: 10.1161/STROKEAHA.115.009808
 200. Schönenerger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purruker JC, Nagel S, Klose C, Pfaff J, Bendszus M, et al. Effect of conscious sedation vs general anesthesia on early neurological improvement among patients with ischemic stroke undergoing endovascular thrombectomy: a randomized clinical trial. *JAMA.* 2016;316:1986–1996. doi: 10.1001/jama.2016.16623
 201. Simonsen CZ, Yoo AJ, Sørensen LH, Juul N, Johnsen SP, Andersen G, Rasmussen M. Effect of general anesthesia and conscious sedation during endovascular therapy on infarct growth and clinical outcomes in acute ischemic stroke: a randomized clinical trial. *JAMA Neurol.* 2018;75:470–477. doi: 10.1001/jamaneurol.2017.4474
 202. Gory B, Haussen DC, Piotin M, Steglich-Arnholm H, Holtmannspötter M, Labreuche J, Kyheng M, Taschner C, Eiden S, Nogueira RG, et al; Thrombectomy In TANdem lesions (TITAN) investigators. Impact of intravenous thrombolysis and emergent carotid stenting on reperfusion and clinical outcomes in patients with acute stroke with tandem lesion treated with thrombectomy: a collaborative pooled analysis. *Eur J Neurol.* 2018;25:1115–1120. doi: 10.1111/ene.13633
 203. Delgado F, Oteros R, Jimenez-Gomez E, Bravo Rey I, Bautista MD, Valverde Moyano R. Half bolus dose of intravenous abiciximab is safe and effective in the setting of acute stroke endovascular treatment. *J Neurointerv Surg.* 2019;11:147–152. doi: 10.1136/neurintsurg-2018-014163
 204. Heck DV, Brown MD. Carotid stenting and intracranial thrombectomy for treatment of acute stroke due to tandem occlusions with aggressive antiplatelet therapy may be associated with a high incidence of intracranial hemorrhage. *J Neurointerv Surg.* 2015;7:170–175. doi: 10.1136/neurintsurg-2014-011224
 205. Ernst M, Butscheid F, Fiehler J, Wittkugel O, Alfke K, Jansen O, Petersen D, Koch C, Eckert B. Glycoprotein IIb/IIIa inhibitor bridging and subsequent endovascular therapy in vertebrobasilar occlusion in 120 patients. *Clin Neuroradiol.* 2016;26:169–175. doi: 10.1007/s00062-014-0341-3
 206. Dippel DW, Majoie CB, Roos YB, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Lingsma HF, Koudstaal PJ, Treurniet KM, vanden Berg LA, et al; for the MR CLEAN Investigators. Influence of device choice on the

- effect of intra-arterial treatment for acute ischemic stroke in MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands). *Stroke*. 2016;47:2574–2581. doi: 10.1161/STROKEAHA.116.013929
207. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke: International Stroke Trial Collaborative Group. *Lancet*. 1997;349:1569–1581.
 208. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641–1649.
 209. Sandercock PA, Counsell C, Tseng MC, Ceconi E. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD000029. doi: 10.1002/14651858.CD000029.pub3
 210. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med*. 2013;369:11–19. doi: 10.1056/NEJMoa1215340
 211. Wang X, Zhao X, Johnston SC, Xian Y, Hu B, Wang C, Wang D, Liu L, Li H, Fang J, et al; CHANCE Investigators. Effect of clopidogrel with aspirin on functional outcome in TIA or minor stroke: CHANCE substudy. *Neurology*. 2015;85:573–579. doi: 10.1212/WNL.0000000000001844
 212. Pan Y, Wang Y, Wang Y. Author response: risks and benefits of clopidogrel-aspirin in minor stroke or TIA: time course analysis of CHANCE. *Neurology*. 2017;89:2121–2122. doi: 10.1212/WNL.0000000000004655
 213. Wang Y, Pan Y, Zhao X, Li H, Wang D, Johnston SC, Liu L, Meng X, Wang A, Wang C, et al Y; on behalf of the CHANCE Investigators. Clopidogrel With Aspirin in Acute Minor Stroke or Transient Ischemic Attack (CHANCE) Trial: one-year outcomes. *Circulation*. 2015;132:40–46. doi: 10.1161/CIRCULATIONAHA.114.014791
 214. Wang Y, Zhao X, Lin J, Li H, Johnston SC, Lin Y, Pan Y, Liu L, Wang D, Wang C, et al; CHANCE Investigators. Association between CYP2C19 loss-of-function allele status and efficacy of clopidogrel for risk reduction among patients with minor stroke or transient ischemic attack. *JAMA*. 2016;316:70–78. doi: 10.1001/jama.2016.8662
 215. Jing J, Meng X, Zhao X, Liu L, Wang A, Pan Y, Li H, Wang D, Johnston SC, Wang Y, et al. Dual antiplatelet therapy in transient ischemic attack and minor stroke with different infarction patterns: subgroup analysis of the CHANCE randomized clinical trial. *JAMA Neurol*. 2018;75:711–719. doi: 10.1001/jamaneurol.2018.0247
 216. Johnston SC, Easton JD, Farrant M, Barsan W, Conwit RA, Elm JJ, Kim AS, Lindblad AS, Palesch YY; Clinical Research Collaboration, Neurological Emergencies Treatment Trials Network, and the POINT Investigators. Clopidogrel and aspirin in acute ischemic stroke and high-risk TIA. *N Engl J Med*. 2018;379:215–225. doi: 10.1056/NEJMoa1800410
 217. Siebler M, Hennerici MG, Schneider D, von Reutern GM, Seitz RJ, Röther J, Witte OW, Hamann G, Junghans U, Villringer A, et al. Safety of Tirofiban in Acute Ischemic Stroke: the SaTIS trial. *Stroke*. 2011;42:2388–2392. doi: 10.1161/STROKEAHA.110.599662
 218. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, del Zoppo G, Kleindorfer D, Woo D, Khatri P, et al; CLEAR Trial Investigators. The combined approach to lysis utilizing eptifibatid and rt-PA in acute ischemic stroke: the CLEAR stroke trial. *Stroke*. 2008;39:3268–3276. doi: 10.1161/STROKEAHA.108.517656
 219. Johnston SC, Amarenco P. Ticagrelor versus aspirin in acute stroke or transient ischemic attack. *N Engl J Med*. 2016;375:1395. doi: 10.1056/NEJMc1610106
 220. Ciccone A, Motto C, Abraha I, Cozzolino F, Santilli I. Glycoprotein IIb/IIIa inhibitors for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD005208. doi: 10.1002/14651858.CD005208.pub3
 221. Adams HP Jr, Effron MB, Torner J, Dávalos A, Frayne J, Teal P, Leclerc J, Oemar B, Padgett L, Barnathan ES, et al; for the AbESTT-II Investigators. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). *Stroke*. 2008;39:87–99. doi: 10.1161/STROKEAHA.106.476648
 222. Mokin M, Kass-Hout T, Kass-Hout O, Radovic V, Siddiqui AH, Levy EI, Snyder KV. Intravenous heparin for the treatment of intraluminal thrombus in patients with acute ischemic stroke: a case series. *J Neurointerv Surg*. 2013;5:144–150. doi: 10.1136/neurintsurg-2011-010134
 223. Vellimana AK, Kadkhodayan Y, Rich KM, Cross DT 3rd, Moran CJ, Zazulia AR, Lee JM, Chicoine MR, Dacey RG Jr, Derdeyn CP, et al. Symptomatic patients with intraluminal carotid artery thrombus: outcome with a strategy of initial anticoagulation. *J Neurosurg*. 2013;118:34–41. doi: 10.3171/2012.9.JNS12406
 224. Kate M, Gioia L, Buck B, Sivakumar L, Jeerakathil T, Shuaib A, Butcher K. Dabigatran therapy in acute ischemic stroke patients without atrial fibrillation. *Stroke*. 2015;46:2685–2687. doi: 10.1161/STROKEAHA.115.010383
 225. Barreto AD, Alexandrov AV, Lyden P, Lee J, Martin-Schild S, Shen L, Wu TC, Sisson A, Pandurengan R, Chen Z, et al. The Argatroban and Tissue-Type Plasminogen Activator Stroke Study: final results of a pilot safety study. *Stroke*. 2012;43:770–775. doi: 10.1161/STROKEAHA.111.625574
 226. Barreto AD, Ford GA, Shen L, Pedroza C, Tyson J, Cai C, Rahbar MH, Grotta JC; on behalf of the ARTSS-2 Investigators. Randomized, multicenter trial of ARTSS-2 (Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke). *Stroke*. 2017;48:1608–1616. doi: 10.1161/STROKEAHA.117.016720
 227. Gioia LC, Kate M, Sivakumar L, Hussain D, Kalashyan H, Buck B, Bussiere M, Jeerakathil T, Shuaib A, Emery D, et al. Early rivaroxaban use after cardioembolic stroke may not result in hemorrhagic transformation: a prospective magnetic resonance imaging study. *Stroke*. 2016;47:1917–1919. doi: 10.1161/STROKEAHA.116.013491
 228. Whiteley WN, Adams HP Jr, Bath PM, Berge E, Sandset PM, Dennis M, Murray GD, Wong KS, Sandercock PA. Targeted use of heparin, heparinoids, or low-molecular-weight heparin to improve outcome after acute ischaemic stroke: an individual patient data meta-analysis of randomised controlled trials. *Lancet Neurol*. 2013;12:539–545. doi: 10.1016/S1474-4422(13)70079-6
 229. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2015:CD000024.
 230. Yi X, Lin J, Wang C, Zhang B, Chi W. Low-molecular-weight heparin is more effective than aspirin in preventing early neurologic deterioration and improving six-month outcome. *J Stroke Cerebrovasc Dis*. 2014;23:1537–1544. doi: 10.1016/j.jstrokecerebrovasdis.2013.12.036
 231. Chang TS, Jensen MB. Haemodilution for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD000103.
 232. Ginsberg MD, Palesch YY, Hill MD, Martin RH, Moy CS, Barsan WG, Waldman BD, Tamariz D, Ryckborst KJ; ALIAS and Neurological Emergencies Treatment Trials (NETT) Investigators. High-dose albumin treatment for acute ischaemic stroke (ALIAS) part 2: a randomised, double-blind, phase 3, placebo-controlled trial. *Lancet Neurol*. 2013;12:1049–1058. doi: 10.1016/S1474-4422(13)70223-0
 233. Martin RH, Yeatts SD, Hill MD, Moy CS, Ginsberg MD, Palesch YY; for the ALIAS Parts 1 and 2 and NETT Investigators. ALIAS (Albumin in Acute Ischaemic Stroke) trials: analysis of the combined data from parts 1 and 2. *Stroke*. 2016;47:2355–2359. doi: 10.1161/STROKEAHA.116.012825
 234. Guluma KZ, Liebeskind DS, Raman R, Rapp KS, Ernstrom KB, Alexandrov AV, Shahripour RB, Barlinn K, Starkman S, Grunberg ID, et al. Feasibility and safety of using external counterpulsation to augment cerebral blood flow in acute ischemic stroke: the Counterpulsation to Upgrade Forward Flow in Stroke (CUFFS) Trial. *J Stroke Cerebrovasc Dis*. 2015;24:2596–2604. doi: 10.1016/j.jstrokecerebrovasdis.2015.07.013
 235. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, Conwit R, Liebeskind DS, Sung G, Kramer I, et al; FAST-MAG Investigators and Coordinators. Prehospital use of magnesium sulfate as neuroprotection in acute stroke. *N Engl J Med*. 2015;372:528–536. doi: 10.1056/NEJMoa1408827
 236. Lapchak PA. Taking a light approach to treating acute ischemic stroke patients: transcranial near-infrared laser therapy translational science. *Ann Med*. 2010;42:576–586. doi: 10.3109/07853890.2010.532811
 237. Stemer AB, Huisa BN, Zivin JA. The evolution of transcranial laser therapy for acute ischemic stroke, including a pooled analysis of NEST-1 and NEST-2. *Curr Cardiol Rep*. 2010;12:29–33. doi: 10.1007/s11886-009-0071-3
 238. Zivin JA, Albers GW, Bornstein N, Chippendale T, Dahlof B, Devlin T, Fisher M, Hacke W, Holt W, Ilic S, et al; for the NeuroThera Effectiveness and Safety Trial-2 Investigators. Effectiveness and safety of transcranial laser therapy for acute ischemic stroke. *Stroke*. 2009;40:1359–1364. doi: 10.1161/STROKEAHA.109.547547
 239. Hacke W, Schellinger PD, Albers GW, Bornstein NM, Dahlof BL, Fulton R, Kasner SE, Shuaib A, Richieri SP, Dilly SG, et al; for the NEST 3 Committees and Investigators. Transcranial laser therapy in acute stroke treatment: results of Neurothera Effectiveness and Safety Trial 3, a phase III clinical end point device trial. *Stroke*. 2014;45:3187–3193. doi: 10.1161/STROKEAHA.114.005795
 240. Anderson CS, Arima H, Lavados P, Billot L, Hackett ML, Olavarria VV, Muñoz Venturelli P, Brunser A, Peng B, Cui L, et al; HeadPoST Investigators and Coordinators. Cluster-randomized, crossover

- trial of head positioning in acute stroke. *N Engl J Med*. 2017;376:2437–2447. doi: 10.1056/NEJMoa1615715
241. Alexandrov AW, Tsvigoulis G, Hill MD, Liebeskind DS, Schellinger P, Ovbiagele B, Arthur AS, Caso V, Nogueira RG, Hemphill JC 3rd, et al. HeadPoST: rightly positioned, or flat out wrong? *Neurology*. 2018;90:885–889. doi: 10.1212/WNL.0000000000005481
 242. Olavarría VV, Lavados PM, Muñoz-Venturelli P, González F, Gaete J, Martins S, Arima H, Anderson CS, Brunser AM. Flat-head positioning increases cerebral blood flow in anterior circulation acute ischemic stroke: a cluster randomized phase IIb trial. *Int J Stroke*. 2018;13:600–611. doi: 10.1177/1747493017711943
 243. Stead LG, Gilmore RM, Vedula KC, Weaver AL, Decker WW, Brown RD Jr. Impact of acute blood pressure variability on ischemic stroke outcome. *Neurology*. 2006;66:1878–1881. doi: 10.1212/01.wnl.0000219628.78513.b5
 244. Horn J, de Haan RJ, Vermeulen M, Limburg M. Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke*. 2001;32:461–465. doi: 10.1161/01.str.32.2.461
 245. Schrader J, Lüders S, Kulschewski A, Berger J, Zidek W, Treib J, Einhäupl K, Diener HC, Dominianiak P, on behalf of the Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke*. 2003;34:1699–1703. doi: 10.1161/01.STR.0000075777.18006.89
 246. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C. Controlling Hypertension and Hypotension Immediately Post-Stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48–56. doi: 10.1016/S1474-4422(08)70263-1
 247. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, James MA, Knight J, Markus HS, Mistri AK, et al; COSSACS Investigators. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol*. 2010;9:767–775. doi: 10.1016/S1474-4422(10)70163-0
 248. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, Tong W, Liu C, Xu T, Ju Z, et al; CATIS Investigators. Effects of immediate blood pressure reduction on death and major disability in patients with acute ischemic stroke: the CATIS randomized clinical trial. *JAMA*. 2014;311:479–489. doi: 10.1001/jama.2013.282543
 249. ENOS Trial Investigators, Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, Sprigg N, Berge E, Beridze M, Caso V, et al. Efficacy of nitric oxide, with or without continuing antihypertensive treatment, for management of high blood pressure in acute stroke (ENOS): a partial-factorial randomised controlled trial. *Lancet*. 2015;385:617–628.
 250. Kaste M, Fogelholm R, Erilä T, Palomäki H, Murros K, Rissanen A, Sarna S. A randomized, double-blind, placebo-controlled trial of nimodipine in acute ischemic hemispheric stroke. *Stroke*. 1994;25:1348–1353. doi: 10.1161/01.str.25.7.1348
 251. Wahlgren NG, MacMahon DG, De Keyser J, Indredavik B, Ryman T. The Intravenous Nimodipine West European Trial (INWEST) of nimodipine in the treatment of acute ischemic stroke. *Cerebrovasc Dis*. 1994;4:204–210.
 252. Eveson DJ, Robinson TG, Potter JF. Lisinopril for the treatment of hypertension within the first 24 hours of acute ischemic stroke and follow-up. *Am J Hypertens*. 2007;20:270–277. doi: 10.1016/j.amjhyper.2006.08.005
 253. Bath PM, Martin RH, Palesch Y, Cotton D, Yusuf S, Sacco R, Diener HC, Toni D, Estol C, Roberts R; for the PROFESS Study Group. Effect of telmisartan on functional outcome, recurrence, and blood pressure in patients with acute mild ischemic stroke: a PROFESS subgroup analysis. *Stroke*. 2009;40:3541–3546. doi: 10.1161/STROKEAHA.109.555623
 254. Sandset EC, Bath PM, Boysen G, Jatuzis D, Körv J, Lüders S, Murray GD, Richter PS, Roine RO, Terént A, et al; SCASST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCASST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741–750. doi: 10.1016/S0140-6736(11)60104-9
 255. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev*. 2014;CD000039.
 256. Oh MS, Yu KH, Hong KS, Kang DW, Park JM, Bae HJ, Koo J, Lee J, Lee BC; Valsartan Efficacy on n modesT blood pressUre REduction in acute ischemic stroke (VENTURE) study group. Modest blood pressure reduction with valsartan in acute ischemic stroke: a prospective, randomized, open-label, blinded-end-point trial. *Int J Stroke*. 2015;10:745–751. doi: 10.1111/ijfs.12446
 257. Lee M, Ovbiagele B, Hong KS, Wu YL, Lee JE, Rao NM, Feng W, Saver JL. Effect of blood pressure lowering in early ischemic stroke: meta-analysis. *Stroke*. 2015;46:1883–1889. doi: 10.1161/STROKEAHA.115.009552
 258. Woodhouse L, Scutt P, Krishnan K, Berge E, Gommans J, Ntaios G, Wardlaw J, Sprigg N, Bath PM; on behalf of the ENOS Investigators. Effect of hyperacute administration (within 6 hours) of transdermal glyceryl trinitrate, a nitric oxide donor, on outcome after stroke: subgroup analysis of the Efficacy of Nitric Oxide in Stroke (ENOS) Trial. *Stroke*. 2015;46:3194–3201. doi: 10.1161/STROKEAHA.115.009647
 259. Rai N, Prasad K, Bhatia R, Vibha D, Singh MB, Rai VK, Kumar A. Development and implementation of acute stroke care pathway in a tertiary care hospital in India: a cluster-randomized study. *Neurol India*. 2016;64(suppl):S39–S45. doi: 10.4103/0028-3886.178038
 260. Middleton S, McElduff P, Ward J, Grimshaw JM, Dale S, D'Este C, Drury P, Griffiths R, Cheung NW, Quinn C, et al; QASC Trialists Group. Implementation of evidence-based treatment protocols to manage fever, hyperglycaemia, and swallowing dysfunction in acute stroke (QASC): a cluster randomised controlled trial. *Lancet*. 2011;378:1699–1706. doi: 10.1016/S0140-6736(11)61485-2
 261. Miles A, Zeng IS, McLauchlan H, Huckabee ML. Cough reflex testing in Dysphagia following stroke: a randomized controlled trial. *J Clin Med Res*. 2013;5:222–233. doi: 10.4021/jocmr1340w
 262. Joundi RA, Martino R, Saposnik G, Giannakeas V, Fang J, Kapral MK. Predictors and outcomes of dysphagia screening after acute ischemic stroke. *Stroke*. 2017;48:900–906. doi: 10.1161/STROKEAHA.116.015332
 263. Sørensen RT, Rasmussen RS, Overgaard K, Lerche A, Johansen AM, Lindhardt T. Dysphagia screening and intensified oral hygiene reduce pneumonia after stroke. *J Neurosci Nurs*. 2013;45:139–146. doi: 10.1097/JNN.0b013e31828a412c
 264. Brady M, Furlanetto D, Hunter RV, Lewis S, Milne V. Staff-led interventions for improving oral hygiene in patients following stroke. *Cochrane Database Syst Rev*. 2006;CD003864.
 265. Wagner C, Marchina S, Deveau JA, Frayne C, Sulmonte K, Kumar S. Risk of stroke-associated pneumonia and oral hygiene. *Cerebrovasc Dis*. 2016;41:35–39. doi: 10.1159/000440733
 266. Dennis M, Lewis S, Cranwick G, Forbes J; FOOD Trial Collaboration. FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technol Assess*. 2006;10:iii–iv, ix.
 267. Geeganage C, Beavan J, Ellender S, Bath PM. Interventions for dysphagia and nutritional support in acute and subacute stroke. *Cochrane Database Syst Rev*. 2012;10:CD000323. doi: 10.1002/14651858.CD000323.pub2
 268. Dennis M, Sandercock P, Reid J, Graham C, Forbes J, Murray G; CLOTS (Clots in Legs Or sTockings after Stroke) Trials Collaboration. Effectiveness of intermittent pneumatic compression in reduction of risk of deep vein thrombosis in patients who have had a stroke (CLOTS 3): a multicentre randomised controlled trial. *Lancet*. 2013;382:516–524. doi: 10.1016/S0140-6736(13)61050-8
 269. Dennis M, Caso V, Kappelle LJ, Pavlovic A, Sandercock P; European Stroke Organisation. European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke. *Eur Stroke J*. 2016;1:6–19. doi: 10.1177/2396987316628384
 270. Meader N, Moe-Byrne T, Llewellyn A, Mitchell AJ. Screening for poststroke major depression: a meta-analysis of diagnostic validity studies. *J Neurol Neurosurg Psychiatry*. 2014;85:198–206. doi: 10.1136/jnnp-2012-304194
 271. Berg A, Lönnqvist J, Palomäki H, Kaste M. Assessment of depression after stroke: a comparison of different screening instruments. *Stroke*. 2009;40:523–529. doi: 10.1161/STROKEAHA.108.527705
 272. Kang HJ, Stewart R, Kim JM, Jang JE, Kim SY, Bae KY, Kim SW, Shin IS, Park MS, Cho KH, et al. Comparative validity of depression assessment scales for screening poststroke depression. *J Affect Disord*. 2013;147:186–191. doi: 10.1016/j.jad.2012.10.035
 273. Williams LS, Kroenke K, Bakas T, Plue LD, Brizendine E, Tu W, Hendrie H. Care management of poststroke depression: a randomized, controlled trial. *Stroke*. 2007;38:998–1003. doi: 10.1161/01.STR.0000257319.14023.61
 274. Westendorp WF, Vermeij JD, Zock E, Hooijenga IJ, Kruyt ND, Bosboom HJ, Kwa VI, Weisfelt M, Remmers MJ, ten Houten R, et al; PASS investigators. The Preventive Antibiotics in Stroke Study (PASS): a pragmatic randomised open-label masked endpoint clinical trial. *Lancet*. 2015;385:1519–1526. doi: 10.1016/S0140-6736(14)62456-9
 275. Kalra L, Irshad S, Hodsoll J, Simpson M, Gulliford M, Smithard D, Patel A, Rebollo-Mesa I; STROKE-INF Investigators. Prophylactic antibiotics after acute stroke for reducing pneumonia in patients with dysphagia (STROKE-INF): a prospective, cluster-randomised, open-label, masked endpoint, controlled clinical trial. *Lancet*. 2015;386:1835–1844. doi: 10.1016/S0140-6736(15)00126-9

276. Liu L, Xiong XY, Zhang Q, Fan XT, Yang QW. The efficacy of prophylactic antibiotics on post-stroke infections: an updated systematic review and meta-analysis. *Sci Rep*. 2016;6:36656. doi: 10.1038/srep36656
277. Zheng F, Spreckelsen NV, Zhang X, Stavrinou P, Timmer M, Dohmen C, Goldbrunner R, Cao F, Zhang Q, Ran Q, et al. Should preventive antibiotics be used in patients with acute stroke? A systematic review and meta-analysis of randomized controlled trials. *PLoS One*. 2017;12:e0186607. doi: 10.1371/journal.pone.0186607
278. Vermeij JD, Westendorp WF, Dippel DW, van de Beek D, Nederkooij PJ. Antibiotic therapy for preventing infections in people with acute stroke. *Cochrane Database Syst Rev*. 2018;1:CD008530. doi: 10.1002/14651858.CD008530.pub3
279. AVERT Trial Collaboration Group, Bernhardt J, Langhorne P, Lindley RI, Thrift AG, Ellery F, Collier J, Churilov L, Moodie M, Dewey H, Donnan G. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet*. 2015;386:46–55.
280. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Boussier MG, van der Worp HB, Hacke W; DECIMAL, DESTINY, and HAMLET Investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215–222. doi: 10.1016/S1474-4422(07)70036-4
281. Christensen MS, Paulson OB, Olesen J, Alexander SC, Skinhoj E, Dam WH, Lassen NA. Cerebral apoplexy (stroke) treated with or without prolonged artificial hyperventilation, 1: cerebral circulation, clinical course, and cause of death. *Stroke*. 1973;4:568–631. doi: 10.1161/01.str.4.4.568
282. Ausina A, Báguena M, Nadal M, Manrique S, Ferrer A, Sahuquillo J, Garnacho A. Cerebral hemodynamic changes during sustained hypocapnia in severe head injury: can hyperventilation cause cerebral ischemia? *Acta Neurochir Suppl*. 1998;71:1–4. doi: 10.1007/978-3-7091-6475-4_1
283. Steiner LA, Balestreri M, Johnston AJ, Czosnyka M, Coles JP, Chatfield DA, Smielewski P, Pickard JD, Menon DK. Sustained moderate reductions in arterial CO₂ after brain trauma time-course of cerebral blood flow velocity and intracranial pressure. *Intensive Care Med*. 2004;30:2180–2187. doi: 10.1007/s00134-004-2463-6
284. Carrera E, Steiner LA, Castellani G, Smielewski P, Zweifel C, Haubrich C, Pickard JD, Menon DK, Czosnyka M. Changes in cerebral compartmental compliances during mild hypocapnia in patients with traumatic brain injury. *J Neurotrauma*. 2011;28:889–896. doi: 10.1089/neu.2010.1377
285. Muizelaar JP, Marmarou A, Ward JD, Kontos HA, Choi SC, Becker DP, Gruemer H, Young HF. Adverse effects of prolonged hyperventilation in patients with severe head injury: a randomized clinical trial. *J Neurosurg*. 1991;75:731–739. doi: 10.3171/jns.1991.75.5.0731
286. Wan YH, Nie C, Wang HL, Huang CY. Therapeutic hypothermia (different depths, durations, and rewarming speeds) for acute ischemic stroke: a meta-analysis. *J Stroke Cerebrovasc Dis*. 2014;23:2736–2747. doi: 10.1016/j.jstrokecerebrovasdis.2014.06.017
287. Maciel CB, Sheth KN. Malignant MCA stroke: an update on surgical decompression and future directions. *Curr Atheroscler Rep*. 2015;17:40. doi: 10.1007/s11883-015-0519-4
288. Yang MH, Lin HY, Fu J, Roodrajeetsing G, Shi SL, Xiao SW. Decompressive hemicraniectomy in patients with malignant middle cerebral artery infarction: a systematic review and meta-analysis. *Surgeon*. 2015;13:230–240. doi: 10.1016/j.surge.2014.12.002
289. Agarwalla PK, Stapleton CJ, Ogilvy CS. Craniectomy in acute ischemic stroke. *Neurosurgery*. 2014;74(suppl 1):S151–S162. doi: 10.1227/NEU.0000000000000226
290. Alexander P, Heels-Ansdell D, Siemieniuk R, Bhatnagar N, Chang Y, Fei Y, Zhang Y, McLeod S, Prasad K, Guyatt G. Hemicraniectomy versus medical treatment with large MCA infarct: a review and meta-analysis. *BMJ Open*. 2016;6:e014390. doi: 10.1136/bmjopen-2016-014390
291. Sundseth J, Sundseth A, Jacobsen EA, Pripp AH, Sorteberg W, Altmann M, Lindegaard KF, Berg-Johnsen J, Thommessen B. Predictors of early in-hospital death after decompressive craniectomy in swollen middle cerebral artery infarction. *Acta Neurochir (Wien)*. 2017;159:301–306. doi: 10.1007/s00701-016-3049-0
292. Suyama K, Horie N, Hayashi K, Nagata I. Nationwide survey of decompressive hemicraniectomy for malignant middle cerebral artery infarction in Japan. *World Neurosurg*. 2014;82:1158–1163. doi: 10.1016/j.wneu.2014.07.015
293. Yu JW, Choi JH, Kim DH, Cha JK, Huh JT. Outcome following decompressive craniectomy for malignant middle cerebral artery infarction in patients older than 70 years old. *J Cerebrovasc Endovasc Neurosurg*. 2012;14:65–74. doi: 10.7461/jcen.2012.14.2.65
294. Jüttler E, Unterberg A, Woitzik J, Bösel J, Amiri H, Sakowitz OW, Gondan M, Schiller P, Limprecht R, Luntz S, et al; DESTINY II Investigators. Hemicraniectomy in older patients with extensive middle-cerebral-artery stroke. *N Engl J Med*. 2014;370:1091–1100. doi: 10.1056/NEJMoa1311367
295. Zhao J, Su YY, Zhang Y, Zhang YZ, Zhao R, Wang L, Gao R, Chen W, Gao D. Decompressive hemicraniectomy in malignant middle cerebral artery infarct: a randomized controlled trial enrolling patients up to 80 years old. *Neurocrit Care*. 2012;17:161–171. doi: 10.1007/s12028-012-9703-3
296. Raco A, Caroli E, Isidori A, Salvati M. Management of acute cerebellar infarction: one institution's experience. *Neurosurgery*. 2003;53:1061–1065. doi: 10.1227/01.neu.0000088766.34559.3e
297. Mostofi K. Neurosurgical management of massive cerebellar infarct outcome in 53 patients. *Surg Neurol Int*. 2013;4:28. doi: 10.4103/2152-7806.107906
298. Heidenreich JO, Hsu D, Wang G, Jesberger JA, Tarr RW, Zaidat OO, Sunshine JL. Magnetic resonance imaging results can affect therapy decisions in hyperacute stroke care. *Acta Radiol*. 2008;49:550–557. doi: 10.1080/02841850801958320
299. North American Symptomatic Carotid Endarterectomy Trial Collaborators, Barnett HJM, Taylor DW, Haynes RB, Sackett DL, Peerless SJ, Ferguson GG, Fox AJ, Rankin RN, Hachinski VC, Wiebers DO, et al. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453. doi: 10.1056/NEJM199108153250701
300. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet*. 1998;351:1379–1387.
301. Amarenco P, Bogousslavsky J, Callahan A 3rd, Goldstein LB, Hennerici M, Rudolph AE, Sillensen H, Simunovic L, Szarek M, Welch KM, et al; Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischaemic attack. *N Engl J Med*. 2006;355:549–559. doi: 10.1056/NEJMoa061894
302. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study, 2: dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1–13. doi: 10.1016/s0022-510x(96)00308-5
303. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE): CAPRIE Steering Committee. *Lancet*. 1996;348:1329–1339. doi: 10.1016/s0140-6736(96)09457-3
304. Sacco RL, Diener HC, Yusuf S, Cotton D, Ounpuu S, Lawton WA, Palesch Y, Martin RH, Albers GW, Bath P, et al; PROFESS Study Group. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–1251. doi: 10.1056/NEJMoa0805002
305. SALT Collaborative Group. Swedish Aspirin Low-Dose Trial (SALT) of 75 mg aspirin as secondary prophylaxis after cerebrovascular ischaemic events. *Lancet*. 1991;338:1345–1349.
306. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033–1041. doi: 10.1016/S0140-6736(01)06178-5
307. Burke JF, Gelb DJ, Quint DJ, Morgenstern LB, Kerber KA. The impact of MRI on stroke management and outcomes: a systematic review. *J Eval Clin Pract*. 2013;19:987–993. doi: 10.1111/jep.12011
308. Wardlaw J, Brazzelli M, Miranda H, Chappell F, McNamee P, Scotland G, Quayyum Z, Martin D, Shuler K, Sandercock P, et al. An assessment of the cost-effectiveness of magnetic resonance, including diffusion-weighted imaging, in patients with transient ischaemic attack and minor stroke: a systematic review, meta-analysis and economic evaluation. *Health Technol Assess*. 2014;18:1–368, v–vi. doi: 10.3310/hta18270
309. Ertl-Wagner B, Brandt T, Seifart C, Forsting M. Diagnostic and therapeutic consequences of repeat brain imaging and follow-up vascular imaging in stroke patients. *AJNR Am J Neuroradiol*. 1999;20:37–42.
310. Schneider LB, Libman RB, Kanner R. Utility of repeat brain imaging in stroke. *AJNR Am J Neuroradiol*. 1996;17:1259–1263.
311. Søndergaard L, Kasner SE, Rhodes JF, Andersen G, Iversen HK, Nielsen-Kudsk JE, Settergren M, Sjöstrand C, Roine RO, Hildick-Smith D, et al; Gore REDUCE Clinical Study Investigators. Patent foramen ovale closure or antiplatelet therapy for cryptogenic stroke. *N Engl J Med*. 2017;377:1033–1042. doi: 10.1056/NEJMoa1707404

312. Mas JL, Derumeaux G, Guillon B, Massardier E, Hosseini H, Mechtouff L, Arquizan C, Béjot Y, Vuillier F, Detante O, et al; CLOSE Investigators. Patent foramen ovale closure or anticoagulation vs. antiplatelets after stroke. *N Engl J Med*. 2017;377:1011–1021. doi: 10.1056/NEJMoa1705915
313. Carroll JD, Saver JL, Thaler DE, Smalling RW, Berry S, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med*. 2013;368:1092–1100. doi: 10.1056/NEJMoa1301440
314. Saver JL, Carroll JD, Thaler DE, Smalling RW, MacDonald LA, Marks DS, Tirschwell DL; RESPECT Investigators. Long-term outcomes of patent foramen ovale closure or medical therapy after stroke. *N Engl J Med*. 2017;377:1022–1032. doi: 10.1056/NEJMoa1610057
315. Meier B, Kalesan B, Mattle HP, Khattab AA, Hildick-Smith D, Dudek D, Andersen G, Ibrahim R, Schuler G, Walton AS, et al; PC Trial Investigators. Percutaneous closure of patent foramen ovale in cryptogenic embolism. *N Engl J Med*. 2013;368:1083–1091. doi: 10.1056/NEJMoa1211716
316. Furlan AJ, Reisman M, Massaro J, Mauri L, Adams H, Albers GW, Felberg R, Herrmann H, Kar S, Landzberg M, et al; CLOSURE I Investigators. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med*. 2012;366:991–999. doi: 10.1056/NEJMoa1009639
317. Lee PH, Song JK, Kim JS, Heo R, Lee S, Kim DH, Song JM, Kang DH, Kwon SU, Kang DW, et al. cryptogenic stroke and high-risk patent foramen ovale: the DEFENSE-PFO Trial. *J Am Coll Cardiol*. 2018;71:2335–2342. doi: 10.1016/j.jacc.2018.02.046
318. Turc G, Calvet D, Guerin P, Sroussi M, Chatellier G, Mas JL, CLOSE Investigators. Closure, anticoagulation, or antiplatelet therapy for cryptogenic stroke with patent foramen ovale: systematic review of randomized trials, sequential meta-analysis, and new insights from the CLOSE Study. *J Am Heart Assoc*. 2018;7:e008356. doi: 10.1161/JAHA.117.008356
319. Mir H, Siemieniuk RAC, Ge L, Foroutan F, Fralick M, Syed T, Lopes LC, Kuijpers T, Mas JL, Vandvik PO, et al. Patent foramen ovale closure, antiplatelet therapy or anticoagulation in patients with patent foramen ovale and cryptogenic stroke: a systematic review and network meta-analysis incorporating complementary external evidence. *BMJ Open*. 2018;8:e023761. doi: 10.1136/bmjopen-2018-023761
320. Qiu B, Cai Y, Wang D, Lin J, Fan Y. Closure versus medical therapy for patent foramen ovale in patients with cryptogenic stroke: an updated meta-analysis of randomized controlled trials. *J Stroke Cerebrovasc Dis*. 2018;27:3463–3472. doi: 10.1016/j.jstrokecerebrovasdis.2018.08.008
321. Giacompo D, Caronna N, Frangieh AH, Michel J, Andò G, Tarantini G, Kasel AM, Capodanno D, Byrne RA. Long-term effectiveness and safety of transcatheter closure of patent foramen ovale compared with antithrombotic therapy alone: a meta-analysis of six randomised clinical trials and 3,560 patients with reconstructed time-to-event data. *EuroIntervention*. 2018;14:857–867. doi: 10.4244/EIJ-D-18-00341
322. Niu X, Ou-Yang G, Yan PF, Huang SL, Zhang ZT, Zhang ZH. Closure of patent foramen ovale for cryptogenic stroke patients: an updated systematic review and meta-analysis of randomized trials. *J Neurol*. 2018;265:1259–1268. doi: 10.1007/s00415-018-8766-2
323. Li J, Liu J, Liu M, Zhang S, Hao Z, Zhang J, Zhang C. Closure versus medical therapy for preventing recurrent stroke in patients with patent foramen ovale and a history of cryptogenic stroke or transient ischemic attack. *Cochrane Database Syst Rev*. 2015:CD009938.
324. McIntyre WF, Spence J, Belley-Cote EP. Assessing the quality of evidence supporting patent foramen ovale closure over medical therapy after cryptogenic stroke. *Eur Heart J*. 2018;39:3618–3619. doi: 10.1093/eurheartj/ehy496
325. Ois A, Cuadrado-Godia E, Rodríguez-Campello A, Jimenez-Conde J, Roquer J. High risk of early neurological recurrence in symptomatic carotid stenosis. *Stroke*. 2009;40:2727–2731. doi: 10.1161/STROKEAHA.109.548032
326. De Rango P, Brown MM, Chaturvedi S, Howard VJ, Jovin T, Mazya MV, Paciaroni M, Manzone A, Farchioni L, Caso V. Summary of evidence on early carotid intervention for recently symptomatic stenosis based on meta-analysis of current risks. *Stroke*. 2015;46:3423–3436. doi: 10.1161/STROKEAHA.115.010764
327. Marnane M, Ni Chroinin D, Callaly E, Sheehan OC, Merwick A, Hannon N, Horgan G, Kyne L, Moroney J, McCormack PM, et al. Stroke recurrence within the time window recommended for carotid endarterectomy. *Neurology*. 2011;77:738–743. doi: 10.1212/WNL.0b013e31822b00cf
328. Johansson EP, Arnerlöf C, Wester P. Risk of recurrent stroke before carotid endarterectomy: the ANSYSCAP study. *Int J Stroke*. 2013;8:220–227. doi: 10.1111/j.1747-4949.2012.00790.x
329. Strömberg S, Nordanstig A, Benzell T, Österberg K, Bergström GM. Risk of early recurrent stroke in symptomatic carotid stenosis. *Eur J Vasc Endovasc Surg*. 2015;49:137–144. doi: 10.1016/j.ejvs.2014.11.004
330. Kazandjian C, Kretz B, Lemogne B, Aboa Eboulé C, Béjot Y, Steinmetz E. Influence of the type of cerebral infarct and timing of intervention in the early outcomes after carotid endarterectomy for symptomatic stenosis. *J Vasc Surg*. 2016;63:1256–1261. doi: 10.1016/j.jvs.2015.10.097
331. Azzini C, Gentile M, De Vito A, Traina L, Sette E, Fainardi E, Mascoli F, Casetta I. Very early carotid endarterectomy after intravenous thrombolysis. *Eur J Vasc Endovasc Surg*. 2016;51:482–486. doi: 10.1016/j.ejvs.2015.11.006
332. Adachi K, Sadato A, Hayakawa M, Maeda S, Hirose Y. Acute carotid artery stenting in symptomatic high-grade cervical carotid artery stenosis. *Neurosurg Rev*. 2017;40:45–51. doi: 10.1007/s10143-016-0737-4
333. Vasconcelos V, Cassola N, da Silva EM, Baptista-Silva JC. Immediate versus delayed treatment for recently symptomatic carotid artery stenosis. *Cochrane Database Syst Rev*. 2016;9:CD011401. doi: 10.1002/14651858.CD011401.pub2
334. Ferguson GG, Eliasziw M, Barr HW, Clagett GP, Barnes RW, Wallace MC, Taylor DW, Haynes RB, Finan JW, Hachinski VC, et al. The North American Symptomatic Carotid Endarterectomy Trial: surgical results in 1415 patients. *Stroke*. 1999;30:1751–1758. doi: 10.1161/01.str.30.9.1751
335. Chimowitz MI, Lynn MJ, Howlett-Smith H, Stern BJ, Hertzberg VS, Frankel MR, Levine SR, Chaturvedi S, Kasner SE, Benesch CG, et al; Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med*. 2005;352:1305–1316. doi: 10.1056/NEJMoa043033
336. Chimowitz MI, Lynn MJ, Derdeyn CP, Turan TN, Fiorella D, Lane BF, Janis LS, Lutsep HL, Barnwell SL, Waters MF, et al; SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med*. 2011;365:993–1003. doi: 10.1056/NEJMoa1105335
337. Derdeyn CP, Chimowitz MI, Lynn MJ, Fiorella D, Turan TN, Janis LS, Montgomery J, Nizam A, Lane BF, Lutsep HL, et al; Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis Trial Investigators. Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *Lancet*. 2014;383:333–341. doi: 10.1016/S0140-6736(13)62038-3
338. Lutsep HL, Barnwell SL, Larsen DT, Lynn MJ, Hong M, Turan TN, Derdeyn CP, Fiorella D, Janis LS, Chimowitz MI; for the SAMMPRIS Investigators. Outcome in patients previously on antithrombotic therapy in the SAMMPRIS trial: subgroup analysis. *Stroke*. 2015;46:775–779. doi: 10.1161/STROKEAHA.114.007752
339. Chaturvedi S, Turan TN, Lynn MJ, Derdeyn CP, Fiorella D, Janis LS, Chimowitz MI; for the SAMMPRIS Trial Investigators. Do patient characteristics explain the differences in outcome between medically treated patients in SAMMPRIS and WASID? *Stroke*. 2015;46:2562–2567. doi: 10.1161/STROKEAHA.115.009656
340. Kallmünzer B, Breuer L, Kahl N, Bobinger T, Raaz-Schrauder D, Huttner HB, Schwab S, Köhrmann M. Serious cardiac arrhythmias after stroke: incidence, time course, and predictors: a systematic, prospective analysis. *Stroke*. 2012;43:2892–2897. doi: 10.1161/STROKEAHA.112.664318
341. Fernández-Menéndez S, García-Santiago R, Vega-Primo A, González Nafria N, Lara-Lezama LB, Redondo-Robles L, Montes-Montes M, Riveira-Rodríguez MC, Tejada-García J. Cardiac arrhythmias in stroke unit patients: evaluation of the cardiac monitoring data. *Neurologia*. 2016;31:289–295. doi: 10.1016/j.nrl.2015.03.013
342. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342:1255–1262.
343. Sposato LA, Cipriano LE, Saposnik G, Ruiz Vargas E, Riccio PM, Hachinski V. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. *Lancet Neurol*. 2015;14:377–387. doi: 10.1016/S1474-4422(15)70027-X
344. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, Rymer MM, Thijs V, Rogers T, Beckers F, et al; CRYSTAL AF Investigators. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med*. 2014;370:2478–2486. doi: 10.1056/NEJMoa1313600
345. Brachmann J, Morillo CA, Sanna T, Di Lazzaro V, Diener HC, Bernstein RA, Rymer M, Ziegler PD, Liu S, Passman RS. Uncovering atrial fibrillation beyond short-term monitoring in cryptogenic stroke patients: three-year results from the Cryptogenic Stroke and Underlying

- Atrial Fibrillation Trial. *Circ Arrhythm Electrophysiol*. 2016;9:e003333. doi: 10.1161/CIRCEP.115.003333
346. Wachter R, Gröschel K, Gelbrich G, Hamann GF, Kermer P, Liman J, Seegers J, Wasser K, Schulte A, Jürries F, et al; Find-AF_{RANDOMISED} Investigators and Coordinators. Holter-electrocardiogram-monitoring in patients with acute ischaemic stroke (Find-AFRandomised): an open-label randomised controlled trial. *Lancet Neurol*. 2017;16:282–290. doi: 10.1016/S1474-4422(17)30002-9
 347. Martin DT, Bersohn MM, Waldo AL, Wathen MS, Choucair WK, Lip GY, Ip J, Holcomb R, Akar JG, Halperin JL; IMPACT Investigators. Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices. *Eur Heart J*. 2015;36:1660–1668. doi: 10.1093/eurheartj/ehv115
 348. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, Vaid H, O'Donnell M, Laupacis A, Côté R, et al; EMBRACE Investigators and Coordinators. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467–2477. doi: 10.1056/NEJMoa1311376
 349. Higgins P, Dawson J, MacFarlane PW, McArthur K, Langhorne P, Lees KR. Predictive value of newly detected atrial fibrillation paroxysms in patients with acute ischemic stroke, for atrial fibrillation after 90 days. *Stroke*. 2014;45:2134–2136. doi: 10.1161/STROKEAHA.114.005405
 350. Bath PM, Woodhouse LJ, Appleton JP, Beridze M, Christensen H, Dineen RA, Duley L, England TJ, Flaherty K, Havard D, et al; TARDIS Investigators. Antiplatelet therapy with aspirin, clopidogrel, and dipyridamole versus clopidogrel alone or aspirin and dipyridamole in patients with acute cerebral ischaemia (TARDIS): a randomised, open-label, phase 3 superiority trial. *Lancet*. 2018;391:850–859. doi: 10.1016/S0140-6736(17)32849-0
 351. Meenan RT, Saha S, Chou R, Swartztrauber K, Krages KP, O'Keefe-Rosetti M, McDonagh M, Chan BK, Hornbrook MC, Helfand M. Effectiveness and cost-effectiveness of echocardiography and carotid imaging in the management of stroke. *Evid Rep Technol Assess (Summ)*. 2002;1–10.
 352. Menon BK, Coulter JJ, Bal S, Godzwon C, Weeks S, Hutchison S, Hill MD, Coutts SB. Acute ischaemic stroke or transient ischaemic attack and the need for inpatient echocardiography. *Postgrad Med J*. 2014;90:434–438. doi: 10.1136/postgradmedj-2013-132220
 353. Holmes M, Rathbone J, Littlewood C, Rawdin A, Stevenson M, Stevens J, Archer R, Evans P, Wang J. Routine echocardiography in the management of stroke and transient ischaemic attack: a systematic review and economic evaluation. *Health Technol Assess*. 2014;18:1–176. doi: 10.3310/hta18160
 354. McGrath ER, Paikin JS, Motlagh B, Salehian O, Kapral MK, O'Donnell MJ. Transesophageal echocardiography in patients with cryptogenic ischemic stroke: a systematic review. *Am Heart J*. 2014;168:706–712. doi: 10.1016/j.ahj.2014.07.025
 355. Zhang L, Harrison JK, Goldstein LB. Echocardiography for the detection of cardiac sources of embolism in patients with stroke or transient ischemic attack. *J Stroke Cerebrovasc Dis*. 2012;21:577–582. doi: 10.1016/j.jstrokecerebrovasdis.2011.01.005
 356. Schaer B, Sticherling C, Lyrer P, Osswald S. Cardiological diagnostic work-up in stroke patients: a comprehensive study of test results and therapeutic implications. *Eur J Neurol*. 2009;16:268–273. doi: 10.1111/j.1468-1331.2008.02413.x
 357. Douen A, Pageau N, Medic S. Usefulness of cardiovascular investigations in stroke management: clinical relevance and economic implications. *Stroke*. 2007;38:1956–1958. doi: 10.1161/STROKEAHA.106.477760
 358. Wolber T, Maeder M, Atefy R, Bluzaitė I, Blank R, Rickli H, Ammann P. Should routine echocardiography be performed in all patients with stroke? *J Stroke Cerebrovasc Dis*. 2007;16:1–7. doi: 10.1016/j.jstrokecerebrovasdis.2006.07.002
 359. Homma S, Thompson JL, Pullicino PM, Levin B, Freudenberger RS, Teerlink JR, Ammon SE, Graham S, Sacco RL, Mann DL, et al; WARCEF Investigators. Warfarin and aspirin in patients with heart failure and sinus rhythm. *N Engl J Med*. 2012;366:1859–1869. doi: 10.1056/NEJMoa1202299
 360. Massie BM, Collins JF, Ammon SE, Armstrong PW, Cleland JG, Ezekowitz M, Jafri SM, Krol WF, O'Connor CM, Schulman KA, et al; for the WATCH Trial Investigators. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. *Circulation*. 2009;119:1616–1624. doi: 10.1161/CIRCULATIONAHA.108.801753
 361. Ahmad O, Ahmad KE, Dear KB, Harvey I, Hughes A, Lueck CJ. Echocardiography in the detection of cardioembolism in a stroke population. *J Clin Neurosci*. 2010;17:561–565. doi: 10.1016/j.jocn.2009.09.016
 362. Secades S, Martín M, Corros C, Rodríguez ML, García-Campos A, de la Hera Galarza JM, Lambert JL. Diagnostic yield of echocardiography in stroke: should we improve patient selection? *Neurologia*. 2013;28:15–18. doi: 10.1016/j.nrl.2012.03.002
 363. Kapral MK, Silver FL. Preventive health care, 1999 update, 2: echocardiography for the detection of a cardiac source of embolus in patients with stroke: Canadian Task Force on Preventive Health Care. *CMAJ*. 1999;161:989–996.
 364. Connors JM. Thrombophilia testing and venous thrombosis. *N Engl J Med*. 2017;377:1177–1187. doi: 10.1056/NEJMra1700365
 365. Morris JG, Singh S, Fisher M. Testing for inherited thrombophilias in arterial stroke: can it cause more harm than good? *Stroke*. 2010;41:2985–2990. doi: 10.1161/STROKEAHA.110.595199
 366. Brown DL, Chervin RD, Hickenbottom SL, Langa KM, Morgenstern LB. Screening for obstructive sleep apnea in stroke patients: a cost-effectiveness analysis. *Stroke*. 2005;36:1291–1293. doi: 10.1161/01.STR.0000166055.52742.2b
 367. Pack AI, Pien GW. Update on sleep and its disorders. *Annu Rev Med*. 2011;62:447–460. doi: 10.1146/annurev-med-050409-104056
 368. Medeiros CA, de Bruin VM, Andrade GM, Coutinho WM, de Castro-Silva C, de Bruin PF. Obstructive sleep apnea and biomarkers of inflammation in ischemic stroke. *Acta Neurol Scand*. 2012;126:17–22. doi: 10.1111/j.1600-0404.2011.01589.x
 369. Camilo MR, Sander HH, Eckeli AL, Fernandes RM, Dos Santos-Pontelli TE, Leite JP, Pontes-Neto OM. SOS score: an optimized score to screen acute stroke patients for obstructive sleep apnea. *Sleep Med*. 2014;15:1021–1024. doi: 10.1016/j.sleep.2014.03.026
 370. Stahl SM, Yaggi HK, Taylor S, Qin L, Ivan CS, Austin C, Ferguson J, Radulescu R, Tobias L, Sico J, et al. Infarct location and sleep apnea: evaluating the potential association in acute ischemic stroke. *Sleep Med*. 2015;16:1198–1203. doi: 10.1016/j.sleep.2015.07.003
 371. Parra O, Sánchez-Armengola A, Bonnin M, Arboix A, Campos-Rodríguez F, Pérez-Ronchel J, Durán-Cantolla J, de la Torre G, González Marcos JR, de la Peña M, et al. Early treatment of obstructive apnoea and stroke outcome: a randomised controlled trial. *Eur Respir J*. 2011;37:1128–1136. doi: 10.1183/09031936.00034410
 372. McEvoy RD, Antic NA, Heeley E, Luo Y, Ou Q, Zhang X, Mediano O, Chen R, Drager LF, Liu Z, et al; SAVE Investigators and Coordinators. CPAP for prevention of cardiovascular events in obstructive sleep apnea. *N Engl J Med*. 2016;375:919–931. doi: 10.1056/NEJMoa1606599
 373. Côté R, Zhang Y, Hart RG, McClure LA, Anderson DC, Talbert RL, Benavente OR. ASA failure: does the combination ASA/clopidogrel confer better long-term vascular protection? *Neurology*. 2014;82:382–389. doi: 10.1212/WNL.0000000000000076
 374. Lee M, Saver JL, Hong KS, Rao NM, Wu YL, Ovbigele B. Antiplatelet regimen for patients with breakthrough strokes while on aspirin: a systematic review and meta-analysis. *Stroke*. 2017;48:2610–2613. doi: 10.1161/STROKEAHA.117.017895
 375. John S, Katzan I. Recurrent stroke while on antiplatelet therapy. *Neurol Clin*. 2015;33:475–489. doi: 10.1016/j.ncl.2014.12.007
 376. Turan TN, Maitan L, Cotsonis G, Lynn MJ, Romano JG, Levine SR, Chimowitz MI; for the Warfarin-Aspirin Symptomatic Intracranial Disease Investigators. Failure of antithrombotic therapy and risk of stroke in patients with symptomatic intracranial stenosis. *Stroke*. 2009;40:505–509. doi: 10.1161/STROKEAHA.108.528281
 377. Kasner SE, Lynn MJ, Chimowitz MI, Frankel MR, Howlett-Smith H, Hertzberg VS, Chaturvedi S, Levine SR, Stern BJ, Benesch CG, et al; Warfarin Aspirin Symptomatic Intracranial Disease (WASID) Trial Investigators. Warfarin vs aspirin for symptomatic intracranial stenosis: subgroup analyses from WASID. *Neurology*. 2006;67:1275–1278. doi: 10.1212/01.wnl.0000238506.76873.2f
 378. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, Rueckert C, Pezzini A, Poli L, Padovani A, et al. Early recurrence and cerebral bleeding in patients with acute ischemic stroke and atrial fibrillation: effect of anticoagulation and its timing: the RAF Study. *Stroke*. 2015;46:2175–2182. doi: 10.1161/STROKEAHA.115.008891
 379. Markus HS, Hayter E, Levi C, Feldman A, Venables G, Norris J; CADISS Trial Investigators. Antiplatelet treatment compared with anticoagulation treatment for cervical artery dissection (CADISS): a randomised trial. *Lancet Neurol*. 2015;14:361–367. doi: 10.1016/S1474-4422(15)70018-9
 380. Larsson SC, King A, Madigan J, Levi C, Norris JW, Markus HS. Prognosis of carotid dissecting aneurysms: results from CADISS and a systematic review. *Neurology*. 2017;88:646–652. doi: 10.1212/WNL.00000000000003617

381. Ahlhelm F, Benz RM, Ulmer S, Lyrer P, Stippich C, Engelter S. Endovascular treatment of cervical artery dissection: ten case reports and review of the literature. *Interv Neurol*. 2013;1:143–150. doi: 10.1159/000351687
382. Kim JT, Heo SH, Park MS, Chang J, Choi KH, Cho KH. Use of anti-thrombotics after hemorrhagic transformation in acute ischemic stroke. *PLoS One*. 2014;9:e89798. doi: 10.1371/journal.pone.0089798
383. England TJ, Bath PM, Sare GM, Geeganage C, Moulin T, O'Neill D, Woimant F, Christensen H, De Deyn P, Leys D, et al; TAIIST Investigators. Asymptomatic hemorrhagic transformation of infarction and its relationship with functional outcome and stroke subtype: assessment from the Tinzaparin in Acute Ischaemic Stroke Trial. *Stroke*. 2010;41:2834–2839. doi: 10.1161/STROKEAHA.109.573063
384. Nissen SE, Stroes E, Dent-Acosta RE, Rosenson RS, Lehman SJ, Sattar N, Preiss D, Bruckert E, Ceska R, Lepor N, et al; GAUSS-3 Investigators. Efficacy and tolerability of evolocumab vs ezetimibe in patients with muscle-related statin intolerance: the GAUSS-3 randomized clinical trial. *JAMA*. 2016;315:1580–1590. doi: 10.1001/jama.2016.3608
385. Moriarty PM, Thompson PD, Cannon CP, Guyton JR, Bergeron J, Zieve FJ, Bruckert E, Jacobson TA, Kopecky SL, Baccara-Dinet MT, et al; ODYSSEY ALTERNATIVE Investigators. Efficacy and safety of alirocumab vs ezetimibe in statin-intolerant patients, with a statin rechallenge arm: the ODYSSEY ALTERNATIVE randomized trial. *J Clin Lipidol*. 2015;9:758–769. doi: 10.1016/j.jacl.2015.08.006
386. Lloyd-Jones DM, Morris MB, Ballantyne CM, Birtcher KK, Daly DD Jr, DePalma SM, Minissian MB, Orringer CE, Smith SC, Jr. 2016 ACC expert consensus decision pathway on the role of non-statin therapies for LDL-cholesterol lowering in the management of atherosclerotic cardiovascular disease risk: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol*. 2016;68:92–125. doi: 10.1016/j.jacc.2016.03.519
387. Sanossian N, Saver JL, Liebeskind DS, Kim D, Razinia T, Ovbiagele B. Achieving target cholesterol goals after stroke: is in-hospital statin initiation the key? *Arch Neurol*. 2006;63:1081–1083. doi: 10.1001/archneur.63.8.1081
388. Hong KS, Lee JS. Statins in acute ischemic stroke: a systematic review. *J Stroke*. 2015;17:282–301. doi: 10.5853/jos.2015.17.3.282
389. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast Assessment of Stroke and Transient Ischaemic Attack to Prevent Early Recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6:961–969. doi: 10.1016/S1474-4422(07)70250-8
390. Yoshimura S, Uchida K, Daimon T, Takashima R, Kimura K, Morimoto T; on behalf of the ASSORT Trial Investigator. Randomized controlled trial of early versus delayed statin therapy in patients with acute ischemic stroke: ASSORT Trial (Administration of Statin on Acute Ischemic Stroke Patient). *Stroke*. 2017;48:3057–3063. doi: 10.1161/STROKEAHA.117.017623
391. Rigotti NA, Clair C, Munafo MR, Stead LF. Interventions for smoking cessation in hospitalised patients. *Cochrane Database Syst Rev*. 2012:CD001837.
392. Lee MJ, Park E, Kim HC, Lee HS, Cha MJ, Kim YD, Heo JH, Nam HS. Timely interventions can increase smoking cessation rate in men with ischemic stroke. *J Korean Acad Nurs*. 2016;46:610–617. doi: 10.4040/jkan.2016.46.4.610
393. Eisenberg MJ, Windle SB, Roy N, Old W, Grondin FR, Bata I, Iskander A, Lauzon C, Srivastava N, Clarke A, et al; EVITA Investigators. Varenicline for smoking cessation in hospitalized patients with acute coronary syndrome. *Circulation*. 2016;133:21–30. doi: 10.1161/CIRCULATIONAHA.115.019634
394. Schwartz J, Dreyer RP, Murugiah K, Ranasinghe I. Contemporary pre-hospital emergency medical services response times for suspected stroke in the United States. *Prehosp Emerg Care*. 2016;20:560–565. doi: 10.3109/10903127.2016.1139219
395. Boden-Albala B, Stillman J, Roberts ET, Quarles LW, Glymour MM, Chong J, Moats H, Torrico V, Parides MC. Comparison of acute stroke preparedness strategies to decrease emergency department arrival time in a multiethnic cohort: the Stroke Warning Information and Faster Treatment Study. *Stroke*. 2015;46:1806–1812. doi: 10.1161/STROKEAHA.114.008502
396. Morgenstern LB, Gonzales NR, Maddox KE, Brown DL, Karim AP, Espinosa N, Moyé LA, Pary JK, Grotta JC, Lisabeth LD, et al. A randomized, controlled trial to teach middle school children to recognize stroke and call 911: the Kids Identifying and Defeating Stroke project. *Stroke*. 2007;38:2972–2978. doi: 10.1161/STROKEAHA.107.490078
397. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field: prospective validation of the Los Angeles Prehospital Stroke Screen (LAPSS). *Stroke*. 2000;31:71–76. doi: 10.1161/01.str.31.1.71
398. Bray JE, Martin J, Cooper G, Barger B, Bernard S, Bladin C. Paramedic identification of stroke: community validation of the Melbourne Ambulance Stroke Screen. *Cerebrovasc Dis*. 2005;20:28–33. doi: 10.1159/000086201
399. Studnek JR, Asimos A, Dodds J, Swanson D. Assessing the validity of the Cincinnati Prehospital Stroke Scale and the Medic Prehospital Assessment for Code Stroke in an urban emergency medical services agency. *Prehosp Emerg Care*. 2013;17:348–353. doi: 10.3109/10903127.2013.773113
400. Chenkin J, Gladstone DJ, Verbeek PR, Lindsay P, Fang J, Black SE, Morrison L. Predictive value of the Ontario prehospital stroke screening tool for the identification of patients with acute stroke. *Prehosp Emerg Care*. 2009;13:153–159. doi: 10.1080/10903120802706146
401. Asimos AW, Ward S, Brice JH, Rosamond WD, Goldstein LB, Studnek J. Out-of-hospital stroke screen accuracy in a state with an emergency medical services protocol for routing patients to acute stroke centers. *Ann Emerg Med*. 2014;64:509–515. doi: 10.1016/j.annemergmed.2014.03.024
402. Pickham D, Valdez A, Demeestere J, Lemmens R, Diaz L, Hopper S, de la Cuesta K, Rackover F, Miller K, Lansberg MG. Prognostic value of BEFAST vs. FAST to identify stroke in a prehospital setting. *Prehosp Emerg Care*. 2019;23:195–200. doi: 10.1080/10903127.2018.1490837
403. van Wijngaarden JD, Dirks M, Niessen LW, Huijsman R, Dippel DW. Do centres with well-developed protocols, training and infrastructure have higher rates of thrombolysis for acute ischaemic stroke? *QJM*. 2011;104:785–791. doi: 10.1093/qjmed/hcr075
404. Jeng JS, Tang SC, Deng IC, Tsai LK, Yeh SJ, Yip PK. Stroke center characteristics which influence the administration of thrombolytic therapy for acute ischemic stroke: a national survey of stroke centers in Taiwan. *J Neurol Sci*. 2009;281:24–27. doi: 10.1016/j.jns.2009.03.004
405. Douglas VC, Tong DC, Gillum LA, Zhao S, Brass LM, Dostal J, Johnston SC. Do the Brain Attack Coalition's criteria for stroke centers improve care for ischemic stroke? *Neurology*. 2005;64:422–427. doi: 10.1212/01.WNL.0000150903.38639.E1
406. Asimos AW, Norton HJ, Price MF, Cheek WM. Therapeutic yield and outcomes of a community teaching hospital code stroke protocol. *Acad Emerg Med*. 2004;11:361–370. doi: 10.1197/jaem.2003.12.016
407. Sauser K, Levine M, Nickles AV, Reeves MJ. Hospital variation in thrombolysis times among patients with acute ischemic stroke: the contributions of door-to-imaging time and imaging-to-needle time. *JAMA Neurol*. 2014;71:1155–1161. doi: 10.1001/jamaneurol.2014.1528
408. Demaerschalk BM, Bobrow BJ, Raman R, Kiernan TE, Aguilar MI, Ingall TJ, Dodick DW, Ward MP, Richemont PC, Brazdys K, et al; for the STRoke DOC AZ TIME Investigators. Stroke team remote evaluation using a digital observation camera in Arizona: the initial Mayo Clinic experience trial. *Stroke*. 2010;41:1251–1258. doi: 10.1161/STROKEAHA.109.574509
409. Meyer BC, Raman R, Hemmen T, Obler R, Zivin JA, Rao R, Thomas RG, Lyden PD. Efficacy of site-independent telemedicine in the STRoke DOC trial: a randomised, blinded, prospective study. *Lancet Neurol*. 2008;7:787–795. doi: 10.1016/S1474-4422(08)70171-6
410. Rai AT, Smith MS, Boo S, Tarabishy AR, Hobbs GR, Carpenter JS. The “pit-crew” model for improving door-to-needle times in endovascular stroke therapy: a Six-Sigma project. *J Neurointerv Surg*. 2016;8:447–452. doi: 10.1136/neurintsurg-2015-012219
411. Muir KW, Ford GA, Messow CM, Ford I, Murray A, Clifton A, Brown MM, Madigan J, Lenthall R, Robertson F, et al; PISTE Investigators. Endovascular therapy for acute ischaemic stroke: the Pragmatic Ischaemic Stroke Thrombectomy Evaluation (PISTE) randomised, controlled trial. *J Neurol Neurosurg Psychiatry*. 2017;88:38–44. doi: 10.1136/jnnp-2016-314117
412. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, Frei D, Shownkeen H, Budzik R, Ajani ZA, et al; THERAPY Trial Investigators. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. *Stroke*. 2016;47:2331–2338. doi: 10.1161/STROKEAHA.116.013372
413. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, et al; Interventional Management of Stroke (IMS) III Investigators. Endovascular therapy after intravenous t-PA versus t-PA alone for stroke. *N Engl J Med*. 2013;368:893–903. doi: 10.1056/NEJMoa1214300
414. Ciccone A, Valvassori L, Nichelatti M, Sgoifo A, Ponzio M, Sterzi R, Boccardi E; SYNTHESIS Expansion Investigators. Endovascular treatment for acute ischemic stroke. *N Engl J Med*. 2013;368:904–913. doi: 10.1056/NEJMoa1213701

415. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer BC, Olson S, Schwamm LH, et al; MR RESCUE Investigators. A trial of imaging selection and endovascular treatment for ischemic stroke. *N Engl J Med*. 2013;368:914–923. doi: 10.1056/NEJMoa1212793
416. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, Liebeskind DS, Smith WS; TREVO 2 Trialists. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial. *Lancet*. 2012;380:1231–1240. doi: 10.1016/S0140-6736(12)61299-9
417. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, Clark W, Budzik R, Zaidat OO; SWIFT Trialists. Solitaire flow restoration device versus the Merci retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet*. 2012;380:1241–1249. doi: 10.1016/S0140-6736(12)61384-1
418. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, Miyamoto S, Sasaki M, Inoue T; for the MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. *Stroke*. 2007;38:2633–2639. doi: 10.1161/STROKEAHA.107.488551
419. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, et al. Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial: Prolyse in Acute Cerebral Thromboembolism. *JAMA*. 1999;282:2003–2011. doi: 10.1001/jama.282.21.2003
420. Brazzelli M, Sandercock PA, Chappell FM, Celani MG, Righetti E, Arestis N, Wardlaw JM, Deeks JJ. Magnetic resonance imaging versus computed tomography for detection of acute vascular lesions in patients presenting with stroke symptoms. *Cochrane Database Syst Rev*. 2009;CD007424.
421. Wardlaw JM, Carpenter T, Sakka E, Mair G, Cohen G, Shuler K, Palmer JM, Innes K, Sandercock PA. Imaging perfusion deficits, arterial patency and thrombolysis safety and efficacy in acute ischaemic stroke An observational study of the effect of advanced imaging methods in the Third International Stroke Trial (IST-3), a randomised controlled trial. In: *Efficacy and Mechanism Evaluation, No. 1.1*. Southampton, UK: NIHR Journals Library; 2014.
422. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, et al; EPITHET Investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol*. 2008;7:299–309. doi: 10.1016/S1474-4422(08)70044-9
423. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W; DEDAS Investigators. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke*. 2006;37:1227–1231. doi: 10.1161/01.STR.0000217403.66996.6d
424. Clark WM, Albers GW, Madden KP, Hamilton S. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study: Thrombolytic Therapy in Acute Ischemic Stroke Study Investigators. *Stroke*. 2000;31:811–816. doi: 10.1161/01.str.31.4.811
425. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS Study: a randomized controlled trial: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA*. 1999;282:2019–2026. doi: 10.1001/jama.282.21.2019
426. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II): Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251. doi: 10.1016/s0140-6736(98)08020-9
427. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne MH. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–1025.
428. Seet RC, Rabinstein AA. Symptomatic intracranial hemorrhage following intravenous thrombolysis for acute ischemic stroke: a critical review of case definitions. *Cerebrovasc Dis*. 2012;34:106–114. doi: 10.1159/000339675
429. Ali K, Warusevitane A, Lally F, Sim J, Sills S, Pountain S, Nevatte T, Allen M, Roffe C. The Stroke Oxygen Pilot Study: a randomized controlled trial of the effects of routine oxygen supplementation early after acute stroke: effect on key outcomes at six months. *PLoS One*. 2014;8:e59274. doi: 10.1371/journal.pone.0059274
430. Singhal A, Partners SPOTRIAS Investigators. A phase IIB clinical trial of normobaric oxygen therapy (NBO) in acute ischemic stroke (AIS) (S02.001). *Neurology*. 2013;80(suppl):S02.001.
431. Roffe C, Ali K, Warusevitane A, Sills S, Pountain S, Allen M, Hodsoll J, Lally F, Jones P, Crome P. The SOS pilot study: a RCT of routine oxygen supplementation early after acute stroke: effect on recovery of neurological function at one week. *PLoS One*. 2011;6:e19113. doi: 10.1371/journal.pone.0019113
432. Roffe C, Sills S, Pountain SJ, Allen M. A randomized controlled trial of the effect of fixed-dose routine nocturnal oxygen supplementation on oxygen saturation in patients with acute stroke. *J Stroke Cerebrovasc Dis*. 2010;19:29–35. doi: 10.1016/j.jstrokecerebrovasdis.2009.02.008
433. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, Buonanno FS, Gonzalez RG, Sorensen AG. A pilot study of normobaric oxygen therapy in acute ischemic stroke. *Stroke*. 2005;36:797–802. doi: 10.1161/01.STR.0000158914.66827.2e
434. Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033–2037. doi: 10.1161/01.str.30.10.2033
435. Adelman EE, Scott PA, Skolarus LE, Fox AK, Frederiksen SM, Meurer WJ. Protocol deviations before and after treatment with intravenous tissue plasminogen activator in community hospitals. *J Stroke Cerebrovasc Dis*. 2016;25:67–73. doi: 10.1016/j.jstrokecerebrovasdis.2015.08.036
436. Kodankandath TV, Shaji J, Kohn N, Arora R, Salamon E, Libman RB, Katz JM. Poor hypertension control and longer transport times are associated with worse outcome in drip-and-ship stroke patients. *J Stroke Cerebrovasc Dis*. 2016;25:1887–1890. doi: 10.1016/j.jstrokecerebrovasdis.2016.04.013
437. Lysterly MJ, Albright KC, Boehme AK, Bavarsad Shahripour R, Houston JT, Rawal PV, Kapoor N, Alvi M, Sisson A, Alexandrov AW, et al. Safety of protocol violations in acute stroke tPA administration. *J Stroke Cerebrovasc Dis*. 2014;23:855–860. doi: 10.1016/j.jstrokecerebrovasdis.2013.07.019
438. Kellert L, Rocco A, Sykora M, Hacke W, Ringleb PA. Frequency of increased blood pressure levels during systemic thrombolysis and risk of intracerebral hemorrhage. *Stroke*. 2011;42:1702–1706. doi: 10.1161/STROKEAHA.110.604744
439. Karaszewski B, Thomas RG, Dennis MS, Wardlaw JM. Temporal profile of body temperature in acute ischemic stroke: relation to stroke severity and outcome. *BMC Neurol*. 2012;12:123. doi: 10.1186/1471-2377-12-123
440. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ, Dippel DW. An early rise in body temperature is related to unfavorable outcome after stroke: data from the PAIS study. *J Neurol*. 2011;258:302–307. doi: 10.1007/s00415-010-5756-4
441. Broessner G, Beer R, Lackner P, Helbok R, Fischer M, Pfaußler B, Rhoer J, Küppers-Tiedt L, Schneider D, Schmutzhard E. Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: bicenter prospective, randomized trial. *Stroke*. 2009;40:e657–e665. doi: 10.1161/STROKEAHA.109.557652
442. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ, Dippel DW; PAIS Investigators. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet Neurol*. 2009;8:434–440. doi: 10.1016/S1474-4422(09)70051-1
443. Horn CM, Sun CH, Nogueira RG, Patel VN, Krishnan A, Glenn BA, Belagaje SR, Thomas TT, Anderson AM, Frankel MR, et al. Endovascular Reperfusion and Cooling in Cerebral Acute Ischemia (ReCLAIM I). *J Neurointerv Surg*. 2014;6:91–95. doi: 10.1136/neurintsurg-2013-010656
444. Su Y, Fan L, Zhang Y, Zhang Y, Ye H, Gao D, Chen W, Liu G. Improved neurological outcome with mild hyperthermia in surviving patients with massive cerebral hemispheric infarction. *Stroke*. 2016;47:457–463. doi: 10.1161/STROKEAHA.115.009789
445. Hong JM, Lee JS, Song HJ, Jeong HS, Jung HS, Choi HA, Lee K. Therapeutic hyperthermia after recanalization in patients with acute ischemic stroke. *Stroke*. 2014;45:134–140. doi: 10.1161/STROKEAHA.113.003143
446. Ovesen C, Brizzi M, Pott FC, Thorsen-Meyer HC, Karlsson T, Ersson A, Christensen H, Norrlin A, Meden P, Krieger DW, et al. Feasibility of endovascular and surface cooling strategies in acute stroke. *Acta Neurol Scand*. 2013;127:399–405. doi: 10.1111/ane.12059
447. Li W, Lin L, Zhang M, Wu Y, Liu C, Li X, Huang S, Liang C, Wang Y, Chen J, et al. Safety and preliminary efficacy of early tirofiban treatment after alteplase in acute ischemic stroke patients. *Stroke*. 2016;47:2649–2651. doi: 10.1161/STROKEAHA.116.014413

448. Wada T, Yasunaga H, Horiguchi H, Fushimi K, Matsubara T, Nakajima S, Yahagi N. Ozagrel for patients with noncardioembolic ischemic stroke: a propensity score-matched analysis. *J Stroke Cerebrovasc Dis.* 2016;25:2828–2837. doi: 10.1016/j.jstrokecerebrovasdis.2016.07.044
449. Mori E, Minematsu K, Nakagawara J, Hasegawa Y, Nagahiro S, Okada Y, Truelsen T, Lindsten A, Ogawa A, Yamaguchi T; on behalf of the DIAS-J Investigators. Safety and tolerability of desmoteplase within 3 to 9 hours after symptoms onset in Japanese patients with ischemic stroke. *Stroke.* 2015;46:2549–2554. doi: 10.1161/STROKEAHA.115.009917
450. Multicenter Acute Stroke Trial—Europe Study Group, Hommel M, Cornu C, Boutitie F, Boissel JP. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med.* 1996;335:145–150. doi: 10.1056/NEJM199607183350301
451. Multicentre Acute Stroke Trial—Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet.* 1995;346:1509–1514.
452. Coutinho JM, Liebeskind DS, Slater LA, Nogueira RG, Clark W, Davalos A, Bonafe A, Jahan R, Fischer U, Gralla J, et al. Combined intravenous thrombolysis and thrombectomy vs thrombectomy alone for acute ischemic stroke: a pooled analysis of the SWIFT and STAR studies. *JAMA Neurol.* 2017;74:268–274. doi: 10.1001/jamaneurol.2016.5374
453. Grech R, Pullicino R, Thornton J, Downer J. An efficacy and safety comparison between different stentriever designs in acute ischaemic stroke: a systematic review and meta-analysis. *Clin Radiol.* 2016;71:48–57. doi: 10.1016/j.crad.2015.09.011
454. Rodrigues FB, Neves JB, Caldeira D, Ferro JM, Ferreira JJ, Costa J. Endovascular treatment versus medical care alone for ischaemic stroke: systematic review and meta-analysis. *BMJ.* 2016;353:i1754. doi: 10.1136/bmj.i1754
455. Touma L, Filion KB, Sterling LH, Atallah R, Windle SB, Eisenberg MJ. Stent retrievers for the treatment of acute ischemic stroke: a systematic review and meta-analysis of randomized clinical trials. *JAMA Neurol.* 2016;73:275–281. doi: 10.1001/jamaneurol.2015.4441
456. Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhfar F, Spears J, Kulkarni AV, Singh S, Alqattani A, Rochwerger B, et al. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA.* 2015;314:1832–1843. doi: 10.1001/jama.2015.13767
457. Chen CJ, Ding D, Starke RM, Mehndiratta P, Crowley RW, Liu KC, Southerland AM, Worrall BB. Endovascular vs medical management of acute ischemic stroke. *Neurology.* 2015;85:1980–1990. doi: 10.1212/WNL.0000000000002176
458. Elgendy IY, Kumbhani DJ, Mahmoud A, Bhatt DL, Bavry AA. Mechanical Thrombectomy for acute ischemic stroke: a meta-analysis of randomized trials. *J Am Coll Cardiol.* 2015;66:2498–2505. doi: 10.1016/j.jacc.2015.09.070
459. Fargen KM, Neal D, Fiorella DJ, Turk AS, Froehler M, Mocco J. A meta-analysis of prospective randomized controlled trials evaluating endovascular therapies for acute ischemic stroke. *J Neurointerv Surg.* 2015;7:84–89. doi: 10.1136/neurintsurg-2014-011543
460. Kumar G, Shahripour RB, Alexandrov AV. Recanalization of acute basilar artery occlusion improves outcomes: a meta-analysis. *J Neurointerv Surg.* 2015;7:868–874. doi: 10.1136/neurintsurg-2014-011418
461. Marmagkiolis K, Hakeem A, Cilingiroglu M, Gundogdu B, Iliescu C, Tsilakidou D, Katramados A. Safety and efficacy of stent retrievers for the management of acute ischemic stroke: comprehensive review and meta-analysis. *JACC Cardiovasc Interv.* 2015;8:1758–1765. doi: 10.1016/j.jcin.2015.07.021
462. Yarbrough CK, Ong CJ, Beyer AB, Lipsey K, Derdeyn CP. Endovascular thrombectomy for anterior circulation stroke: systematic review and meta-analysis. *Stroke.* 2015;46:3177–3183. doi: 10.1161/STROKEAHA.115.009847
463. Almekhlafi MA, Menon BK, Freiheit EA, Demchuk AM, Goyal M. A meta-analysis of observational intra-arterial stroke therapy studies using the Merci device, Penumbra system, and retrievable stents. *AJNR Am J Neuroradiol.* 2013;34:140–145. doi: 10.3174/ajnr.A3276
464. Fields JD, Khatri P, Nesbit GM, Liu KC, Barnwell SL, Lutsep HL, Clark WM, Lansberg MG. Meta-analysis of randomized intra-arterial thrombolytic trials for the treatment of acute stroke due to middle cerebral artery occlusion. *J Neurointerv Surg.* 2011;3:151–155. doi: 10.1136/jnis.2010.002766
465. Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, Sundeman H, Dunker D, Schnabel K, Wikholm G, Hellström M, et al. General anesthesia versus conscious sedation for endovascular treatment of acute ischemic stroke: the AnStroke trial (Anesthesia During Stroke). *Stroke.* 2017;48:1601–1607. doi: 10.1161/STROKEAHA.117.016554
466. Brinjikji W, Murad MH, Rabinstein AA, Cloft HJ, Lanzino G, Kallmes DF. Conscious sedation versus general anesthesia during endovascular acute ischemic stroke treatment: a systematic review and meta-analysis. *AJNR Am J Neuroradiol.* 2015;36:525–529. doi: 10.3174/ajnr.A4159
467. Wada T, Yasunaga H, Horiguchi H, Matsubara T, Fushimi K, Nakajima S, Yahagi N. Outcomes of argatroban treatment in patients with atherothrombotic stroke: observational nationwide study in Japan. *Stroke.* 2016;47:471–476. doi: 10.1161/STROKEAHA.115.011250
468. Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2008:CD000024.
469. Wang Q, Chen C, Chen XY, Han JH, Soo Y, Leung TW, Mok V, Wong KS. Low-molecular-weight heparin and early neurologic deterioration in acute stroke caused by large artery occlusive disease. *Arch Neurol.* 2012;69:1454–1460. doi: 10.1001/archneurol.2012.1633
470. Wang QS, Chen C, Chen XY, Han JH, Soo Y, Leung TW, Mok V, Wong KS. Low-molecular-weight heparin versus aspirin for acute ischemic stroke with large artery occlusive disease: subgroup analyses from the Fraxiparin in Stroke Study for the treatment of ischemic stroke (FISS-tris) study. *Stroke.* 2012;43:346–349. doi: 10.1161/STROKEAHA.111.628347
471. Abdul-Rahim AH, Fulton RL, Frank B, Tatlisumak T, Paciaroni M, Caso V, Diener HC, Lees KR; VISTA Collaborators. Association of improved outcome in acute ischaemic stroke patients with atrial fibrillation who receive early antithrombotic therapy: analysis from VISTA. *Eur J Neurol.* 2015;22:1048–1055. doi: 10.1111/ene.12577
472. Jensen J, Salottolo K, Frei D, Loy D, McCarthy K, Wagner J, Whaley M, Bellon R, Bar-Or D. Comprehensive analysis of intra-arterial treatment for acute ischemic stroke due to cervical artery dissection. *J Neurointerv Surg.* 2017;9:654–658. doi: 10.1136/neurintsurg-2016-012421
473. Deleted in proof.
474. Seedat J, Penn C. Implementing oral care to reduce aspiration pneumonia amongst patients with dysphagia in a South African setting. *S Afr J Commun Disord.* 2016;63. doi: 10.4102/sajcd.v63i1.102
475. Geeganage CM, Sprigg N, Bath MW, Bath PM. Balance of symptomatic pulmonary embolism and symptomatic intracerebral hemorrhage with low-dose anticoagulation in recent ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. *J Stroke Cerebrovasc Dis.* 2013;22:1018–1027. doi: 10.1016/j.jstrokecerebrovasdis.2012.03.005
476. Qaseem A, Chou R, Humphrey LL, Starkey M, Shekelle P; Clinical Guidelines Committee of the American College of Physicians. Venous thromboembolism prophylaxis in hospitalized patients: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2011;155:625–632. doi: 10.7326/0003-4819-155-9-20111010-00011
477. Wang SB, Wang YY, Zhang QE, Wu SL, Ng CH, Ungvari GS, Chen L, Wang CX, Jia FJ, Xiang YT. Cognitive behavioral therapy for post-stroke depression: a meta-analysis. *J Affect Disord.* 2018;235:589–596. doi: 10.1016/j.jad.2018.04.011
478. Qin B, Chen H, Gao W, Zhao LB, Zhao MJ, Qin HX, Chen W, Chen L, Yang MX. Efficacy, acceptability, and tolerability of antidepressant treatments for patients with post-stroke depression: a network meta-analysis. *Braz J Med Biol Res.* 2018;51:e7218. doi: 10.1590/1414-431x20187218
479. Cui M, Huang CY, Wang F. Efficacy and safety of citalopram for the treatment of poststroke depression: a meta-analysis. *J Stroke Cerebrovasc Dis.* 2018;27:2905–2918. doi: 10.1016/j.jstrokecerebrovasdis.2018.07.027
480. Deng L, Qiu S, Yang Y, Wang L, Li Y, Lin J, Wei Q, Yang L, Wang D, Liu M. Efficacy and tolerability of pharmacotherapy for post-stroke depression: a network meta-analysis. *Oncotarget.* 2018;9:23718–23728. doi: 10.18632/oncotarget.23891
481. Sun Y, Liang Y, Jiao Y, Lin J, Qu H, Xu J, Zhao C. Comparative efficacy and acceptability of antidepressant treatment in poststroke depression: a multiple-treatments meta-analysis. *BMJ Open.* 2017;7:e016499. doi: 10.1136/bmjopen-2017-016499
482. Deng L, Sun X, Qiu S, Xiong Y, Li Y, Wang L, Wei Q, Wang D, Liu M. Interventions for management of post-stroke depression: a bayesian network meta-analysis of 23 randomized controlled trials. *Sci Rep.* 2017;7:16466. doi: 10.1038/s41598-017-16663-0
483. Shen X, Liu M, Cheng Y, Jia C, Pan X, Gou Q, Liu X, Cao H, Zhang L. Repetitive transcranial magnetic stimulation for the treatment of post-stroke depression: a systematic review and meta-analysis of randomized controlled clinical trials. *J Affect Disord.* 2017;211:65–74. doi: 10.1016/j.jad.2016.12.058
484. Xu XM, Zou DZ, Shen LY, Liu Y, Zhou XY, Pu JC, Dong MX, Wei YD. Efficacy and feasibility of antidepressant treatment in patients with post-stroke depression. *Medicine (Baltimore).* 2016;95:e5349. doi: 10.1097/MD.00000000000005349

485. Tan S, Huang X, Ding L, Hong H. Efficacy and safety of citalopram in treating post-stroke depression: a meta-analysis. *Eur Neurol*. 2015;74:188–201. doi: 10.1159/000441446
486. Hackett ML, Anderson CS, House A, Xia J. Interventions for treating depression after stroke. *Cochrane Database Syst Rev*. 2008;CD003437.
487. Herisson F, Godard S, Volteau C, Le Blanc E, Guillon B, Gaudron M; SEVEL Study Group. Early Sitting in Ischemic Stroke Patients (SEVEL): a randomized controlled trial. *PLoS One*. 2016;11:e0149466. doi: 10.1371/journal.pone.0149466
488. Morreale M, Marchione P, Pili A, Lauta A, Castiglia SF, Spallone A, Pierelli F, Giacomini P. Early versus delayed rehabilitation treatment in hemiplegic patients with ischemic stroke: proprioceptive or cognitive approach? *Eur J Phys Rehabil Med*. 2016;52:81–89.
489. Meenan RT, Saha S, Chou R, Swartztrauber K, Pyle Krages K, O'Keefe-Rosetti MC, McDonagh M, Chan BK, Hornbrook MC, Helfand M. Cost-effectiveness of echocardiography to identify intracardiac thrombus among patients with first stroke or transient ischemic attack. *Med Decis Making*. 2007;27:161–177. doi: 10.1177/0272989X06297388
490. McNamara RL, Lima JA, Whelton PK, Powe NR. Echocardiographic identification of cardiovascular sources of emboli to guide clinical management of stroke: a cost-effectiveness analysis. *Ann Intern Med*. 1997;127:775–787. doi: 10.7326/0003-4819-127-9-199711010-00001
491. Shariat A, Yaghoubi E, Farazdaghi M, Aghasadeghi K, Borhani Haghighi A. Comparison of medical treatments in cryptogenic stroke patients with patent foramen ovale: a randomized clinical trial. *J Res Med Sci*. 2013;18:94–98.
492. Homma S, Sacco RL, Di Tullio MR, Sciacca RR, Mohr JP; for the PFO in Cryptogenic Stroke Study (PICSS) Investigators. Effect of medical treatment in stroke patients with patent foramen ovale: Patent Foramen Ovale in Cryptogenic Stroke Study. *Circulation*. 2002;105:2625–2631. doi: 10.1161/01.cir.0000017498.88393.44
493. Ma Y, Li D, Bai F, Qin F, Li J, Li Y, Liu N, Xie H, Zhou S, Liu Q. Patent foramen ovale closure or medical therapy for secondary prevention of cryptogenic stroke: an update meta-analysis of randomized controlled trials. *Medicine (Baltimore)*. 2018;97:e11965. doi: 10.1097/MD.00000000000011965
494. Schulze V, Lin Y, Karathanos A, Brockmeyer M, Zeus T, Polzin A, Perings S, Kelm M, Wolff G. Patent foramen ovale closure or medical therapy for cryptogenic ischemic stroke: an updated meta-analysis of randomized controlled trials. *Clin Res Cardiol*. 2018;107:745–755. doi: 10.1007/s00392-018-1224-4
495. Fiorelli EM, Carandini T, Gagliardi D, Bozzano V, Bonzi M, Tobaldini E, Comi GP, Scarpini EA, Montano N, Solbiati M. Secondary prevention of cryptogenic stroke in patients with patent foramen ovale: a systematic review and meta-analysis. *Intern Emerg Med*. 2018;13:1287–1303. doi: 10.1007/s11739-018-1909-8
496. Xu HB, Zhang H, Qin Y, Xue F, Xiong G, Yang L, Bai H, Wu J. Patent foramen ovale closure versus medical therapy for cryptogenic stroke: An updated meta-analysis. *J Neurol Sci*. 2018;390:139–149. doi: 10.1016/j.jns.2018.04.029
497. Tsvigoulis G, Katsanos AH, Mavridis D, Frogoudaki A, Vrettou AR, Ikonomidis I, Parissis J, Deftereos S, Karapanayiotides T, Palaiodimos L, et al. Percutaneous patent foramen ovale closure for secondary stroke prevention: network meta-analysis. *Neurology*. 2018;91:e8–e18. doi: 10.1212/WNL.0000000000005739
498. Ahmad Y, Howard JP, Arnold A, Shin MS, Cook C, Petraco R, Demir O, Williams L, Iglesias JF, Sutaria N, et al. Patent foramen ovale closure vs. medical therapy for cryptogenic stroke: a meta-analysis of randomized controlled trials. *Eur Heart J*. 2018;39:1638–1649. doi: 10.1093/eurheartj/ehy121
499. Riaz H, Khan MS, Schenone AL, Waheed AA, Khan AR, Krasuski RA. Transcatheter closure of patent foramen ovale following cryptogenic stroke: an updated meta-analysis of randomized controlled trials. *Am Heart J*. 2018;199:44–50. doi: 10.1016/j.ahj.2018.01.008
500. Shah R, Nayyar M, Jovin IS, Rashid A, Bondy BR, Fan TM, Flaherty MP, Rao SV. Device closure versus medical therapy alone for patent foramen ovale in patients with cryptogenic stroke: a systematic review and meta-analysis. *Ann Intern Med*. 2018;168:335–342. doi: 10.7326/M17-2679
501. De Rosa S, Sievert H, Sabatino J, Polimeni A, Sorrentino S, Indolfi C. Percutaneous closure versus medical treatment in stroke patients with patent foramen ovale: a systematic review and meta-analysis. *Ann Intern Med*. 2018;168:343–350. doi: 10.7326/M17-3033
502. Zhang XL, Kang LN, Wang L, Xu B. Percutaneous closure versus medical therapy for stroke with patent foramen ovale: a systematic review and meta-analysis. *BMC Cardiovasc Disord*. 2018;18:45. doi: 10.1186/s12872-018-0780-x
503. Palaiodimos L, Kokkinidis DG, Faillace RT, Foley TR, Dargas GD, Price MJ, Mastoris I. Percutaneous closure of patent foramen ovale vs. medical treatment for patients with history of cryptogenic stroke: a systematic review and meta-analysis of randomized controlled trials. *Cardiovasc Revasc Med*. 2018;19(pt B):852–858. doi: 10.1016/j.carrev.2018.02.014
504. Ando T, Holmes AA, Pahuja M, Javed A, Briasoulis A, Telila T, Takagi H, Schreiber T, Afonso L, Grines CL, et al. Meta-analysis comparing patent foramen ovale closure versus medical therapy to prevent recurrent cryptogenic stroke. *Am J Cardiol*. 2018;121:649–655. doi: 10.1016/j.amjcard.2017.11.037
505. Lattanzi S, Brigo F, Cagnetti C, Di Napoli M, Silvestrini M. Patent foramen ovale and cryptogenic stroke or transient ischemic attack: to close or not to close? A systematic review and meta-analysis. *Cerebrovasc Dis*. 2018;45:193–203. doi: 10.1159/000488401
506. Higgins JP, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA; Cochrane Bias Methods Group; Cochrane Statistical Methods Group. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;343:d5928. doi: 10.1136/bmj.d5928
507. Johansson E, Cuadrado-Godia E, Hayden D, Bjellerup J, Ois A, Roquer J, Wester P, Kelly PJ. Recurrent stroke in symptomatic carotid stenosis awaiting revascularization: a pooled analysis. *Neurology*. 2016;86:498–504. doi: 10.1212/WNL.0000000000002354
508. Bazan HA, Zea N, Jennings B, Smith TA, Vidal G, Sternbergh WC 3rd. Urgent carotid intervention is safe after thrombolysis for minor to moderate acute ischemic stroke. *J Vasc Surg*. 2015;62:1529–1538. doi: 10.1016/j.jvs.2015.07.082
509. Chisci E, Pigozzi C, Troisi N, Tramacere L, Zaccara G, Cincotta M, Ercolini L, Michelagnoli S. Thirty-day neurologic improvement associated with early versus delayed carotid endarterectomy in symptomatic patients. *Ann Vasc Surg*. 2015;29:435–442. doi: 10.1016/j.avsg.2014.08.028
510. Devlin TG, Phade SV, Hutson RK, Fugate MW, Major GR 2nd, Albers GW, Sirelkhatim AA, Sapkota BL, Quartford SD, Baxter BW. Computed tomography perfusion imaging in the selection of acute stroke patients to undergo emergent carotid endarterectomy. *Ann Vasc Surg*. 2015;29:125.e1–125.11. doi: 10.1016/j.avsg.2014.07.023
511. Steglich-Arnholm H, Holtmannspötter M, Kondziella D, Wagner A, Stavngaard T, Cronqvist ME, Hansen K, Højgaard J, Taudorf S, Krieger DW. Thrombectomy assisted by carotid stenting in acute ischemic stroke management: benefits and harms. *J Neurol*. 2015;262:2668–2675. doi: 10.1007/s00415-015-7895-0
512. Ferrero E, Ferri M, Viazzo A, Labate C, Berardi G, Pecchio A, Piazza S, Ripepi M, Nessi F. A retrospective study on early carotid endarterectomy within 48 hours after transient ischemic attack and stroke in evolution. *Ann Vasc Surg*. 2014;28:227–238. doi: 10.1016/j.avsg.2013.02.015
513. Liu L, Wong KS, Leng X, Pu Y, Wang Y, Jing J, Zou X, Pan Y, Wang A, Meng X, et al; CHANCE Investigators. Dual antiplatelet therapy in stroke and ICAS: subgroup analysis of CHANCE. *Neurology*. 2015;85:1154–1162. doi: 10.1212/WNL.0000000000001972
514. Jung JM, Kang DW, Yu KH, Koo JS, Lee JH, Park JM, Hong KS, Cho YJ, Kim JS, Kwon SU; TOSS-2 Investigators. Predictors of recurrent stroke in patients with symptomatic intracranial arterial stenosis. *Stroke*. 2012;43:2785–2787. doi: 10.1161/STROKEAHA.112.659185
515. Coutts SB, Wein TH, Lindsay MP, Buck B, Cote R, Ellis P, Foley N, Hill MD, Jaspers S, Jin AY, et al; Heart and Stroke Foundation Canada Canadian Stroke Best Practices Advisory Committee. Canadian stroke best practice recommendations: secondary prevention of stroke guidelines, update 2014. *Int J Stroke*. 2015;10:282–291. doi: 10.1111/ijvs.12439
516. Lanza G, Ricci S, Setacci C, Castelli P, Novallil C, Pratesi C, Speziale F, Cremonesi A, Morlacchi E, Lanza J, et al. An update on Italian Stroke Organization guidelines on carotid endarterectomy and stenting. *Int J Stroke*. 2014;9(suppl A100):14–19. doi: 10.1111/ijvs.12226
517. Kakisis JD, Avgerinos ED, Antonopoulos CN, Giannakopoulos TG, Moulakakis K, Liapis CD. The European Society for Vascular Surgery guidelines for carotid intervention: an updated independent assessment and literature review. *Eur J Vasc Endovasc Surg*. 2012;44:238–243.
518. Paraskevas KI, Mikhailidis DP, Veith FJ. Comparison of the five 2011 guidelines for the treatment of carotid stenosis. *J Vasc Surg*. 2012;55:1504–1508.
519. Brott TG, Halperin JL, Abbara S, Bacharach JM, Barr JD, Bush RL, Cates CU, Creager MA, Fowler SB, Friday G, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice

- Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery [published correction appears in *Circulation*. 2011;124:e145]. *Circulation*. 2011;124:489–532. doi: 10.1161/CIR.0b013e31820d8d78
520. Ricotta JJ, Aburahma A, Ascher E, Eskandari M, Faries P, Lal BK; Society for Vascular Surgery. Updated Society for Vascular Surgery guidelines for management of extracranial carotid disease: executive summary. *J Vasc Surg*. 2011;54:832–836. doi: 10.1016/j.jvs.2011.07.004
 521. Carotid Stenting Guidelines Committee: an Intercollegiate Committee of the RACP, RACS AND RANZCR. Guidelines for patient selection and performance of carotid artery stenting. *Intern Med J*. 2011;41:344–347. doi: 10.1111/j.1445-5994.2011.02445.x
 522. Sheffet AJ, Roubin G, Howard G, Moore W, Meschia JF, Hobson RW 2nd, Brott TG. Design of the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST). *Int J Stroke*. 2010;5:40–46. doi: 10.1111/j.1747-4949.2009.00405.x
 523. Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, Hobson R, Kidwell CS, Koroshetz WJ, Mathews V, et al; on behalf of the American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. *Stroke*. 2009;40:3646–3678. doi: 10.1161/STROKEAHA.108.192616
 524. European Stroke Organisation Executive Committee and ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507. doi: 10.1159/000131083
 525. Masdeu JC, Irimia P, Asenbaum S, Bogousslavsky J, Brainin M, Chabriat H, Herholz K, Markus HS, Martinez-Vila E, Niederkorn K, et al; EFNS. EFNS guideline on neuroimaging in acute stroke: report of an EFNS task force. *Eur J Neurol*. 2006;13:1271–1283. doi: 10.1111/j.1468-1331.2006.01507.x
 526. Limone BL, Baker WL, Mearns ES, White CM, Kluger J, Coleman CI. Common flaws exist in published cost-effectiveness models of pharmacologic stroke prevention in atrial fibrillation. *J Clin Epidemiol*. 2014;67:1093–1102. doi: 10.1016/j.jclinepi.2014.05.013
 527. Higgins P, MacFarlane PW, Dawson J, McInnes GT, Langhorne P, Lees KR. Noninvasive cardiac event monitoring to detect atrial fibrillation after ischemic stroke: a randomized, controlled trial. *Stroke*. 2013;44:2525–2531. doi: 10.1161/STROKEAHA.113.001927
 528. Miles JA, Garber L, Ghosh S, Spevack DM. Association of transthoracic echocardiography findings and long-term outcomes in patients undergoing workup of stroke. *J Stroke Cerebrovasc Dis*. 2018;27:2943–2950. doi: 10.1016/j.jstrokecerebrovasdis.2018.06.023
 529. Haeusler KG, Wollboldt C, Bentheim LZ, Herm J, Jäger S, Kunze C, Eberle HC, Deluigi CC, Bruder O, Malsch C, et al. Feasibility and diagnostic value of cardiovascular magnetic resonance imaging after acute ischemic stroke of undetermined origin. *Stroke*. 2017;48:1241–1247. doi: 10.1161/STROKEAHA.116.016227
 530. Katsanos AH, Giannopoulos S, Frogoudaki A, Vrettou AR, Ikonomidis I, Paraskevaidis I, Zompola C, Vadikolias K, Boviatsis E, Parissis J, et al. The diagnostic yield of transesophageal echocardiography in patients with cryptogenic cerebral ischaemia: a meta-analysis. *Eur J Neurol*. 2016;23:569–579. doi: 10.1111/ene.12897
 531. Gaudron M, Bonnaud I, Ros A, Patat F, de Toffol B, Giraudeau B, Debiais S. Diagnostic and therapeutic value of echocardiography during the acute phase of ischemic stroke. *J Stroke Cerebrovasc Dis*. 2014;23:2105–2109. doi: 10.1016/j.jstrokecerebrovasdis.2014.03.018
 532. Kim SJ, Choe YH, Park SJ, Kim GM, Chung CS, Lee KH, Bang OY. Routine cardiac evaluation in patients with ischaemic stroke and absence of known atrial fibrillation or coronary heart disease: transthoracic echocardiography vs. multidetector cardiac computed tomography. *Eur J Neurol*. 2012;19:317–323. doi: 10.1111/j.1468-1331.2011.03505.x
 533. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, Marsh EE 3rd. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993;24:35–41. doi: 10.1161/01.str.24.1.35
 534. Galougahi KK, Stewart T, Choong CY, Storey CE, Yates M, Tofler GH. The utility of transoesophageal echocardiography to determine management in suspected embolic stroke. *Intern Med J*. 2010;40:813–818. doi: 10.1111/j.1445-5994.2009.02103.x
 535. Deleted in proof.
 536. de Bruijn SF, Agema WR, Lammers GJ, van der Wall EE, Wolterbeek R, Holman ER, Bollen EL, Bax JJ. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke*. 2006;37:2531–2534. doi: 10.1161/01.STR.0000241064.46659.69
 537. Harloff A, Handke M, Reinhard M, Geibel A, Hetzel A. Therapeutic strategies after examination by transesophageal echocardiography in 503 patients with ischemic stroke. *Stroke*. 2006;37:859–864. doi: 10.1161/01.STR.0000202592.87021.b7
 538. Abreu TT, Mateus S, Correia J. Therapy implications of transthoracic echocardiography in acute ischemic stroke patients. *Stroke*. 2005;36:1565–1566. doi: 10.1161/01.STR.0000170636.08554.49
 539. Vitebskiy S, Fox K, Hoit BD. Routine transesophageal echocardiography for the evaluation of cerebral emboli in elderly patients. *Echocardiography*. 2005;22:770–774. doi: 10.1111/j.1540-8175.2005.00079.x
 540. Kim JT, Park MS, Choi KH, Cho KH, Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, et al. Different antiplatelet strategies in patients with new ischemic stroke while taking aspirin. *Stroke*. 2016;47:128–134. doi: 10.1161/STROKEAHA.115.011595
 541. Lee M, Wu YL, Saver JL, Lee HC, Lee JD, Chang KC, Wu CY, Lee TH, Wang HH, Rao NM, et al. Is clopidogrel better than aspirin following breakthrough strokes while on aspirin? A retrospective cohort study. *BMJ Open*. 2014;4:e006672. doi: 10.1136/bmjopen-2014-006672
 542. Aronow HD, Novaro GM, Lauer MS, Brennan DM, Lincoff AM, Topol EJ, Kereiakes DJ, Nissen SE. In-hospital initiation of lipid-lowering therapy after coronary intervention as a predictor of long-term utilization: a propensity analysis. *Arch Intern Med*. 2003;163:2576–2582. doi: 10.1001/archinte.163.21.2576
 543. Stead LF, Koilpillai P, Fanshawe TR, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev*. 2016;3:CD008286. doi: 10.1002/14651858.CD008286.pub3
 544. Stead LF, Koilpillai P, Lancaster T. Additional behavioural support as an adjunct to pharmacotherapy for smoking cessation. *Cochrane Database Syst Rev*. 2015:CD009670. doi: 10.1002/14651858.CD009670.pub3