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

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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

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

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Background and Purpose—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. The intended audiences are prehospital care providers, physicians, allied health professionals, and hospital administrators. These guidelines supersede the 2013 guidelines and subsequent updates.

Methods—Members of the writing group were appointed by the American Heart Association Stroke Council's Scientific Statements Oversight Committee, representing various areas of medical expertise. Strict adherence to the American Heart Association conflict of interest policy was maintained. Members were not allowed to participate in discussions or to vote on topics relevant to their relations with industry. The members of the writing group unanimously approved all recommendations except when relations with industry precluded members voting. Prerelease review of the draft guideline was performed by 4 expert peer reviewers and by the members of the Stroke Council's Scientific Statements Oversight

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

This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on November 29, 2017, and the American Heart Association Executive Committee on December 11, 2017. A copy of the document is available at http://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.

Data Supplement 1 (Evidence Tables) is available with this article at http://stroke.ahajournals.org/lookup/suppl/doi:10.1161/STR.0000000000000158/-/DC1.

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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 http://professional.heart.org/statements. Select the "Guidelines & Statements" drop-down menu, then click "Publication Development."

Committee and Stroke Council Leadership Committee. These guidelines use the American College of Cardiology/American Heart Association 2015 Class of Recommendations and Levels of Evidence and the new American Heart Association guidelines format.

***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 are based on the best evidence currently available. In many instances, however, only limited data exist demonstrating the urgent need for continued research on treatment of acute ischemic stroke. **(*Stroke.* 2018;49:e46–e99. DOI: 10.1161/STR.0000000000000158.)**

Key Words: AHA Scientific Statements ■ secondary prevention ■ stroke ■ therapeutics

New high-quality evidence has produced major changes in the evidence-based treatment of patients with acute ischemic stroke (AIS) since the publication of the most recent "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 they 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 this guideline. The systematic reviews "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"[3] and "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"[4] are published in conjunction with this guideline.

These guidelines use the American College of Cardiology (ACC)/AHA 2015 Class of Recommendations (COR) and Levels of Evidence (LOE) (Table 1) and the new AHA guidelines format. 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. 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 group 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 relationships 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 relationships with industry precluded members voting. Prerelease review of the draft guideline 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.

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

CLASS I (STRONG) — **Benefit >>> Risk**

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

CLASS IIa (MODERATE) — **Benefit >> Risk**

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

CLASS IIb (WEAK) — **Benefit ≥ Risk**

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

CLASS III: No Benefit (MODERATE) — **Benefit = Risk**
(Generally, LOE A or B use only)

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

CLASS III: Harm (STRONG) — **Risk > Benefit**

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

LEVEL (QUALITY) OF EVIDENCE‡

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

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

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

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

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

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

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

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

Document Title	Publication Year	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
"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"[8]	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"[9]	2014	2014 Cerebral Edema
"Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association"[10]	2014	2014 Palliative Care
"Clinical Performance Measures for Adults Hospitalized With Acute Ischemic Stroke: Performance Measures for Healthcare Professionals From the American Heart Association/American Stroke Association"[12]	2014	N/A
"Part 15: First Aid: 2015 American Heart Association and American Red Cross Guidelines Update for First Aid"[13]	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"[14]	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"[15]	2015	2015 IV Alteplase
"Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association"[16]	2016	2016 Rehab Guidelines

ACC indicates American College of Cardiology; AHA, American Heart Association; AIS, acute ischemic stroke; CPR, cardiopulmonary resuscitation; ECC, emergency cardiovascular care; HRS, Heart Rhythm Society; IV, intravenous; and N/A, not applicable.

Table 3. Abbreviations in This Guideline

ACC	American College of Cardiology
AHA	American Heart Association
AIS	Acute ischemic stroke
ARD	Absolute risk difference
ASCVD	Atherosclerotic cardiovascular disease
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
BP	Blood pressure
CEA	Carotid endarterectomy
CeAD	Cervical artery dissection
CI	Confidence interval
CMB	Cerebral microbleed
COR	Class of recommendation
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
ICH	Intracerebral hemorrhage
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
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
RCT	Randomized clinical trial
RR	Relative risk
rtPA	recombinant tissue-type plasminogen activator
sICH	Symptomatic intracerebral hemorrhage
TIA	Transient ischemic attack
UFH	Unfractionated heparin

(*Continued*)

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-R	Recommendation revised from 2013 Stroke Systems of Care. COR and LOE added.
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.[17] 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.[18] Thus, stroke education campaigns should be designed in a targeted manner to optimize their effectiveness.[18]			See Tables I and II in online Data Supplement 1.
2. 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Emergency medical services (EMS) use by stroke patients has been independently associated with earlier emergency department (ED) arrival (onset-to-door time ≤3 hours; adjusted odds ratio [OR], 2.00; 95% confidence interval [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),[18] yet only ≈60% of all stroke patients use EMS.[19] Men, blacks, and Hispanics are less likely to use EMS.[17,19] 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.
3. To increase both the number of patients who are treated and the quality of care, educational stroke programs for physicians, hospital personnel, and EMS personnel are recommended.	I	B-NR	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
On 9-1-1 activation, EMS dispatch and clinical personnel should prioritize the potential stroke case, minimize on-scene times, and transport the patient as quickly as possible to the most appropriate hospital. A recent US-based analysis of EMS response times found that median EMS response time (9-1-1 call to ED arrival) in 184 179 cases in which EMS provider impression was stroke was 36 minutes (interquartile range, 28.7–48.0 minutes).[20] On-scene time (median, 15 minutes) was the largest component of this time, and longer times were noted for patients 65 to 74 years of age, whites, and women and in nonurban areas. Dispatch designation of stroke was associated with minimally faster response times (36.0 versus 36.7 minutes; $P<0.01$). Notably, only 52% of cases were identified by dispatch as stroke.			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 system by first aid providers, including EMS dispatch personnel, is recommended.	I	B-NR	Recommendation reworded for clarity from 2015 CPR/ECC. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
2. EMS personnel should begin the initial management of stroke in the field. Implementation of a stroke protocol to be used by EMS personnel is strongly encouraged.	I	B-NR	Recommendation revised from 2013 AIS Guidelines.
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).[21] 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).[22] In both cases, use of a prehospital stroke scale improved stroke identification, but better stroke identification tools are needed in the prehospital setting.			See Table III in online Data Supplement 1.

1.2. EMS Assessment and Management (Continued)	COR	LOE	New, Revised, or Unchanged
3. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
In the 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 versus 31 minutes), shorter DTN times (78 versus 80 minutes), and shorter symptom onset-to-needle times (141 versus 145 minutes).[23]			See Table I in online Data Supplement 1.

1.3. EMS Systems

1.3. EMS Systems	COR	LOE	New, Revised, or Unchanged
1. 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 instrument for stroke screening, such as the FAST (face, arm, speech test) scale, Los Angeles Prehospital Stroke Screen, or Cincinnati Prehospital Stroke Scale.	I	B-NR	Recommendation reworded for clarity from 2013 Stroke Systems of Care. Class and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
			See Table IV in online Data Supplement 1.
2. 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. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
3. Patients with a positive stroke screen and/or a strong suspicion of stroke should be transported rapidly to the closest healthcare facilities that can capably administer IV alteplase.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. See Table LXXXIII 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.			

1.5. Hospital Stroke Teams

1.5. Hospital Stroke Teams	COR	LOE	New, Revised, or Unchanged
1. An organized protocol for the emergency evaluation of patients with suspected stroke is recommended.	I	B-NR	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. It is recommended that DTN time goals be established. A primary goal of achieving DTN times within 60 minutes in ≥50% of AIS patients treated with IV alteplase should be established.	I	B-NR	Recommendation revised from 2013 AIS Guidelines.
In GWTG-Stroke hospitals, median DTN time for 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) to 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).[35] 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.[36]			See Table VII in online Data Supplement 1.
3. It may be reasonable to establish a secondary DTN time goal of achieving DTN times within 45 minutes in ≥50% of patients with AIS who were treated with IV alteplase.	IIb	C-EO	New recommendation.
In a cohort of 888 GWTG-Stroke hospitals surveyed between June 2014 and April 2015, 16 901 patients with ischemic stroke were treated with IV alteplase within 4.5 hours of symptom onset. The patient-level median DTN time was 56 minutes (interquartile range, 42–75 minutes), with 30.4% treated within 45 minutes after hospital arrival.[36] This recommendation mirrors Target: Stroke phase II objectives.[37]			See Table VII in online Data Supplement 1.
4. 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.	I	B-NR	Recommendation wording modified from 2013 AIS Guidelines to match Class I stratifications. Class unchanged. LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
5. Multicomponent quality improvement initiatives, which include ED education and multidisciplinary teams with access to neurological expertise, are recommended to safely increase IV thrombolytic treatment.	I	A	New recommendation.
Multicomponent quality improvement programs to improve stroke care have demonstrated utility in safely increasing alteplase use in the community hospital setting. 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.[38] 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 thrombolysis (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).[39]			See Tables VIII and IX in online Data Supplement 1.

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 useful in supporting rapid imaging interpretation in time for IV alteplase administration decision making.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE revised. See Table LXXXIII in online Data Supplement 1 for original wording.
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.[40–45]			See Table X in online Data Supplement 1.
4. Telestroke/teleradiology evaluations of AIS patients can be effective for correct IV alteplase eligibility decision making.	IIa	B-R	New recommendation.
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.[46]			See Table XI in online Data Supplement 1.
5. Administration of IV alteplase guided by telestroke consultation for patients with AIS may be as safe and as beneficial as that of stroke centers.	IIb	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. Symptomatic intracerebral hemorrhage (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.[47]			See Table XII in online Data Supplement 1.
6. 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.	IIb	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.[48]			See Table XIII in online Data Supplement 1.
7. Telestroke networks may be reasonable for triaging patients with AIS who may be eligible for interfacility transfer in order to be considered for acute mechanical thrombectomy.	IIb	B-NR	New recommendation.
An observational study compared clinical outcomes of endovascular treatment (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.[49]			See Table XII 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. 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 endovascular intervention and to reduce the time to EVT.	**IIb**	**C-LD**	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Between 2006 and 2010, the proportion of ischemic strokes undergoing computed tomography (CT) angiography (CTA) increased from 3.8% to 9.1% (P<0.0001). CT 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 CT of the head alone (4.0%; P<0.0001).[50] 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.			
2. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. 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.
4. 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.
5. It may be beneficial 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.
Multiple studies evaluating fibrinolytic therapy and mechanical thrombectomy, alone or in combination, have demonstrated substantial cost-effectiveness of 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 thrombolysis 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 emerging economic barriers to treatment is important as acute stroke care complexity evolves.[51–56]			

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	New recommendation.
In GWTG-Stroke hospitals, participation in a stroke data repository 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.[35,57]			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 establishment of a stroke care data bank 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 and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
In GWTG-Stroke hospitals, 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.[35,57] Identification of stroke treatment barriers with targeted interventions has demonstrated benefit in improving stroke treatment in community hospitals.[38]			See Tables VIII and IX in online Data Supplement 1.
2. 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. Class and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
3. Stroke outcome measures should include adjustments for baseline severity.	I	B-NR	Recommendation revised from 2013 Stroke Systems of Care. Class and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
Data indicate 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.[35,38,57] Stroke outcome measures are strongly influenced by baseline stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS).[58–61] Other identified predictors of poor outcomes include age, blood glucose, and infarct on imaging.[61] Quality improvement efforts should recognize these predictors in order to have meaningful comparisons between stroke care systems.			See Tables VIII, IX, and XIV 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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.[63,64] Use of a standardized scale quantifies the degree of neurological deficit, facilitates communication, helps identify patients for thrombolytic or mechanical intervention, allows objective measurement of changing clinical status, and identifies those at higher risk for complications such as intracerebral hemorrhage (ICH).[59–61,65]			See Table III 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
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.[62]

2.2. Brain Imaging

2.2. Brain Imaging	COR	LOE	New, Revised, or Unchanged
1. All patients admitted to hospital with suspected acute stroke should receive brain imaging evaluation on arrival to hospital. In most cases, noncontrast CT (NCCT) will provide the necessary information to make decisions about acute management.	I	B-NR	Recommendation revised from 2013 AIS Guidelines.
Diagnostic testing is most cost-effective when it leads to a change in treatment that improves outcomes, not just a change in treatment. Although diffusion-weighted magnetic resonance imaging (DW-MRI) is more sensitive than CT for detecting AIS,[66,67] routine use in all patients with AIS is not cost-effective.[68,69] NCCT scanning of all patients with acute stroke has been shown to be cost-effective primarily because of the detection of acute ICH and the avoidance of antithrombotic treatment in these patients.[70] 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.[66,71,72] In some patients with negative NCCT such as those with puzzling clinical presentations or those with uncertain clinical stroke localization for early carotid endarterectomy (CEA) or stenting, demonstration of an area of restricted diffusion on DW-MRI may lead to a change in treatment that improves outcomes. There are inadequate data at this time to establish which patients will benefit from DW-MRI, and more research is needed to determine criteria for its cost-effective use.			See Table XV in online Data Supplement 1.
2. Systems should be established so that brain imaging studies can be performed within 20 minutes of arrival in the ED in at least 50% of patients who may be candidates for IV alteplase and/or mechanical thrombectomy.	I	B-NR	New recommendation.
The benefit of both IV alteplase and mechanical thrombectomy is time dependent, with earlier treatment within the therapeutic window leading to bigger proportional benefits.[32,73] A brain imaging study to exclude ICH is recommended as part of the initial evaluation of patients who are potentially eligible for these therapies. 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.[74–76]			See Table XVI in online Data Supplement 1.
3. There remains insufficient evidence to identify a threshold of acute CT hypoattenuation severity or extent that affects treatment response to IV alteplase. The extent and severity of acute hypoattenuation or early ischemic changes should not be used as a criterion to withhold therapy for such patients who otherwise qualify.	III: No Benefit	B-R	Recommendation revised from 2015 IV Alteplase.
Analysis of data from randomized clinical trials (RCTs) of IV alteplase for AIS has shown no statistically significant deleterious interaction on clinical outcomes between alteplase treatment and baseline CT hypodensity or hypoattenuation.[77–81] In the National Institute of Neurological Disorders (NINDS) rtPA (recombinant tissue-type plasminogen activator) trial, subsequent analysis showed there was no significant modification of the effect of alteplase by the following findings on baseline CT: early ischemic changes (loss of gray/white matter distinction, hypoattenuation, or compression of cerebrospinal fluid spaces), the Alberta Stroke Program Early Computed Tomography Score (ASPECTS), or the Van Swieten score for leukoaraiosis.[78] In both ECASS (European Cooperative Acute Stroke Study) II and IST (International Stroke Trial)-3, there was no interaction with baseline ASPECTS.[77,79] A meta-analysis of NINDS rtPA, ECASS II, PROACT (Intra-Arterial Prourokinase for Acute Ischemic Stroke) II, and IST-3 showed no significant interactions for IV alteplase with functional outcomes for ASPECTS subgroups.[77] A pooled analysis of NINDS rtPA, ECASS I, ECASS II, and IST-3 showed no significant interaction between baseline CT leukoaraiosis and the effect of IV alteplase.[82] Patients with baseline CT hypoattenuation of greater than one third of the middle cerebral artery (MCA) territory were excluded from both ECASS I and ECASS II but not from NINDS rtPA and IST-3.			See Table XVII in online Data Supplement 1.
4. The CT hyperdense MCA sign should not be used as a criterion to withhold IV alteplase from patients who otherwise qualify.	III: No Benefit	B-R	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 rtPA trial, there was no interaction between hyperdense MCA sign and treatment for outcomes at 3 months measured by any of the 4 clinical scales (modified Rankin Scale [mRS] score 0–1, NIHSS score 0–1, Barthel Index ≥95, Glasgow Outcome Scale score 0–1) or for death.[83] 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.[77,84]			See Table XVIII in online Data Supplement 1.
5. Routine use of magnetic resonance imaging (MRI) to exclude cerebral microbleeds (CMBs) before administration of IV alteplase is not recommended.	III: No Benefit	B-NR	New recommendation.
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 have shown that sICH is more common in patients with baseline CMBs (OR, 2.18; 95% CI, 1.12–4.22; OR, 2.36; 95% CI, 1.21–4.61).[85,86] However, sICH in patients with baseline CMBs is not more common (6.1%, 6.5%)[85,86] than in the NINDS rtPA trial (6.4%).[87] One meta-analysis reported that the sICH rate was 40% in patients with >10 CMBs, but this was based on only 6 events in 15 patients, and patients with >10 CMBs constituted only 0.8% of the sample.[86]			See Table XIX in online Data Supplement 1.

2.2. Brain Imaging (Continued)	COR	LOE	New, Revised, or Unchanged
6. Use of imaging criteria to select ischemic stroke patients who awoke with stroke or have unclear time of symptom onset for treatment with IV alteplase is not recommended outside a clinical trial.	**III: No Benefit**	**B-NR**	Recommendation unchanged from 2015 IV Alteplase. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
7. Multimodal CT and MRI, including perfusion imaging, should not delay administration of IV alteplase.	**III: Harm**	**B-NR**	New recommendation.
Analysis of trials using advanced, multimodal pretreatment imaging (including CTP measures of penumbral imaging, diffusion-perfusion mismatch, or vessel imaging) for IV fibrinolytics has failed to demonstrate clinical efficacy in patients with various pretreatment imaging biomarkers compared with those without those markers.[88–95]			See Table XX and XXI in online Data Supplement 1.
8. For patients who otherwise meet criteria for EVT, a noninvasive intracranial vascular study is recommended during the initial imaging evaluation of the acute stroke patient, but should not delay IV alteplase if indicated. For patients who qualify for IV alteplase according to guidelines from professional medical societies, initiating IV alteplase before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible.	**I**	**A**	Recommendation reworded for clarity from 2015 Endovascular. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
A recent systematic review evaluated the accuracy of prediction instruments for diagnosing LVO.[3] 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 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.			
9. For patients who otherwise meet criteria for EVT, it is reasonable to proceed with CTA if indicated in patients with suspected intracranial LVO before obtaining a serum creatinine concentration in patients without a history of renal impairment.	**IIa**	**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.[96–101]			See Table XXII in online Data Supplement 1.
10. In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, is reasonable to provide useful information on patient eligibility and endovascular procedural planning.	**IIa**	**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.			
12. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP, DW-MRI, or MRI perfusion is recommended to aid in patient selection for mechanical thrombectomy, but only when imaging and other eligibility criteria from RCTs showing benefit are being strictly applied in selecting patients for mechanical thrombectomy.	**I**	**A**	New recommendation.
The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical imaging mismatch (a combination of NIHSS and imaging findings 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).[108] 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; $P<0.0001$).[109] 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.			See Table XXIII in online Data Supplement 1.

2.2. Brain Imaging (Continued)	COR	LOE	New, Revised, or Unchanged
13. 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.
Several studies, including secondary analyses from MR CLEAN 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.[110,111]			See Table XXIV 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-R**	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
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 ECG 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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.	**I**	**B-NR**	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE revised. See Table LXXXIII 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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 thrombolytics. 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 versus 58.3 minutes; P=0.0001).[112]			See Table XXV 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

3.1. Airway, Breathing, and Oxygenation (Continued)	COR	LOE	New, Revised, or Unchanged
2. Supplemental oxygen should be provided to maintain oxygen saturation >94%.	I	C-LD	Recommendation and Class 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.[113]			See Table XXVI in online Data Supplement 1.
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.[114] HBO therapy is associated with claustrophobia and middle ear barotrauma,[115] as well as an increased risk of seizures.[116] 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 XXVII 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 best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others have not.[117–124] No studies have addressed 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.[125] No studies have compared different isotonic fluids.			See Table XXVIII 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 systolic BP 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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 acute 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[126–132] and in patients with more BP variability.[133] The exact BP at which the risk of hemorrhage after thrombolysis increases is unknown. It is thus reasonable to target the BPs used in the RCTs of IV thrombolysis.			See Table XXIX in online Data Supplement 1.
4. The usefulness of drug-induced hypertension in patients with AIS is not well established.	IIb	C-LD	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE revised.

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

Class IIb, LOE C-EO
Patient otherwise eligible for acute 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 ≤185/110 mm Hg, do not administer alteplase
Management of BP during and after alteplase or other acute reperfusion therapy to maintain BP ≤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; IV, intravenous; and LOE, Level of Evidence.

*Different treatment options may be appropriate in patients who have comorbid conditions that may benefit from acute 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-EO**	Recommendation and Class 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.[134]			See Tables XXX and XXXI in online Data Supplement 1.
2. The benefit of induced hypothermia for treating patients with ischemic stroke is not well established. Hypothermia should be offered only in the context of ongoing clinical trials.	**IIb**	**B-R**	Recommendation revised from 2013 AIS Guidelines.
Hypothermia is a promising neuroprotective strategy, but its benefit in patients with AIS has not been proven. Most studies suggest that induction of hypothermia is associated with an increase in the risk of infection, including pneumonia.[135–138] Therapeutic hypothermia should be undertaken only in the context of a clinical trial.			See Tables XXXII and XXXIII in online Data Supplement 1.

3.4. Blood Glucose

3.4. Blood Glucose	COR	LOE	New, Revised, or Unchanged
1. 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS.	**I**	**C-LD**	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

3.5. IV Alteplase

3.5. IV Alteplase	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 may 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 6 to determine patient eligibility.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. Class and LOE unchanged. See Table LXXXIII 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[90,139,140] and confirmed by extensive community experience in many countries.[141] 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.[15] Eligibility recommendations for IV alteplase in patients with AIS are summarized in Table 6. The benefit of IV alteplase is well established for adult patients with disabling stroke symptoms regardless of age and stroke severity.[73,142] 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 thrombolysis 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 equivalent to standard-dose IV alteplase for the reduction of death and disability at 90 days.[143] Main elements of postthrombolysis care are listed in Table 7.			See Table XXXIV in online Data Supplement 1.
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. Physicians should review the criteria outlined in Table 6 determine patient eligibility.	I	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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[144] and pooled analysis of multiple trials testing IV alteplase within various time windows[90,139,140] support the value of IV thrombolysis 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 scientific statement indicates that these exclusion criteria from the trial may not be justified in practice (Table 6).[15]			See Table XXXIV in online Data Supplement 1.
3. For otherwise eligible patients with mild stroke presenting in the 3- to 4.5-hour window, treatment with IV alteplase may be reasonable. Treatment risks should be weighed against possible benefits.	IIb	B-NR	New recommendation.
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.[144] Patients with a minor neurological deficit were excluded. Only 128 patients with an NIHSS score of 0 to 5 were included, and they were not analyzed separately.[145] 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.[146] Similarly, in the 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.[147]			See Tables XXXV and XXXVI in online Data Supplement 1.
4. In otherwise eligible patients who have had a previously demonstrated small number (1–10) of CMBs on MRI, administration of IV alteplase is reasonable.	IIa	B-NR	New recommendation.
5. In otherwise eligible patients who have had a previously demonstrated high burden of CMBs (>10) 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.
MRI with hemosiderin-sensitive sequences has shown that clinically silent CMBs occur in approximately one fourth of patients who have received IV alteplase. 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 have shown that sICH is more common in patients with baseline CMBs (OR, 2.18; 95% CI, 1.12–4.22; OR, 2.36; 95% CI, 1.21–4.61).[85,86] However, sICH in patients with baseline CMBs is not more common (6.1%, 6.5%)[85,86] than in the NINDS rtPA trial (6.4%).[87] In patients with >10 CMBs, the sICH rate was 40%, but this is based on only 6 events in 15 patients, and patients with >10 CMBs constituted only 0.8% of the sample.[86] Meta-analysis of the 4 studies that provided 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; P=0.002).[85] 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 thrombolysis. It is also unknown whether the location and number of CMBs may differentially influence outcomes. These questions deserve further investigation.			See Table XIX in online Data Supplement 1.

3.5. IV Alteplase (Continued)	COR	LOE	New, Revised, or Unchanged
6. 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.[148]			See Table XXXVII in online Data Supplement 1.
7. Abciximab should not be administered concurrently with IV alteplase.	**III: Harm**	**B-R**	Recommendation revised from 2013 AIS Guidelines.
8. IV alteplase should not be administered to patients who have received a 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. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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 (*Class III; Level of Evidence B*)."[15] This statement was updated in a subsequently published erratum to specify that the contraindication does not apply to prophylactic doses.			
9. The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making.	**I**	**C-EO**	Recommendation and Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
10. 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 Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
11. 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. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
12. 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 Class III stratifications and reworded for clarity. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
13. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
See Table 8 for options for management of symptomatic intracranial bleeding occurring within 24 hours after administration of IV alteplase for treatment of AIS and Table 9 for options for management of orolingual angioedema associated with IV alteplase administration for AIS.			
14. BP should be maintained <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment.	**I**	**B-NR**	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

3.5. IV Alteplase (Continued)	COR	LOE	New, Revised, or Unchanged
15. The risk of antithrombotic therapy within the first 24 hours after treatment with IV alteplase (with or without EVT) 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.	**IIb**	**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 versus benefit.[166]			See Table XXXVIII in online Data Supplement 1.
16. 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. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.

Table 6. Eligibility Recommendations for IV Alteplase in Patients With AIS

Indications (Class 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.† (*Class I; LOE A*)
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.† (*Class I; LOE A*)
Severity	For severe stroke symptoms, 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.† (*Class I; LOE A*)
	For patients with mild but disabling stroke symptoms, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms, in the opinion of the treating physician, from treatment with IV alteplase because there is proven clinical benefit for those patients.† (*Class 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.† (*Class I; LOE B-R*)‡
Age Diabetes mellitus Prior stroke Severity OACs Imaging	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.† (*Class 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.† (*Class I; LOE A*)
BP	IV alteplase is recommended in patients whose BP can be lowered safely (to <185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase.† (*Class I; LOE B-NR*)‡
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.† (*Class 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).† (*Class I; LOE A*)
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.† (*Class 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.† (*Class I; LOE B-NR*)‡
End-stage renal disease	In patients with end-stage renal disease on hemodialysis and normal aPTT, IV alteplase is recommended.† (*Class I; LOE C-LD*)‡ However, those with elevated aPTT may have elevated risk for hemorrhagic complications.
Contraindications (Class III)	
Time of onset	IV alteplase is not recommended in ischemic stroke patients who have an unclear time and/ or unwitnessed symptom onset and in whom the time last known to be at baseline state is >3 or 4.5 h.† (*Class III: No Benefit; LOE B-NR*)‡§

(*Continued*)

Table 6. Continued

	IV alteplase is not recommended in ischemic stroke patients who awoke with stroke with time last known to be at baseline state >3 or 4.5 h.† (*Class III: No Benefit; LOE B-NR*)‡§
CT	IV alteplase should not be administered to a patient whose CT reveals an acute intracranial hemorrhage.† (*Class III: Harm; LOE C-EO*)‡§
	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.† (*Class III: No Benefit; LOE* A)§
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.† (*Class 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.† (*Class III: Harm; LOE C-EO*)‡§
	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.† (*Class III: Harm; LOE C-EO*)‡§ (Recommendation wording modified to match Class 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.† (*Class III: Harm; LOE C-EO*)‡§
History of intracranial hemorrhage	IV alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful.† (*Class III: Harm; LOE C-EO*)‡§
Subarachnoid hemorrhage	IV alteplase is contraindicated in patients presenting with symptoms and signs most consistent with an SAH.† (*Class 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.† (*Class 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.† (*Class 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 Class III stratifications.)
LMWH	IV alteplase should not be administered to patients who have received a treatment dose of LMWH within the previous 24 h.† (*Class III: Harm; LOE B-NR*)‖ (Recommendation wording modified to match Class III stratifications.)
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.† (*Class 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 Class III stratifications.)
Glycoprotein IIb/IIIa receptor inhibitors	Antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor should not be administered concurrently with IV alteplase outside a clinical trial.† (*Class III: Harm; LOE B-R*)‡§ (Recommendation wording modified to match Class III stratifications.)
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.† (*Class III: Harm; LOE C-LD*)‡§ (Recommendation wording modified to match Class 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.† (*Class III: Harm; LOE C-EO*)‡§ (Recommendation wording modified to match Class III stratifications.)
Intra-axial intracranial neoplasm	IV alteplase treatment for patients with AIS who harbor an intra-axial intracranial neoplasm is potentially harmful.† (*Class III: Harm; LOE C-EO*)‡§
Additional recommendations for treatment with IV alteplase for patients with AIS (Class II)	
Extended 3- to 4.5-h window	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.† (*Class IIa; LOE B-NR*)‡

(*Continued*)

Table 6. Continued

	For patients taking warfarin and with an INR ≤1.7 who present in the 3- to 4.5-h window, IV alteplase appears safe and may be beneficial.† (*Class IIb; LOE B-NR*)‡
	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.† (*Class IIb; LOE B-NR*)‡
Severity 0- to 3-h window	Within 3 h from symptom onset, treatment of patients with mild ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio.† (*Class IIb; LOE C-LD*)‡
Severity 3- to 4.5-h window	For otherwise eligible patients with mild stroke 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. Treatment risks should be weighed against possible benefits. (*Class IIb; LOE B-NR*)‖
	The benefit of IV alteplase between 3 and 4.5 h from symptom onset for patients with very severe stroke symptoms (NIHSS > 25) is uncertain.† (*Class IIb; LOE C-LD*)
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. Thrombolytic 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.† (*Class 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.† (*Class 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.† (*Class 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.† (*Class 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. [*Class IIb; LOE C-LD*])‡
Coagulopathy	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.† (*Class IIb; LOE C-EO*)‡
	IV alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤1.7 and/or a PT <15 s.† (*Class IIb; LOE B-NR*)‡
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.† (*Class 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.† (*Class 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. [*Class 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.† (*Class 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.† (*Class IIb; LOE C-LD*‡ (Note: Alteplase administration within 21 d of a GI bleeding event is not recommended; see Contraindications.)
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.† (*Class 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.† (*Class IIb; LOE C-LD*)‡
	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.† (*Class IIa; LOE C-EO*)‡
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.† (*Class 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.† (*Class IIb; LOE C-LD*)‡

(*Continued*)

Table 6. Continued

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.† (*Class 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.† (*Class 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.† (*Class 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 secondary to thrombolysis.† (*Class 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. (*Class 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. (*Class 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.† (*Class 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.† (*Class 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.† (*Class 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.† (*Class 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.† (*Class IIb; LOE C-LD*)‡
Other cardiac diseases	For patients with major AIS likely to produce severe disability and acute pericarditis, treatment with IV alteplase may be reasonable† (*Class 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.† (*Class IIb; LOE C-EO*)‡
	For patients with major AIS likely to produce severe disability and known left atrial or ventricular thrombus, treatment with IV alteplase may be reasonable.† (*Class 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.† (*Class IIb; LOE C-LD*)‡
	For patients with major AIS likely to produce severe disability and cardiac myxoma, treatment with IV alteplase may be reasonable.† (*Class 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.† (*Class 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.† (*Class IIa; LOE A*)‡
Systemic malignancy	The safety and efficacy of alteplase in patients with current malignancy are not well established.† (*Class 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.† (*Class 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.† (*Class 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.† (*Class IIa; LOE B-NR*)‡
Sickle cell disease	IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial. (*Class IIa; LOE B-NR*)‖

(*Continued*)

Table 6. Continued

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.† (*Class 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.† (*Class IIa; LOE B-NR*)

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.[15]

AC indicates anticoagulants; ACC, American College of Cardiology; AIS, acute ischemic stroke; AHA, American Heart Association; aPTT, activated partial thromboplastin time; BP, blood pressure; CMB, cerebral microbleed; CT, computed tomography; 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, prothromboplastin 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 LXXXIII in online Data Supplement 1 for original wording.

‡LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

§COR amended to conform with ACC/AHA 2015 Recommendation Classification System.

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

Table 7. 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.

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Table 8. Management of Symptomatic Intracranial Bleeding Occurring Within 24 Hours After Administration of IV Alteplase for Treatment of AIS

Class IIb, LOE C-EO
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 <200 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)
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; 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,[149] Mahaffey et al,[150] Goldstein et al,[151] French et al,[152] Yaghi et al,[153–155] Stone et al,[156] and Frontera et al.[157]

Table 9. Management of Orolingual Angioedema Associated With IV Alteplase Administration for AIS

Class IIb, LOE C-EO
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 post-IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.
Discontinue IV alteplase infusion and hold ACEIs
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 total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACEI-related angioedema
Supportive care

ACEI indicates angiotensin-converting enzyme inhibitor; AIS, acute ischemic stroke; IV, intravenous; and LOE, Level of Evidence.

Sources: Foster-Goldman and McCarthy,[158] Gorski and Schmidt,[159] Lewis,[160] Lin et al,[161] Correia et al,[162] O'Carroll and Aguilar,[163] Myslimi et al,[164] and Pahs et al.[165]

3.6. Other IV Thrombolytics and Sonothrombolysis

3.6. Other IV Thrombolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. The benefit of IV defibrinogenating agents and of IV fibrinolytic agents other than alteplase and tenecteplase is unproven; therefore, their administration is not recommended outside a clinical trial.	**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 or large intracranial artery occlusion or severe stenosis.[92,95,167,168]			See Table XXXIX 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 to 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.[89,91,169,170] 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.[170] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XXXIX in online Data Supplement 1.
3. The use of sonothrombolysis as adjuvant therapy with IV thrombolysis is not recommended.	**III: No Benefit**	**B-R**	New recommendation.
Since the publication of the 2013 AIS Guidelines, a further RCT of sonothrombolysis as adjuvant therapy for IV thrombolysis has 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.[171] At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV thrombolysis.			See Table XL in online Data Supplement 1.

3.7. Mechanical Thrombectomy

3.7. Mechanical Thrombectomy	COR	LOE	New, Revised, or Unchanged
1. Patients eligible for IV alteplase should receive IV alteplase even if EVTs are being considered.	**I**	**A**	Recommendation reworded for clarity from 2015 Endovascular. See Table LXXXIII in online Data Supplement 1 for original wording.
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.
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 scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: common odds ratio (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.[32] 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).[32] These 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.			See Tables XXIII and XLI in online Data Supplement 1.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
3. 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.
Results from 6 recent randomized trials of mechanical thrombectomy using predominantly stent retriever devices (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE) support Class I, LOE A recommendations for a defined group of patients as described in the 2015 guidelines.[102–107] 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 old (cOR, 3.68; 95% CI, 1.95–6.92).[172] 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 old (3.46; 95% CI, 1.58–7.60).[173] 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 patient age <70 and ≥70 years: OR, 2.41; 95% CI, 1.51–3.84; and OR, 2.26; 95% CI, 1.20–4.26, respectively).[174] 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.			See Tables XXIII and XLI in online Data Supplement 1.
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 MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.	IIb	B-R	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE revised. See Table LXXXIII in online Data Supplement 1 for original wording.
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 common OR was not significant (1.28; 95% CI, 0.51–3.21).[172] 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, 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.[173] 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).[175] Therefore, the recommendation for mechanical thrombectomy for M2/M3 occlusions does not change substantively from the 2015 AHA/American Stroke Association focused update.			See Tables XXIII and XLI in online Data Supplement 1.
5. 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.	IIb	C-EO	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
6. 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). Additional randomized trial data are needed.	IIb	B-R	Recommendation unchanged from 2015 Endovascular.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
7. 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.
8. 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.	IIa	B-R	New recommendation.
The DAWN trial used clinical imaging 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).[108] 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; $P<0.0001$).[109] 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.			See Table XXIII in online Data Supplement 1.
9. The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) 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 LXXXIII 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.[176,177] 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 mTICI 2b/3.[172] 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%). The additional benefit of pursuing mTICI of 3 rather than 2b deserves further investigation.			
10. As with IV alteplase, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible within the therapeutic window.	I	B-R	Recommendation revised from 2015 Endovascular.
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.[32] 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).[32] In the DAWN trial, the likelihood of achieving an mRS score of 0 to 2 at 90 days in the mechanical thrombectomy group declined with time since last known normal.[108] Therefore, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.[129,130] 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.[172] 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%).			See Tables XXIII and XLI in online Data Supplement 1.
11. Use of stent retrievers is indicated in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device.	I	A	Recommendation unchanged from 2015 Endovascular.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
12. The use of mechanical thrombectomy devices other than stent retrievers as first-line devices for mechanical thrombectomy may be reasonable in some circumstances, but stent retrievers remain the first choice.	**IIb**	**B-R**	Recommendation revised from 2015 Endovascular.
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 EVT for successful revascularization within 6 hours among patients with acute anterior circulation ischemic stroke and LVO. 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). The primary end point in ASTER was technical (successful revascularization after all interventions), and the trial was not powered to detect a smaller yet potentially clinically important difference between groups. Given its superiority design to detect a 15% difference in the primary end point, this trial was not designed to establish noninferiority.[178]			See Table XXIII in online Data Supplement 1.
13. 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. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization.	**IIa**	**C-LD**	Recommendation and Class unchanged from 2015 Endovascular. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
14. Use of salvage technical adjuncts including intra-arterial thrombolysis may be reasonable to achieve mTICI 2b/3 angiographic results.	**IIb**	**C-LD**	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Intra-arterial lytic 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.[179] 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.			
15. EVT of tandem occlusions (both extracranial and intracranial occlusions) at the time of thrombectomy may be reasonable.	**IIb**	**B-R**	Recommendation revised from 2015 Endovascular.
Tandem occlusions were considered 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.[172] 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.[106] 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). Multiple retrospective reports detail the technical success of EVT 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 XXIII and XLI in online Data Supplement 1.
16. It is reasonable to select an anesthetic technique during endovascular therapy for AIS on the basis of individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics. Further randomized trial data are needed.	**IIa**	**B-R**	Recommendation revised from 2015 Endovascular.
Conscious sedation (CS) was widely used 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 of general anesthesia (GA) compared with CS.[180] In THRACE, 51 of 67 patients receiving GA and 43 of 69 patients receiving CS achieved TICI 2b/3 (*P*=0.059) with no impact on outcome.[106] Thirty-five of 67 patients with GA and 36 of 74 with CS had mRS scores of 0 to 2 at 90 days. Although several retrospective studies suggest that GA produces worsening of functional outcomes, there are limited prospective randomized data. Two small (≤150 participants) single-center RCTs have compared GA with CS. Both failed to show superiority of either treatment for the primary clinical end point.[181,182] Until further data are available, either method of procedural sedation is reasonable.			See Tables XLII and XLIII in online Data Supplement 1.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
17. In patients who undergo mechanical thrombectomy, it is reasonable to maintain the BP ≤180/105 mm Hg during and for 24 hours after the procedure.	**IIa**	**B-NR**	New recommendation.
18. 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.
There are very limited data to guide BP therapy 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 under 6-hour RCTs received IV alteplase and the trial protocols stipulated management according to local guidelines with BP ≤80/105 during and for 24 hours after the procedure for these participants. Two trial protocols provided additional recommendations. The ESCAPE protocol states that systolic BP ≥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.[104] The DAWN protocol recommends maintaining systolic BP <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).[183]			See Table XXIII in online Data Supplement 1.

3.8. Other EVTs

3.8. Other EVTs	COR	LOE	New, Revised, or Unchanged
1. Initial treatment with intra-arterial thrombolysis is beneficial for carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA.	**I**	**B-R**	Recommendation and Class unchanged from 2015 Endovascular. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System.
2. Regarding the previous recommendation about intra-arterial thrombolysis, these data are derived from clinical trials that no longer reflect current practice, including the use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial alteplase is not established, and alteplase does not have US Food and Drug Administration approval for intra-arterial use. As a consequence, mechanical thrombectomy with stent retrievers is recommended over intra-arterial thrombolysis as first-line therapy.	**I**	**C-EO**	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. Intra-arterial thrombolysis 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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.
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.[184,185] This has recently been confirmed by a large Cochrane review of aspirin trials.[186] 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. 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 versus 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.			See Table XXXVIII in online Data Supplement 1.

3.9. Antiplatelet Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
2. Aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy.	**III: No Benefit**	**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.			
3. The efficacy of IV tirofiban and eptifibatide is not well established. Further clinical trials are needed.	**IIb**	**B-R**	Recommendation revised from 2013 AIS Guidelines.
Prospective, randomized, open-label phase II trials of tirofiban[187] and eptifibatide[188] 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.[189,190]			See Table XLIV in online Data Supplement 1.
4. The administration of other glycoprotein IIb/IIIa receptor antagonists, including abciximab, in the treatment of AIS is potentially harmful and should not be performed. Further research testing the safety and efficacy of these medications in patients with AIS is required.	**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.[191] 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.[192]			See Table XLV in online Data Supplement 1.
5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.	**IIa**	**B-R**	New recommendation.
The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled trial conducted in China to study the efficacy of short-term dual antiplatelet therapy begun within 24 hours, clopidogrel plus aspirin for 21 days followed by clopidogrel alone to 90 days, in patients with minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD^2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). 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).[193] 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.[194] The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the United States, Canada, Europe, and Australia is ongoing.[195]			See Table XLV in online Data Supplement 1.
6. Ticagrelor is not recommended (over aspirin) in the acute treatment of patients with minor 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 (ABCD^2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). With a primary outcome of time to the composite end point of stroke, myocardial infarction (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).[196] 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 XLV in online Data Supplement 1.

3.10. Anticoagulants

3.10. Anticoagulants	COR	LOE	New, Revised, or Unchanged
1. 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. Class 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.[197,198] 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).[199]			See Table XLV in online Data Supplement 1.

3.10. Anticoagulants (Continued)	COR	LOE	New, Revised, or Unchanged
2. 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. 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, vertebrobasilar arteries) remains uncertain. Several small observational studies have suggested the safety of short-term IV heparin or LMWH in this setting,[203,204] but further research is required to establish safety and efficacy.			See Table XLVII in online Data Supplement 1.
4. At present, the usefulness of argatroban, dabigatran, or other thrombin inhibitors for the treatment of patients with AIS is not well established. Further clinical trials are needed.	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.[201] 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.[205] 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.[206]			See Table XLVII in online Data Supplement 1.
5. The safety and usefulness of factor Xa inhibitors in the treatment of AIS are not well established. Further clinical trials are needed.	IIb	C-LD	New recommendation.
Limited data exist on the use of factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban) in the acute treatment of patients with ischemic stroke.[207] Several prospective observational studies and early-phase trials are ongoing (NCT02279940, NCT02042534, NCT02283294).			See Table LXXVII 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. Class 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.[208]			See Table XLVIII 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.[209] Combined analysis of the ALIAS parts I and II trials demonstrated no difference between groups in 90-day disability.[210]			See Table XLVIII in online Data Supplement 1.
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. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. At present, use of devices to augment cerebral blood flow for the treatment of patients with AIS is not well established. These devices should be used only in the setting of clinical trials.	IIb	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

3.12. Neuroprotective Agents

3.12. Neuroprotective Agents	COR	LOE	New, Revised, or Unchanged
1. At present, no pharmacological or non-pharmacological treatments with putative neuroprotective actions have demonstrated efficacy in improving outcomes after ischemic stroke, and therefore, other neuroprotective agents 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 LXXXIII in online Data Supplement 1 for original wording.
Recent trials of both pharmacological and nonpharmacological neuroprotective treatments in AIS have been negative. The FAST-MAG trial (Field Administration of Stroke Therapy–Magnesium) of hyperacute 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.[103] A recent Cochrane review of neuroprotection trials in AIS further confirms the recommendation of no benefit with previously studied interventions to date.[114]			See Table XLVIII in online Data Supplement 1.

3.13. Emergency CEA/Carotid Angioplasty and Stenting Without Intracranial Clot

3.13. Emergency CEA/Carotid Angioplasty and Stenting Without Intracranial Clot	COR	LOE	New, Revised, or Unchanged
1. The usefulness of emergent or urgent CEA 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 and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System.
2. In patients with unstable neurological status (eg, stroke-in-evolution), the efficacy of emergency or urgent CEA is not well established.	**IIb**	**B-NR**	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII 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.[211–213] 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.[214] 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 XLIX 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.2. Supplemental Oxygen

4.2. 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 Class 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 Class 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 LXXXIII in online Data Supplement 1 for original wording.
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.[113]			See Table XXVI in online Data Supplement 1.

4.3. Blood Pressure

4.3. Blood Pressure	COR	LOE	New, Revised, or Unchanged
1. 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, postthrombolysis sICH, or preeclampsia/eclampsia). Lowering BP initially by 15% is probably safe.	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.[215] Ideal management in these situations should be individualized, but in general, initial BP reduction by 15% is a reasonable goal.			
3. In patients with BP ≥220/120 mm Hg who did not receive IV alteplase or EVT and have no comorbid conditions requiring acute 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.[218,219,222,223,225,228] BP reduction has been traditionally 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.			See Table L in online Data Supplement 1.
4. Although no solid data are available to guide selection of medications for BP lowering after AIS, the antihypertensive medications and doses included in Table 5 are reasonable options.	IIa	C-EO	Recommendation/table revised from 2013 AIS Guidelines.
There are no data to show that 1 strategy to lower BP is better than another after AIS. The medications and doses in Table 5 are all reasonable options.			
5. 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.
Starting or restarting antihypertensive medications has been shown to be associated with improved control of the BP after discharge in 2 trials.[223,225] 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 hypertension[223] or enrolled mostly patients with previous hypertension.[225] 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.			See Table L in online Data Supplement 1.

4.3. Blood Pressure (Continued)	COR	LOE	New, Revised, or Unchanged
6. 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 the best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others do not.[117–124] 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.[125] No studies have compared different isotonic fluids.			See Table XXVIII in online Data Supplement 1.

4.4. Temperature

4.4. 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-EO	Recommendation and Class 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.[134]			See Tables XXX and XXXI in online Data Supplement 1.
2. The benefit of induced hypothermia for treating patients with ischemic stroke is not well established. Hypothermia should be offered only in the context of ongoing clinical trials.	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.
Hypothermia is a promising neuroprotective strategy, but its benefit in patients with AIS has not been proven. Most studies suggest that induction of hypothermia is associated with an increase in the risk of infection, including pneumonia.[135–138] Therapeutic hypothermia should be undertaken only in the context of a clinical trial.			See Tables XXXII and XXXIII in online Data Supplement 1.

4.5. Glucose

4.5. Glucose	COR	LOE	New, Revised, or Unchanged
1. 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with AIS.	I	C-LD	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.6. Dysphagia Screening

4.6. Dysphagia Screening	COR	LOE	New, Revised, or Unchanged
2. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. An instrumental 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 Class IIa stratifications. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
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).	**IIb**	**C-LD**	Recommendation reworded for clarity from 2016 Rehab Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

4.7. Nutrition

4.7. 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).	**IIa**	**C-EO**	New recommendation.
The FOOD RCTs (Feed Or Ordinary Diet; phases I–III), completed in 131 hospitals in 18 countries,[235] 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.[235] 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.[236] 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<.00001).			See Table LIII in online Data Supplement 1.
3. Nutritional supplements are reasonable to consider for patients who are malnourished or at risk of malnourishment.	**IIa**	**B-R**	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.7. Nutrition (Continued)	COR	LOE	New, Revised, or Unchanged
4. Implementing oral hygiene protocols to reduce the risk of pneumonia after stroke may be reasonable.	**IIb**	**B-NR**	New recommendation.
Limited studies suggest that intensive oral hygiene protocols might reduce the risk of aspiration pneumonia. In patients with acute stroke, Sørensen et al[237] 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).[238] Wagner et al[239] 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).			See Tables LIV and LV in online Data Supplement 1.

4.8. Deep Vein Thrombosis Prophylaxis

4.8. 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.
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 to 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 IPC participants (9.6%) compared with 174 of 1245 no-IPC participants (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.[403] A meta-analysis including this trial and 2 smaller trials confirmed these results.[240]			See Table LVI in online Data Supplement 1.
2. The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile 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) and 4 small trials of UFH, 8 small trials of LMWHs or heparinoids, and 1 trial of a heparinoid.[240] 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, most of which were asymptomatic (OR, 0.21; 95% CI, 0.15–0.29). 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). 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.[197,198,240]			See Table LVI in online Data Supplement 1.

4.8. Deep Vein Thrombosis Prophylaxis (Continued)	COR	LOE	New, Revised, or Unchanged
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.[240] 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 LVI 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 Class III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.9. Depression Screening

4.9. Depression Screening	COR	LOE	New, Revised, or Unchanged
1. Administration of a structured depression inventory is recommended to routinely screen for poststroke depression, but the optimal timing of screening is uncertain.	**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.[241] However, further research is needed to determine the optimal screening method and timing to diagnose and treat poststroke depression.[242]			See Table LVII 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 Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.10. Other

4.10. Other	COR	LOE	New, Revised, or Unchanged
1. Routine use of prophylactic antibiotics has not been shown to be beneficial.	**III: No Benefit**	**B-R**	Recommendation unchanged from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. 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 Class III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. 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 Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. 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 Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
5. It is reasonable for patients and families with stroke to be directed to palliative care resources as appropriate. Caregivers should ascertain and include patient-centered preferences in decision making, especially during prognosis formation and considering interventions or limitations in care.	**IIa**	**C-EO**	New recommendation.
The AHA scientific statement for palliative care in stroke[10] outlines, in detail, a number of palliative care considerations for patients with AIS. The consensus is that patient- and family-centered care, aimed at improving the well-being of survivors and family members while preserving the dignity of patients, is the cornerstone of care. Appropriate consultations, educational resources, and other aids should be identified in order to support patients and families.			

4.11. Rehabilitation

4.11. 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 Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. 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 Class III stratifications. LOE revised. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.
The AVERT RCT (A Very Early Rehabilitation Trial) compared high-dose, very early mobilization with standard-of-care mobility.[243] 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 the 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.			See Table LVIII in online Data Supplement 1.
4. 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 Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
5. 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 Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
6. The effectiveness of fluoxetine or other selective serotonin reuptake inhibitors to enhance motor recovery is not well established.	IIb	C-LD	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE revised from 2016 Rehab Guidelines.

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

5.1. Cerebellar and Cerebral Edema

5.1. Cerebellar and Cerebral Edema	COR	LOE	New, Revised, or Unchanged
1. Ventriculostomy is recommended in the treatment of obstructive hydrocephalus after a cerebellar infarct. Concomitant or subsequent decompressive craniectomy may or may not be necessary on the basis of factors such as infarct size, neurological condition, degree of brainstem compression, and effectiveness of medical management.	I	C-LD	Recommendation revised from 2014 Cerebral Edema.
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 ischemic cerebellar stroke.[244,245] Thus, in patients who develop symptoms of obstructive hydrocephalus from a cerebellar stroke, emergency ventriculostomy is a reasonable first step in the surgical management paradigm. If cerebrospinal diversion by ventriculostomy fails to improve neurological function, decompressive suboccipital craniectomy should be performed.[244–246] 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 infarct causes significant edema or mass effect.[244,245]			See Table LIX in online Data Supplement 1.

5.1. Cerebellar and Cerebral Edema (Continued)	COR	LOE	New, Revised, or Unchanged
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 Cerebral Edema.
The data support decompressive cerebellar craniectomy for the management of acute ischemic cerebellar stroke with mass effect.[244–246] This surgery is indicated as a therapeutic intervention in cases of neurological deterioration caused by cerebral edema as a result of cerebellar infarction that cannot be otherwise managed with medical therapy or ventriculostomy in the setting of obstructive hydrocephalus.[244,245]			See Table LIX in online Data Supplement 1.
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 sub-occipital craniectomy.	IIb	C-LD	Recommendation and Class unchanged from 2014 Cerebral Edema. Wording revised and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. Patients with large territorial supratentorial infarctions are at high risk for complicating brain edema and increased intracranial pressure. Discussion of care options and possible outcomes should take place quickly with patients (if possible) and caregivers. Medical professionals and caregivers should ascertain and include patient-centered preferences in shared decision making, especially during prognosis formation and considering interventions or limitations in care.	I	C-EO	New recommendation.
Cerebral edema can cause serious and even life-threatening complications in patients with large territorial supratentorial infarctions. Although less severe edema 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.[247] 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.			
5. Patients with major infarctions are at high risk for complicating brain edema. Measures to lessen the risk of edema 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 edema to an institution with neurosurgical expertise should be considered.	I	C-LD	Recommendation revised from 2013 AIS Guidelines. LOE revised.
6. In patients ≤60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is reasonable because it reduces mortality by close to 50%, with 55% of the surgical survivors achieving moderate disability (able to walk) or better (mRS score 2 or 3) and 18% achieving independence (mRS score 2) at 12 months.	IIa	A	Recommendation revised from 2014 Cerebral Edema.
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.[247] 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.[248,249] 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; P=0.045) of the total nonsurgical group and 75% (9 of 12; P=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.[245,247–250]			See Tables LIX and LX in online Data Supplement 1.
7. In patients >60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion may be considered because it reduces mortality by close to 50%, with 11% of the surgical survivors achieving moderate disability (able to walk [mRS score 3]) and none achieving independence (mRS score ≤2) at 12 months.	IIb	B-R	Recommendation revised from 2014 Cerebral Edema.
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.[248,249,251–255] 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 LIX and LX in online Data Supplement 1.

5.1. Cerebellar and Cerebral Edema (Continued)	COR	LOE	New, Revised, or Unchanged
8. 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.	**IIa**	**A**	Recommendation, Class, and LOE unchanged from 2014 Cerebral Edema.
9. Use of osmotic therapy for patients with clinical deterioration from cerebral swelling associated with cerebral infarction is reasonable.	**IIa**	**C-LD**	Recommendation reworded for clarity from 2014 Cerebral Edema. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
10. Use of brief moderate hyperventilation (Pco_2 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-EO**	New recommendation.
Hyperventilation is a very effective treatment to rapidly improve brain swelling, but it works by inducing cerebral vasoconstriction, which can worsen ischemia if the hypocapnia is sustained or profound.[256] Thus, hyperventilation should be induced rapidly but should be used as briefly as possible and avoid excessive hypocapnia (<30 mm Hg).			
11. 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 Cerebral Edema. COR amended to conform with ACC/AHA 2015 Recommendation Classification System.
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.[257] Further research is recommended.			See Tables LIX and LX in online Data Supplement 1.
12. 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 cerebral edema and increased intracranial pressure complicating ischemic stroke.	**III: Harm**	**A**	Recommendation wording modified from 2013 AIS Guidelines to match Class III stratifications. LOE unchanged. Class 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 anti-seizure drugs should be selected based upon specific patient characteristics.	**I**	**C-LD**	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
2. Prophylactic use of anti-seizure drugs is not recommended.	**III: No Benefit**	**B-R**	Recommendation reworded for clarity from 2013 AIS Guidelines. LOE revised. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

Additional reference support for this guideline is provided in online Data Supplement 1.[200,202,216,217,220,221,224,226,227,229,322,323,325,326,336-402,404-421]

Disclosures

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*Modest.

†Significant.

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*Modest.

References

1. Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM, Khatri P, McMullan PW Jr, Qureshi AI, Rosenfield K, Scott PA, Summers DR, Wang DZ, Wintermark M, Yonas H; 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.
3. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec D. 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: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e111–e122. doi: 10.1161/STR.0000000000000160.
4. Smith EE, Kent DM, Bulsara KR, Leung LY, Lichtman JH, Reeves MJ, Towfighi A, Whiteley WN, Zahuranec D. 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: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2018;49:e123–e128. doi: 10.1161/STR.0000000000000159.
5. Schwamm LH, Audebert HJ, Amarenco P, Chumbler NR, Frankel MR, George MG, Gorelick PB, Horton KB, Kaste M, Lackland DT, Levine SR, Meyer BC, Meyers PM, Patterson V, Stranne SK, White CJ; 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, Peterson ED, Rosenwasser RH, Saver JL, Schwamm L, Summers D, Wechsler L, Wood JP; 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;44:2961–2984. doi: 10.1161/STR.0b013e3182a6d2b2.
7. Deleted.
8. January CT, Wann LS, Alpert JS, Calkins H, Cigarroa JE, Cleveland JC Jr, Conti JB, Ellinor PT, Ezekowitz MD, Field ME, Murray KT, Sacco RL, Stevenson WG, Tchou PJ, Tracy CM, Yancy CW. 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 [published correction appears in *Circulation*. 2014;130:e270–271]. *Circulation*. 2014;130:2071–2104. doi: 10.1161/CIR.0000000000000040.
9. 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.
10. Holloway RG, Arnold RM, Creutzfeldt CJ, Lewis EF, Lutz BJ, McCann RM, Rabinstein AA, Saposnik G, Sheth KN, Zahuranec DB, Zipfel GJ, Zorowitz RD; 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.
11. Deleted.
12. 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.
13. Singletary EM, Charlton NP, Epstein JL, Ferguson JD, Jensen JL, MacPherson AI, Pellegrino JL, Smith WW, Swain JM, Lojero-Wheatley LF, Zideman DA. 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.
14. Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC, Johnston KC, Johnston SC, Khalessi AA, Kidwell CS, Meschia JF, Ovbiagele B, Yavagal DR; 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.
15. Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC, Khalessi AA, Levy EI, Palesch YY, Prabhakaran S, Saposnik G, Saver JL, Smith EE; 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.
16. Winstein CJ, Stein J, Arena R, Bates B, Cherney LR, Cramer SC, Deruyter F, Eng JJ, Fisher B, Harvey RL, Lang CE, MacKay-Lyons M, Ottenbacher KJ, Pugh S, Reeves MJ, Richards LG, Stiers W, Zorowitz RD; 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 corrections appear in *Stroke*. 2017;48:e78 and *Stroke*. 2017;48:e369]. *Stroke*. 2016;47:e98–e169. doi: 10.1161/STR.0000000000000098.

17. 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.
18. 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.
19. 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.
20. 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.
21. 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.
22. 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.
23. Lin CB, Peterson ED, Smith EE, Saver JL, Liang L, Xian Y, Olson DM, Shah BR, Hernandez AF, Schwamm LH, Fonarow GC. 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.

24–31. Deleted.

32. Saver JL, Goyal M, van der Lugt A, Menon BK, Majoie CB, Dippel DW, Campbell BC, Nogueira RG, Demchuk AM, Tomasello A, Cardona P, Devlin TG, Frei DF, du Mesnil de Rochemont R, Berkhemer OA, Jovin TG, Siddiqui AH, van Zwam WH, Davis SM, Castaño C, Sapkota BL, Fransen PS, Molina C, van Oostenbrugge RJ, Chamorro Á, Lingsma H, Silver FL, Donnan GA, Shuaib A, Brown S, Stouch B, Mitchell PJ, Davalos A, Roos YB, Hill MD; 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.

33–34. Deleted.

35. 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.
36. Xian Y, Xu H, Lytle B, Blevins J, Peterson ED, Hernandez AF, Smith EE, Saver JL, Messe SR, Paulsen M, Suter RE, Reeves MJ, Jauch EC, Schwamm LH, Fonarow GC. 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. doi: 10.1161/CIRCOUTCOMES.116.003227.
37. Target Stroke Phase II website http://www.strokeassociation.org/STROKEORG/Professionals/TargetStroke/Target-Stroke-Phase-II_UCM_469859_Article.jsp#.Wk1CBd-nF3g. Accessed January 3, 2018.
38. Scott PA, Meurer WJ, Frederiksen SM, Kalbfleisch JD, Xu Z, Haan MN, Silbergleit R, Morgenstern LB; INSTINCT Investigators. A multilevel 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.
39. Dirks M, Niessen LW, van Wijngaarden JD, Koudstaal PJ, Franke CL, van Oostenbrugge RJ, Huijsman R, Lingsma HF, Minkman MM, Dippel DW; 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.
40. Phabphal K, Hirunpatch S. The effectiveness of low-cost teleconsultation for emergency head computer tomography in patients with suspected stroke. *J Telemed Telecare*. 2008;14:439–442. doi: 10.1258/jtt.2008.080603.
41. Mitchell JR, Sharma P, Modi J, Simpson M, Thomas M, Hill MD, Goyal M. A smartphone client-server teleradiology system for primary diagnosis of acute stroke. *J Med Internet Res*. 2011;13:e31. doi: 10.2196/jmir.1732.
42. Johnston KC, Worrall BB; Teleradiology Assessment of Computerized Tomographs Online Reliability Study. Teleradiology Assessment of Computerized Tomographs Online Reliability Study (TRACTORS) for acute stroke evaluation. *Telemed J E Health*. 2003;9:227–233. doi: 10.1089/153056203322502605.
43. Demaerschalk BM, Bobrow BJ, Raman R, Ernstrom K, Hoxworth JM, Patel AC, Kiernan TE, Aguilar MI, Ingall TJ, Dodick DW, Meyer BC; 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.
44. Spokoyny 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.
45. Puetz V, Bodechtel U, Gerber JC, Dzialowski I, Kunz A, Wolz M, Hentschel H, Schultheiss T, Kepplinger J, Schneider H, Wiedemann B, Wojciechowski C, Reichmann H, Gahn G, von Kummer R. Reliability of brain CT evaluation by stroke neurologists in telemedicine. *Neurology*. 2013;80:332–338. doi: 10.1212/WNL.0b013e31827f07d0.
46. 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.
47. 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.
48. Fong WC, Ismail M, Lo JW, Li JT, Wong AH, Ng YW, Chan PY, Chan AL, Chan GH, Fong KW, Cheung NY, Wong GC, Ho HF, Chan ST, Kwok VW, Yuen BM, Chan JH, Li PC. 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.
49. Barlinn J, Gerber J, Barlinn K, Pallesen LP, Siepmann T, Zerna C, Wojciechowski C, Puetz V, von Kummer R, Reichmann H, Linn J, Bodechtel U. 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.
50. 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.
51. 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.
52. 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.
53. Penaloza-Ramos MC, Sheppard JP, Jowett S, Barton P, Mant J, Quinn T, Mellor RM, Sims D, Sandler D, McManus RJ; on behalf of the BBC CLAHRC Investigators. Cost-effectiveness of optimizing acute stroke

care services for thrombolysis. *Stroke*. 2014;45:553–562. doi: 10.1161/STROKEAHA.113.003216.
54. 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.
55. Health Quality Ontario. Mechanical thrombectomy in patients with acute ischemic stroke: a health technology assessment. *Ont Health Technol Assess Ser*. 2016;16:1–79.
56. 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.
57. Song S, Fonarow GC, Olson DM, Liang L, Schulte PJ, Hernandez AF, Peterson ED, Reeves MJ, Smith EE, Schwamm LH, Saver JL. Association of Get With The Guidelines–Stroke program participation and clinical outcomes for Medicare beneficiaries with ischemic stroke. *Stroke*. 2016;47:1294–1302. doi: 10.1161/STROKEAHA.115.011874.
58. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1997;28:2119–2225.
59. 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.
60. 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.
61. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erilä T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Köhrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G; 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.
62. 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.
63. 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.
64. 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.
65. Fonarow GC, Saver JL, Smith EE, Broderick JP, Kleindorfer DO, Sacco RL, Pan W, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. 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. doi: 10.1161/JAHA.111.000034.
66. 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.
67. Hwang DY, Silva GS, Furie KL, Greer DM. Comparative sensitivity of computed tomography vs. magnetic resonance imaging for detecting acute posterior fossa infarct. *J Emerg Med*. 2012;42:559–565. doi: 10.1016/j.jemermed.2011.05.101.
68. 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.
69. Wardlaw J, Brazzelli M, Miranda H, Chappell F, McNamee P, Scotland G, Quayyum Z, Martin D, Shuler K, Sandercock P, Dennis M. 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. doi: 10.3310/hta18270.
70. 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.
71. 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.
72. 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.
73. Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA, Grotta JC, Kaste M, von Kummer R, Lansberg MG, Lindley RI, Lyden P, Murray GD, Sandercock PA, Toni D, Toyoda K, Wardlaw JM, Whiteley WN, Baigent C, Hacke W, Howard G; 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.
74. Aghaebrahim A, Streib C, Rangaraju S, Kenmuir CL, Giurgiutiu DV, Horev A, Saeed Y, Callaway CW, Guyette FX, Martin-Gill C, Pacella C, Ducruet AF, Jankowitz BT, Jovin TG, Jadhav AP. Streamlining door to recanalization processes in endovascular stroke therapy. *J Neurointerv Surg*. 2017;9:340–345. doi: 10.1136/neurintsurg-2016-012324.
75. Messe SR, Khatri P, Reeves MJ, Smith EE, Saver JL, Bhatt DL, Grau-Sepulveda MV, Cox M, Peterson ED, Fonarow GC, Schwamm LH. Why are acute ischemic stroke patients not receiving IV tPA? Results from a national registry. *Neurology*. 2016;87:1565–1574.
76. 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.
77. IST-3 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.
78. Demchuk AM, Khan F, Hill MD, Barber PA, Silver B, Patel S, Levine SR; NINDS rt-PA Stroke Study Group. Importance of leukoaraiosis on CT for tissue plasminogen activator decision making: evaluation of the NINDS rt-PA Stroke Study. *Cerebrovasc Dis*. 2008;26:120–125. doi: 10.1159/000139658.
79. Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, von Kummer R. Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. *Stroke*. 2006;37:973–978. doi: 10.1161/01.STR.0000206215.62441.56.
80. Demchuk AM, Hill MD, Barber PA, Silver B, Patel SC, Levine SR; for the NINDS rtPA Stroke Study Group, NIH. Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. *Stroke*. 2005;36:2110–2115. doi: 10.1161/01.STR.0000181116.15426.58.
81. Patel SC, Levine SR, Tilley BC, Grotta JC, Lu M, Frankel M, Haley EC Jr, Brott TG, Broderick JP, Horowitz S, Lyden PD, Lewandowski CA, Marler JR, Welch KM; National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA*. 2001;286:2830–2838.
82. Charidimou A, Pasi M, Fiorelli M, Shams S, von Kummer R, Pantoni L, Rost N. Leukoaraiosis, cerebral hemorrhage, and outcome after intravenous thrombolysis for acute ischemic stroke: a meta-analysis (v1). *Stroke*. 2016;47:2364–2372. doi: 10.1161/STROKEAHA.116.014096.
83. 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.
84. Mair G, von Kummer R, Morris Z, von Heijne A, Bradey N, Cala L, Peeters A, Farrall AJ, Adami A, Potter G, Cohen G, Sandercock PA, Lindley RI, Wardlaw JM; IST-3 Collaborative Group. Effect of alteplase on the CT hyperdense artery sign and outcome after ischemic stroke. *Neurology*. 2016;86:118–125. doi: 10.1212/WNL.0000000000002236.
85. Charidimou A, Shoamanesh 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.
86. Tsivgoulis G, Zand R, Katsanos AH, Turc G, Nolte CH, Jung S, Cordonnier C, Fiebach JB, Scheitz JF, Klinger-Gratz PP, Oppenheim C, Goyal N, Safouris A, Mattle HP, Alexandrov AW, Schellinger PD, Alexandrov AV. 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.
87. 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.
88. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP; DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study. *Ann Neurol*. 2006;60:508–517. doi: 10.1002/ana.20976.
89. 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.
90. Wardlaw JM, Murray V, Berge E, del Zoppo GJ. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD000213.
91. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, O'Brien B, Bladin C, McElduff P, Allen C, Bateman G, Donnan G, Davis S, Levi C. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med*. 2012;366:1099–1107. doi: 10.1056/NEJMoa1109842.
92. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, Kaste M, Lipka LJ, Pedraza S, Ringleb PA, Rowley HA, Schneider D, Schwamm LH, Leal JS, Söhngen M, Teal PA, Wilhelm-Ogunbiyi K, Wintermark M, Warach S. 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.
93. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM; 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.
94. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W; for the 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.
95. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S; 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.
96. 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.
97. Aulicky P, Mikulík R, Goldemund 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.
98. Lima FO, Lev MH, Levy RA, Silva GS, Ebril M, de Camargo EC, Pomerantz S, Singhal AB, Greer DM, Ay H, González RG, Koroshetz WJ, Smith WS, Furie KL. 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.
99. 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.
100. 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.
101. 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.
102. Jovin TG, Chamorro A, Cobo E, de Miquel MA, Molina CA, Rovira A, San Román L, Serena J, Abilleira S, Ribó M, Millán M, Urra X, Cardona P, López-Cancio E, Tomasello A, Castaño C, Blasco J, Aja L, Dorado L, Quesada H, Rubiera M, Hernandez-Pérez M, Goyal M, Demchuk AM, von Kummer R, Gallofré M, Dávalos A; 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.
103. Saver JL, Goyal M, Bonafe A, Diener HC, Levy EI, Pereira VM, Albers GW, Cognard C, Cohen DJ, Hacke W, Jansen O, Jovin TG, Mattle HP, Nogueira RG, Siddiqui AH, Yavagal DR, Baxter BW, Devlin TG, Lopes DK, Reddy VK, du Mesnil de Rochemont R, Singer OC, Jahan R; 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.
104. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, Roy D, Jovin TG, Willinsky RA, Sapkota BL, Dowlatshahi D, Frei DF, Kamal NR, Montanera WJ, Poppe AY, Ryckborst KJ, Silver FL, Shuaib A, Tampieri D, Williams D, Bang OY, Baxter BW, Burns PA, Choe H, Heo JH, Holmstedt CA, Jankowitz B, Kelly M, Linares G, Mandzia JL, Shankar J, Sohn SI, Swartz RH, Barber PA, Coutts SB, Smith EE, Morrish WF, Weill A, Subramaniam S, Mitha AP, Wong JH, Lowerison MW, Sajobi TT, Hill MD; ESCAPE Trial Investigators. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015;372:1019–1030. doi: 10.1056/NEJMoa1414905.
105. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, Yan B, Dowling RJ, Parsons MW, Oxley TJ, Wu TY, Brooks M, Simpson MA, Miteff F, Levi CR, Krause M, Harrington TJ, Faulder KC, Steinfort BS, Priglinger M, Ang T, Scroop R, Barber PA, McGuinness B, Wijeratne T, Phan TG, Chong W, Chandra RV, Bladin CF, Badve M, Rice H, de Villiers L, Ma H, Desmond PM, Donnan GA, Davis SM; EXTEND-IA Investigators. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015;372:1009–1018. doi: 10.1056/NEJMoa1414792.
106. 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.
107. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, Schonewille WJ, Vos JA, Nederkoorn PJ, Wermer MJ, van Walderveen MA, Staals J, Hofmeijer J, van Oostayen JA, Lycklama à Nijeholt GJ, Boiten J, Brouwer PA, Emmer BJ, de Bruijn SF, van Dijk LC, Kappelle LJ, Lo RH, van Dijk EJ, de Vries J, de Kort PL, van Rooij WJ, van den Berg JS, van Hasselt BA, Aerden LA, Dallinga RJ, Visser MC, Bot JC, Vroomen PC, Eshghi O, Schreuder TH, Heijboer RJ, Keizer K, Tielbeek AV, den Hertog HM, Gerrits DG, van den Berg-Vos RM, Karas GB, Steyerberg EW, Flach HZ, Marquering HA, Sprengers ME, Jenniskens SF, Beenen LF, van den Berg R, Koudstaal PJ, van Zwam WH, Roos YB, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW; 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.
108. Nogueira RG, Jadhav AP, Haussen DC, Bonafe A, Budzik RF, Bhuva P, Yavagal DR, Ribo M, Cognard C, Hanel RA, Sila CA, Hassan AE, Millan M, Levy EI, Mitchell P, Chen M, English JD, Shah QA, Silver FL, Pereira VM, Mehta BP, Baxter BW, Abraham MG, Cardona P, Veznedaroglu E, Hellinger FR, Feng L, Kirmani JF, Lopes DK, Jankowitz BT, Frankel MR, Costalat V, Vora NA, Yoo AJ, Malik AM, Furlan AJ, Rubiera M, Aghaebrahim A, Olivot JM, Tekle WG, Shields R, Graves T, Lewis RJ, Smith WS, Liebeskind DS, Saver JL, Jovin TG DAWN Trial Investigators. Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct [published online ahead of print November 11, 2017]. *N Engl J Med*. doi: 10.1056/NEJMoa1706442. http://www.nejm.org/doi/full/10.1056/NEJMoa1706442.
109. Albers GW, Marks MP, Kemp S, Christensen S, Tsai JP, Ortega-Gutierrez S, McTaggart R, Torbey MT, Kim-Tenser M, Leslie-Mazwi T, Sarraj A, Kasner SE, Ansari SA, Yeatts SD, Hamilton S, Mylnash M, Heit JJ, Zaharchuk G, Kim S, Carrozzella J, Palesch YY, Demchuk AM, Bammer R, Lavori PW, Broderick JP, Lansberg MG; on behalf of the DEFUSE 3

Investigators. Thrombectomy for stroke with perfusion imaging selection at 6–16 hours. *N Engl J Med*. In press.
110. Berkhemer OA, Jansen IG, Beumer D, Fransen PS, van den Berg LA, Yoo AJ, Lingsma HF, Sprengers ME, Jenniskens SF, Lycklama À Nijeholt GJ, van Walderveen MA, van den Berg R, Bot JC, Beenen LF, Boers AM, Slump CH, Roos YB, van Oostenbrugge RJ, Dippel DW, van der Lugt A, van Zwam WH, Marquering HA, Majoie CB; 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.
111. Menon BK, Qazi E, Nambiar V, Foster LD, Yeatts SD, Liebeskind D, Jovin TG, Goyal M, Hill MD, Tomsick TA, Broderick JP, Demchuk AM; 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.
112. 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.
113. Roffe C, Nevatte 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.
114. Bennett MH, Weibel S, Wasiak J, Schnabel A, French C, Kranke P. Hyperbaric oxygen therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD004954.
115. 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.
116. Heyboer M 3rd, Jennings S, Grant WD, Ojevwe C, Byrne J, Wojcik SM. Seizure incidence by treatment pressure in patients undergoing hyperbaric oxygen therapy. *Undersea Hyperb Med*. 2014;41:379–385.
117. 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.
118. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos 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.
119. 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.
120. 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.
121. 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.
122. 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.
123. 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.
124. 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.
125. Visvanathan A, Dennis M, Whiteley W. Parenteral fluid regimens for improving functional outcome in people with acute stroke. *Cochrane Database Syst Rev*. 2015:CD011138.
126. Butcher K, Christensen S, Parsons M, De Silva DA, Ebinger M, Levi C, Jeerakathil T, Campbell BC, Barber PA, Bladin C, Fink J, Tress B, Donnan GA, Davis SM; for the EPITHET Investigators. Postthrombolysis blood pressure elevation is associated with hemorrhagic transformation. *Stroke*. 2010;41:72–77. doi: 10.1161/STROKEAHA.109.563767.
127. 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.
128. 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.
129. Mazya M, Egido 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.
130. 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.
131. Endo K, Kario K, Koga M, Nakagawara J, Shiokawa Y, Yamagami H, Furui E, Kimura K, Hasegawa Y, Okada Y, Okuda S, Namekawa M, Miyagi T, Osaki M, Minematsu K, Toyoda K. 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.
132. 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.
133. 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.
134. Saxena M, Young P, Pilcher D, Bailey M, Harrison D, Bellomo R, Finfer S, Beasley R, Hyam J, Menon D, Rowan K, Myburgh J. 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.
135. Lyden P, Hemmen T, Grotta J, Rapp K, Ernstrom K, Rzesiewicz T, Parker S, Concha M, Hussain S, Agarwal S, Meyer B, Jurf J, Altafullah I, Raman R. 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.
136. 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.
137. Piironen K, Tiainen 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.
138. 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.
139. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; 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.
140. 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.
141. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G; 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.

142. IST-3 Collaborative Group, Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, Ricci S, Murray V, Berge E, Slot KB, Hankey GJ, Correia M, Peeters A, Matz K, Lyrer P, Gubitz G, Phillips SJ, Arauz A. 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.
143. Anderson CS, Robinson T, Lindley RI, Arima H, Lavados PM, Lee TH, Broderick JP, Chen X, Chen G, Sharma VK, Kim JS, Thang NH, Cao Y, Parsons MW, Levi C, Huang Y, Olavarría VV, Demchuk AM, Bath PM, Donnan GA, Martins S, Pontes-Neto OM, Silva F, Ricci S, Roffe C, Pandian J, Billot L, Woodward M, Li Q, Wang X, Wang J, Chalmers J; 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.
144. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D, von Kummer R, Wahlgren N, Toni D; 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.
145. 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.
146. 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.
147. Romano JG, Smith EE, Liang L, Gardener H, Camp S, Shuey L, Cook A, Campo-Bustillo I, Khatri P, Bhatt DL, Fonarow GC, Sacco RL, Schwamm LH. 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.
148. 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.
149. 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.
150. Mahaffey KW, Granger CB, Sloan MA, Green CL, Gore JM, Weaver WD, White HD, Simoons ML, Barbash GI, Topol EJ, Califf RM. 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.
151. Goldstein JN, Marrero M, Masrur S, Pervez M, Barrocas AM, Abdullah A, Oleinik A, Rosand J, Smith EE, Dzik WH, Schwamm LH. Management of thrombolysis-associated symptomatic intracerebral hemorrhage. *Arch Neurol*. 2010;67:965–969. doi: 10.1001/archneurol.2010.175.
152. 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.
153. 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.
154. 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.
155. Yaghi S, Boehme AK, Dibu J, Leon Guerrero CR, Ali S, Martin-Schild S, Sands KA, Noorian AR, Blum CA, Chaudhary S, Schwamm LH, Liebeskind DS, Marshall RS, Willey JZ. Treatment and outcome of thrombolysis-related hemorrhage: a multicenter retrospective study. *JAMA Neurol*. 2015;72:1451–1457. doi: 10.1001/jamaneurol.2015.2371.
156. 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.
157. Frontera JA, Lewin JJ 3rd, Rabinstein AA, Aisiku IP, Alexandrov AW, Cook AM, del Zoppo GJ, Kumar MA, Peerschke EI, Stiefel MF, Teitelbaum JS, Wartenberg KE, Zerfoss CL. 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.
158. 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.
159. 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.
160. Lewis LM. Angioedema: etiology, pathophysiology, current and emerging therapies. *J Emerg Med*. 2013;45:789–796. doi: 10.1016/j.jemermed.2013.03.045.
161. Lin SY, Tang SC, Tsai LK, Yeh SJ, Hsiao YJ, Chen YW, Chen KH, Yip BS, Shen LJ, Wu FL, Jeng JS. 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.
162. Correia AS, Matias G, Calado S, Lourenço A, Viana-Baptista M. Orolingual angiodema 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.
163. O'Carroll CB, Aguilar MI. Management of postthrombolysis hemorrhagic and orolingual angioedema complications. *Neurohospitalist*. 2015;5:133–141. doi: 10.1177/1941874415587680.
164. 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.
165. 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.
166. 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.
167. von Kummer R, Mori E, Truelsen T, Jensen JS, Grønning BA, Fiebach JB, Lovblad KO, Pedraza S, Romero JM, Chabriat H, Chang KC, Dávalos A, Ford GA, Grotta J, Kaste M, Schwamm LH, Shuaib A, Albers GW; 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.
168. Albers GW, von Kummer R, Truelsen T, Jensen JK, Ravn GM, Grønning BA, Chabriat H, Chang KC, Davalos AE, Ford GA, Grotta J, Kaste M, Schwamm LH, Shuaib A; 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.
169. Haley EC Jr, Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, Fanale C, Libman R, Kwiatkowski TG, Llinas RH, Levine SR, Johnston KC, Buchsbaum R, Levy G, Levin B; 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.
170. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Rønning OM, Thommessen B, Amthor KF, Ihle-Hansen H, Kurz M, Tobro H, Kaur K, Stankiewicz M, Carlsson M, Morsund Å, Idicula T, Aamodt AH, Lund C, Næss H, Waje-Andreassen U, Thomassen L. 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.

171. 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.
172. Goyal M, Menon BK, van Zwam WH, Dippel DW, Mitchell PJ, Demchuk AM, Dávalos A, Majoie CB, van der Lugt A, de Miquel MA, Donnan GA, Roos YB, Bonafe A, Jahan R, Diener HC, van den Berg LA, Levy EI, Berkhemer OA, Pereira VM, Rempel J, Millán M, Davis SM, Roy D, Thornton J, Román LS, Ribó M, Beumer D, Stouch B, Brown S, Campbell BC, van Oostenbrugge RJ, Saver JL, Hill MD, Jovin TG; 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.
173. Campbell BC, Hill MD, Rubiera M, Menon BK, Demchuk A, Donnan GA, Roy D, Thornton J, Dorado L, Bonafe A, Levy EI, Diener HC, Hernández-Pérez M, Pereira VM, Blasco J, Quesada H, Rempel J, Jahan R, Davis SM, Stouch BC, Mitchell PJ, Jovin TG, Saver JL, Goyal M. 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.
174. 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.
175. Lemmens R, Hamilton SA, Liebeskind DS, Tomsick TA, Demchuk AM, Nogueira RG, Marks MP, Jahan R, Gralla J, Yoo AJ, Yeatts SD, Palesch YY, Saver JL, Pereira VM, Broderick JP, Albers GW, Lansberg MG; 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.
176. Yoo AJ, Simonsen CZ, Prabhakaran S, Chaudhry ZA, Issa MA, Fugate JE, Linfante I, Liebeskind DS, Khatri P, Jovin TG, Kallmes DF, Dabus G, Zaidat OO; 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.
177. 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.
178. Lapergue B, Blanc R, Gory B, Labreuche J, Duhamel A, Marnat G, Saleme S, Costalat V, Bracard S, Desal H, Mazighi M, Consoli A, Piotin M; 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.
179. Dippel DW, Majoie CB, Roos YB, van der Lugt A, van Oostenbrugge RJ, van Zwam WH, Lingsma HF, Koudstaal PJ, Treurniet KM, van den Berg LA, Beumer D, Fransen PS, Berkhemer OA; 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.
180. Berkhemer OA, van den Berg LA, Fransen PS, Beumer D, Yoo AJ, Lingsma HF, Schonewille WJ, van den Berg R, Wermer MJ, Boiten J, Lycklama À Nijeholt GJ, Nederkoorn PJ, Hollmann MW, van Zwam WH, van der Lugt A, van Oostenbrugge RJ, Majoie CB, Dippel DW, Roos YB; 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.
181. Löwhagen Hendén P, Rentzos A, Karlsson JE, Rosengren L, Leiram B, Sundeman H, Dunker D, Schnabel K, Wikholm G, Hellström M, Ricksten SE. 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.
182. Schönenberger S, Uhlmann L, Hacke W, Schieber S, Mundiyanapurath S, Purrucker JC, Nagel S, Klose C, Pfaff J, Bendszus M, Ringleb PA, Kieser M, Möhlenbruch MA, Bösel J. 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.
183. Jovin TG, Saver JL, Ribo M, Pereira V, Furlan A, Bonafe A, Baxter B, Gupta R, Lopes D, Jansen O, Smith W, Gress D, Hetts S, Lewis RJ, Shields R, Berry SM, Graves TL, Malisch T, Rai A, Sheth KN, Liebeskind DS, Nogueira RG. Diffusion-weighted imaging or computerized tomography perfusion assessment with clinical mismatch in the triage of wake up and late presenting strokes undergoing neurointervention with Trevo (DAWN) trial methods. *Int J Stroke*. 2017;12:641–652. doi: 10.1177/1747493017710341.
184. 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.
185. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke: CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet*. 1997;349:1641–1649.
186. Sandercock PA, Counsell C, Tseng MC, Cecconi E. Oral antiplatelet therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD000029.
187. Siebler M, Hennerici MG, Schneider D, von Reutern GM, Seitz RJ, Röther J, Witte OW, Hamann G, Junghans U, Villringer A, Fiebach JB. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. *Stroke*. 2011;42:2388–2392. doi: 10.1161/STROKEAHA.110.599662.
188. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, del Zoppo G, Kleindorfer D, Woo D, Khatri P, Castaldo J, Frey J, Gebel J Jr, Kasner S, Kidwell C, Kwiatkowski T, Libman R, Mackenzie R, Scott P, Starkman S, Thurman RJ; for the CLEAR Trial Investigators. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: the CLEAR stroke trial. *Stroke*. 2008;39:3268–3276. doi: 10.1161/STROKEAHA.108.517656.
189. 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 eptifibatide 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.
190. Adeoye O, Sucharew H, Khoury J, Vagal A, Schmit PA, Ewing I, Levine SR, Demel S, Eckerle B, Katz B, Kleindorfer D, Stettler B, Woo D, Khatri P, Broderick JP, Pancioli AM. Combined approach to lysis utilizing eptifibatide 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.
191. Ciccone A, Motto C, Abraha I, Cozzolino F, Santilli I. Glycoprotein IIb-IIIa inhibitors for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD005208.
192. Adams HP Jr, Effron MB, Torner J, Dávalos A, Frayne J, Teal P, Leclerc J, Oemar B, Padgett L, Barnathan ES, Hacke W; 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.
193. Wang Y, Wang Y, Zhao X, Liu L, Wang D, Wang C, Wang C, Li H, Meng X, Cui L, Jia J, Dong Q, Xu A, Zeng J, Li Y, Wang Z, Xia H, Johnston SC; 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.
194. Wang Y, Pan Y, Zhao X, Li H, Wang D, Johnston SC, Liu L, Meng X, Wang A, Wang C, Wang 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.
195. Johnston SC, Easton JD, Farrant M, Barsan W, Battenhouse H, Conwit R, Dillon C, Elm J, Lindblad A, Morgenstern L, Poisson SN, Palesch Y. Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke (POINT) trial: rationale and design. *Int J Stroke*. 2013;8:479–483. doi: 10.1111/ijs.12129.
196. 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.
197. 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.
198. Sandercock PA, Counsell C, Kane EJ. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2015:CD000024.
199. 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.
200. 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.
201. 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.
202. Paciaroni M, Agnelli G, Falocci N, Caso V, Becattini C, Marcheselli S, Rueckert C, Pezzini A, Poli L, Padovani A, Csiba L, Szabó L, Sohn SI, Tassinari T, Abdul-Rahim AH, Michel P, Cordier M, Vanacker P, Remillard S, Alberti A, Venti M, Scoditti U, Denti L, Orlandi G, Chiti A, Gialdini G, Bovi P, Carletti M, Rigatelli A, Putaala J, Tatlisumak T, Masotti L, Lorenzini G, Tassi R, Guideri F, Martini G, Tsivgoulis G, Vadikolias K, Liantinioti C, Corea F, Del Sette M, Ageno W, De Lodovici ML, Bono G, Baldi A, D'Anna S, Sacco S, Carolei A, Tiseo C, Acciarresi M, D'Amore C, Imberti D, Zabzuni D, Doronin B, Volodina V, Consoli D, Galati F, Pieroni A, Toni D, Monaco S, Baronello MM, Barlinn K, Pallesen LP, Kepplinger J, Bodechtel U, Gerber J, Deleu D, Melikyan G, Ibrahim F, Akhtar N, Mosconi MG, Bubba V, Silvestri I, Lees KR. 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.
203. 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.
204. Vellimana AK, Kadkhodayan Y, Rich KM, Cross DT 3rd, Moran CJ, Zazulia AR, Lee JM, Chicoine MR, Dacey RG Jr, Derdeyn CP, Zipfel GJ. 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.
205. Barreto AD, Alexandrov AV, Lyden P, Lee J, Martin-Schild S, Shen L, Wu TC, Sisson A, Pandurengan R, Chen Z, Rahbar MH, Balucani C, Barlinn K, Sugg RM, Garami Z, Tsivgoulis G, Gonzales NR, Savitz SI, Mikulik R, Demchuk AM, Grotta JC. 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.
206. 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.
207. Gioia LC, Kate M, Sivakumar L, Hussain D, Kalashyan H, Buck B, Bussiere M, Jeerakathil T, Shuaib A, Emery D, Butcher K. 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.
208. Chang TS, Jensen MB. Haemodilution for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2014:CD000103.
209. 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.
210. 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 Ischemic Stroke) trials: analysis of the combined data from parts 1 and 2. *Stroke*. 2016;47:2355–2359. doi: 10.1161/STROKEAHA.116.012825.
211. 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.
212. 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.
213. Zivin JA, Albers GW, Bornstein N, Chippendale T, Dahlof B, Devlin T, Fisher M, Hacke W, Holt W, Ilic S, Kasner S, Lew R, Nash M, Perez J, Rymer M, Schellinger P, Schneider D, Schwab S, Veltkamp R, Walker M, Streeter J; 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.
214. Hacke W, Schelinger PD, Albers GW, Bornstein NM, Dahlof BS, Kasner SE, Howard G, Shuaib A, Richieri SP, Dilly S, Zivin J. Transcranial laser therapy (TLT) for acute ischemic stroke: results of NEST 3, a pivotal phase III randomized clinical trial (RCT). *Cerebrovasc Dis*. 2013;35:191.
215. 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.
216. 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.
217. 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.
218. 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.
219. Schrader J, Lüders S, Kulschewski A, Berger J, Zidek W, Treib J, Einhäupl K, Diener HC, Dominiak 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.
220. 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.
221. 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.
222. 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.
223. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, James MA, Knight J, Markus HS, Mistri AK, Poulter NR; 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.
224. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, Murray GD, Richter PS, Roine RO, Terént A, Thijs V, Berge E; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741–750. doi: 10.1016/S0140-6736(11)60104-9.
225. He J, Zhang Y, Xu T, Zhao Q, Wang D, Chen CS, Tong W, Liu C, Xu T, Ju Z, Peng Y, Peng H, Li Q, Geng D, Zhang J, Li D, Zhang F, Guo L, Sun Y, Wang X, Cui Y, Li Y, Ma D, Yang G, Gao Y, Yuan X, Bazzano LA, Chen J; 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.
226. Bath PM, Krishnan K. Interventions for deliberately altering blood pressure in acute stroke. *Cochrane Database Syst Rev*. 2014:CD000039.
227. Oh MS, Yu KH, Hong KS, Kang DW, Park JM, Bae HJ, Koo J, Lee J, Lee BC; Valsartan Efficacy oN 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/ijs.12446.

228. Enos Trial Investigators, Bath PM, Woodhouse L, Scutt P, Krishnan K, Wardlaw JM, Bereczki D, Sprigg N, Berge E, Beridze M, Caso V, Chen C, Christensen H, Collins R, El Etribi A, Laska AC, Lees KR, Ozturk S, Phillips S, Pocock S, de Silva HA, Szatmari S, Utton S. 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;385:617–28.
229. 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.

230–234. Deleted.

235. Dennis M, Lewis S, Cranswick 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.
236. 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.
237. 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.
238. 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.
239. 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.
240. Dennis M, Caso V, Kappelle LJ, Pavlovic A, Sandercock P. European Stroke Organisation (ESO) guidelines for prophylaxis for venous thromboembolism in immobile patients with acute ischaemic stroke. *Eur Stroke J*. 2016;1:6–19.
241. 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.
242. Towfighi A, Ovbiagele B, El Husseini 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.
243. AVERT Trial Collaboration Group. Efficacy and safety of very early mobilisation within 24 h of stroke onset (AVERT): a randomised controlled trial. *Lancet*. 2015;386:46–55.
244. Raco A, Caroli E, Isidori A, Salvati M. Management of acute cerebellar infarction: one institution's experience. *Neurosurgery*. 2003;53:1061–1605.
245. Agarwalla PK, Stapleton CJ, Ogilvy CS. Craniectomy in acute ischemic stroke. *Neurosurgery*. 2014;74(suppl 1):S151–S162. doi: 10.1227/NEU.0000000000000226.
246. Mostofi K. Neurosurgical management of massive cerebellar infarct outcome in 53 patients. *Surg Neurol Int*. 2013;4:28. doi: 10.4103/2152-7806.107906.
247. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser 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.
248. 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.
249. 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.
250. 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.
251. 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.
252. 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.
253. 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.
254. Jüttler E, Unterberg A, Woitzik J, Bösel J, Amiri H, Sakowitz OW, Gondan M, Schiller P, Limprecht R, Luntz S, Schneider H, Pinzer T, Hobohm C, Meixensberger J, Hacke W; 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.
255. 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.
256. Curley G, Kavanagh BP, Laffey JG. Hypocapnia and the injured brain: more harm than benefit. *Crit Care Med*. 2010;38:1348–1359. doi: 10.1097/CCM.0b013e3181d8cf2b.
257. 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.

258–321. Deleted.

322. Kim JT, Heo SH, Park MS, Chang J, Choi KH, Cho KH. Use of antithrombotics after hemorrhagic transformation in acute ischemic stroke. *PLoS One*. 2014;9:e89798. doi: 10.1371/journal.pone.0089798.
323. England TJ, Bath PM, Sare GM, Geeganage C, Moulin T, O'Neill D, Woimant F, Christensen H, De Deyn P, Leys D, Ringelstein EB; on behalf of the TAIST 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.
324. Deleted.
325. 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.0000000000003617.
326. 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.

327–335. Deleted.

336. Schwartz J, Dreyer RP, Murugiah K, Ranasinghe I. Contemporary prehospital 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.
337. Morgenstern LB, Gonzales NR, Maddox KE, Brown DL, Karim AP, Espinosa N, Moyé LA, Pary JK, Grotta JC, Lisabeth LD, Conley KM. 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.
338. 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.
339. Kim JT, Chung PW, Starkman S, Sanossian N, Stratton SJ, Eckstein M, Pratt FD, Conwit R, Liebeskind DS, Sharma L, Restrepo L, Tenser MK, Valdes-Sueiras M, Gornbein J, Hamilton S, Saver JL; 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.
340. 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*. 2017:1–8.

341. Sauser K, Levine DA, 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.
342. 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.
343. 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.
344. 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.
345. 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.
346. Demaerschalk BM, Bobrow BJ, Raman R, Kiernan TE, Aguilar MI, Ingall TJ, Dodick DW, Ward MP, Richemont PC, Brazdys K, Koch TC, Miley ML, Hoffman Snyder CR, Corday DA, Meyer BC; 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.
347. 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.
348. 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.
349. 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. *Efficacy Mech Eval*. 2014;1(3). doi: 10.3310/eme.01030.
350. Mocco J, Zaidat OO, von Kummer R, Yoo AJ, Gupta R, Lopes D, Frei D, Shownkeen H, Budzik R, Ajani ZA, Grossman A, Altschul D, McDougall C, Blake L, Fitzsimmons BF, Yavagal D, Terry J, Farkas J, Lee SK, Baxter B, Wiesmann M, Knauth M, Heck D, Hussain S, Chiu D, Alexander MJ, Malisch T, Kirmani J, Miskolczi L, Khatri P; THERAPY Trial Investigators. Aspiration thrombectomy after intravenous alteplase versus intravenous alteplase alone. *Stroke*. 2016;47:2331–2338. doi: 10.1161/STROKEAHA.116.013372.
351. Broderick JP, Palesch YY, Demchuk AM, Yeatts SD, Khatri P, Hill MD, Jauch EC, Jovin TG, Yan B, Silver FL, von Kummer R, Molina CA, Demaerschalk BM, Budzik R, Clark WM, Zaidat OO, Malisch TW, Goyal M, Schonewille WJ, Mazighi M, Engelter ST, Anderson C, Spilker J, Carrozzella J, Ryckborst KJ, Janis LS, Martin RH, Foster LD, Tomsick TA; 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.
352. 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.
353. Kidwell CS, Jahan R, Gornbein J, Alger JR, Nenov V, Ajani Z, Feng L, Meyer BC, Olson S, Schwamm LH, Yoo AJ, Marshall RS, Meyers PM, Yavagal DR, Wintermark M, Guzy J, Starkman S, Saver JL; 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.
354. 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.
355. 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.
356. 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.
357. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. 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.
358. 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.
359. Singhal A, Partners SPOTRIAS Investigators. A phase IIB clinical trial of normobaric oxygen therapy (NBO) in acute ischemic stroke (AIS). *Neurology*. 2013;80(suppl):S02.001.
360. 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.
361. 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.
362. 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.
363. Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033–2037.
364. 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.
365. 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.
366. Lyerly MJ, Albright KC, Boehme AK, Bavarsad Shahripour R, Houston JT, Rawal PV, Kapoor N, Alvi M, Sisson A, Alexandrov AW, Alexandrov AV. 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.
367. 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.
368. 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.
369. 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.
370. Broessner G, Beer R, Lackner P, Helbok R, Fischer M, Pfausler B, Rhorer 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.
371. 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.
372. Horn CM, Sun CH, Nogueira RG, Patel VN, Krishnan A, Glenn BA, Belagaje SR, Thomas TT, Anderson AM, Frankel MR, Schindler KM, Gupta R. Endovascular Reperfusion and Cooling in Cerebral Acute

Ischemia (ReCCLAIM I). *J Neurointerv Surg*. 2014;6:91–95. doi: 10.1136/neurintsurg-2013-010656.
373. Su Y, Fan L, Zhang Y, Zhang Y, Ye H, Gao D, Chen W, Liu G. Improved neurological outcome with mild hypothermia in surviving patients with massive cerebral hemispheric infarction. *Stroke*. 2016;47:457–463. doi: 10.1161/STROKEAHA.115.009789.
374. Hong JM, Lee JS, Song HJ, Jeong HS, Jung HS, Choi HA, Lee K. Therapeutic hypothermia after recanalization in patients with acute ischemic stroke. *Stroke*. 2014;45:134–140. doi: 10.1161/STROKEAHA.113.003143.
375. Ovesen C, Brizzi M, Pott FC, Thorsen-Meyer HC, Karlsson T, Ersson A, Christensen H, Norrlin A, Meden P, Krieger DW, Petersson J. Feasibility of endovascular and surface cooling strategies in acute stroke. *Acta Neurol Scand*. 2013;127:399–405. doi: 10.1111/ane.12059.
376. 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: Thromblytic Therapy in Acute Ischemic Stroke Study Investigators. *Stroke*. 2000;31:811–816.
377. 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.
378. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. 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.
379. 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.
380. 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.
381. Coutinho JM, Liebeskind DS, Slater LA, Nogueira RG, Clark W, Davalos A, Bonafe A, Jahan R, Fischer U, Gralla J, Saver JL, Pereira VM. 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.
382. 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.
383. 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.
384. 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.
385. Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J, Kulkarni AV, Singh S, Alqahtani A, Rochwerg B, Alshahrani M, Murty NK, Alhazzani A, Yarascavitch B, Reddy K, Zaidat OO, Almenawer SA. Endovascular thrombectomy for acute ischemic stroke: a meta-analysis. *JAMA*. 2015;314:1832–1843. doi: 10.1001/jama.2015.13767.
386. 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.
387. 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.
388. 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.
389. 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.
390. Marmagkiolis K, Hakeem A, Cilingiroglu M, Gundogdu B, Iliescu C, Tsitlakidou 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.
391. 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.
392. 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.
393. 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.
394. 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.
395. Li W, Lin L, Zhang M, Wu Y, Liu C, Li X, Huang S, Liang C, Wang Y, Chen J, Feng W. 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.
396. 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.
397. Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2008:CD000024.
398. 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.
399. 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.
400. Saver JL, Starkman S, Eckstein M, Stratton SJ, Pratt FD, Hamilton S, Conwit R, Liebeskind DS, Sung G, Kramer I, Moreau G, Goldweber R, Sanossian N; 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.
401. Hacke W, Schellinger PD, Albers GW, Bornstein NM, Dahlof BL, Fulton R, Kasner SE, Shuaib A, Richieri SP, Dilly SG, Zivin J, Lees KR; 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.
402. 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.
403. 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.
404. 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.
405. 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: 10.7326/0003-4819-155-9-201111010-00011.
406. 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.
407. 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.
408. 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.
409. 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.
410. 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.
411. Devlin TG, Phade SV, Hutson RK, Fugate MW, Major GR 2nd, Albers GW, Sirelkhatim AA, Sapkota BL, Quartfordt 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.
412. 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.
413. 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.
414. 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.
415. 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.
416. 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.
417. Kim JT, Park MS, Choi KH, Cho KH, Kim BJ, Han MK, Park TH, Park SS, Lee KB, Lee BC, Yu KH, Oh MS, Cha JK, Kim DH, Nah HW, Lee J, Lee SJ, Ko YC, Kim JG, Park JM, Kang K, Cho YJ, Hong KS, Choi JC, Kim DE, Ryu WS, Shin DI, Yeo MJ, Kim WJ, Lee J, Lee JS, Saver JL, Bae HJ. Different antiplatelet strategies in patients with new ischemic stroke while taking aspirin. *Stroke*. 2016;47:128–134. doi: 10.1161/STROKEAHA.115.011595.
418. Lee M, Wu YL, Saver JL, Lee HC, Lee JD, Chang KC, Wu CY, Lee TH, Wang HH, Rao NM, Ovbiagele B. 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.
419. 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.
420. 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.
421. 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.