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

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

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

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

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

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

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

This statement was approved by the American Heart Association Science Advisory and Coordinating Committee on September 12, 2019, and the American Heart Association Executive Committee on October 3, 2019. A copy of the document is available at https://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 843-216-2533 or email kelle.ramsay@wolterskluwer.com.

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

The American Heart Association requests that this document be cited as follows: Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC, Kidwell CS, Leslie-Mazwi TM, Ovbiagele B, Scott PA, Sheth KN, Southerland AM, Summers DV, Tirschwell DL; on behalf of the American Heart Association Stroke Council. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2019;50:e344–e418 doi: 10.1161/STR.0000000000000211.

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when appropriate. The current final document was approved by all members of the writing group except when relationships with industry precluded members from voting and by the governing bodies of the AHA. These guidelines use the American College of Cardiology/AHA 2015 Class of Recommendations and Level of Evidence and the new AHA guidelines format.

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

Conclusions—These guidelines provide general recommendations based on the currently available evidence to guide clinicians caring for adult patients with acute arterial ischemic stroke. In many instances, however, only limited data exist demonstrating the urgent need for continued research on treatment of acute ischemic stroke. **(*Stroke*. 2019;50:e344–e418. DOI: 10.1161/STR.0000000000000211.)**

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

See related article, p 3331

New high-quality evidence has produced major changes in the evidence-based treatment of acute ischemic stroke (AIS) since the publication of the guidelines for the early management of patients with acute ischemic stroke in 2013.[1] Much of this new evidence has been incorporated into American Heart Association (AHA) focused updates, guidelines, or scientific statements on specific topics relating to the management of patients with AIS since 2013. The purpose of these guidelines is to provide an up-to-date comprehensive set of recommendations for clinicians caring for adult patients with acute arterial ischemic stroke in a single document. These guidelines address prehospital care, urgent and emergency evaluation and treatment with intravenous (IV) and intra-arterial therapies, and in-hospital management, including secondary prevention measures that are often begun during the initial hospitalization. We have restricted our recommendations to adults and to secondary prevention measures that are appropriately instituted within the first 2 weeks. We have not included recommendations for cerebral venous sinus thrombosis because these were covered in a 2011 scientific statement and there is no new evidence that would change those conclusions.[2]

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

These guidelines use the American College of Cardiology (ACC)/AHA Class of Recommendations (COR) and Level of Evidence (LOE) format shown in Table 1. New or revised recommendations that supersede previous guideline recommendations are accompanied by 250-word knowledge bytes and data supplement tables summarizing the key studies supporting the recommendations in place of extensive text. These data supplement tables can be found in Data Supplement 1 and literature search information for all data supplement tables can be found in Data Supplement 2. Because this guideline represents an update of the 2018 AIS Guidelines, the term "New Recommendation" refers to recommendations that are new to either the 2018 AIS Guidelines or to this 2019 update. Existing recommendations that are unchanged are reiterated with reference to the previous publication. These previous publications and their abbreviations used in this document are listed in Table 2. When there is no new pertinent evidence for these unchanged recommendations, no knowledge byte or data supplement is provided. For some unchanged recommendations, there are new pertinent data that support the existing recommendation, and these are provided. Additional abbreviations used in this guideline are listed in Table 3.

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

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.

Section 3.7.2., Recommendation 2 resulted. To allow these modifications to be incorporated, the standard peer review process was abbreviated, with review provided by the members of the Stroke Council's Scientific Statements Oversight Committee and by liaisons from the endorsing organizations listed on the masthead. The list of these reviewers is provided at the end of the guideline. The final document was approved by the AHA Science Advisory and Coordinating Committee and Executive Committee.

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

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

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

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

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

Table 3. Abbreviations in This Guideline

ACC	American College of Cardiology
AHA	American Heart Association
AIS	Acute ischemic stroke
ARD	Absolute risk difference
ASA	American Stroke Association
ASCVD	Atherosclerotic cardiovascular disease
ASPECTS	Alberta Stroke Program Early Computed Tomography Score
BP	Blood pressure
CEA	Carotid endarterectomy
CeAD	Cervical artery dissection
CMB	Cerebral microbleed
COR	Class of recommendation
CPAP	Continuous positive airway pressure
CS	Conscious sedation
CT	Computed tomography
CTA	Computed tomographic angiography
CTP	Computed tomographic perfusion
DTN	Door-to-needle
DVT	Deep vein thrombosis
DW-MRI	Diffusion-weighted magnetic resonance imaging
ED	Emergency department
EMS	Emergency medical services
EVT	Endovascular therapy
GA	General anesthesia
GWTG	Get With The Guidelines
HBO	Hyperbaric oxygen
HR	Hazard ratio
HT	Hemorrhagic transformation
ICH	Intracerebral hemorrhage
IPC	Intermittent pneumatic compression
IV	Intravenous
LDL-C	Low-density lipoprotein cholesterol
LMWH	Low-molecular-weight heparin
LOE	Level of evidence
LVO	Large vessel occlusion
M1	Middle cerebral artery segment 1
M2	Middle cerebral artery segment 2
M3	Middle cerebral artery segment 3
MCA	Middle cerebral artery
MI	Myocardial infarction
MR	Magnetic resonance
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRS	Modified Rankin Scale
mTICI	Modified Thrombolysis in Cerebral Infarction
NCCT	Noncontrast computed tomography
NIHSS	National Institutes of Health Stroke Scale
NINDS	National Institute of Neurological Disorders and Stroke
OR	Odds ratio
OSA	Obstructive sleep apnea
PFO	Patent foramen ovale
RCT	Randomized clinical trial
RR	Relative risk
rt-PA	Recombinant tissue-type plasminogen activator
SBP	Systolic blood pressure
sICH	Symptomatic intracerebral hemorrhage
TIA	Transient ischemic attack
UFH	Unfractionated heparin

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

1.2. EMS Assessment and Management

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

1.3. EMS Systems

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

1.4. Hospital Stroke Capabilities

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

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

1.5. Hospital Stroke Teams (Continued)	COR	LOE	New, Revised, or Unchanged
4. It is recommended that stroke systems of care be developed so that fibrinolytic-eligible patients and mechanical thrombectomy-eligible patients receive treatment in the fastest achievable onset-to-treatment time.	I	A	Recommendation revised from 2013 AIS Guidelines.
Treatment of AIS with IV tissue-type plasminogen activator is of proven benefit for select patients given up to 4.5 hours after symptom onset.[48,49] Pooled data from RCTs indicate the benefit is greatest when treatment occurs early after stroke onset and declines with time.[50] Registry data from AHA GWTG-Stroke hospitals confirm this temporal relationship. In an analysis of 58 353 alteplase-treated patients, treatment started more rapidly (evaluated in 15-minute increments) was associated with reduced in-hospital mortality (OR, 0.96 [95% CI, 0.95–0.98]; $P<0.001$), reduced symptomatic intracerebral hemorrhage (sICH) (OR, 0.96 [95% CI, 0.95–0.98]; $P<0.001$), increased independent ambulation at discharge (OR, 1.04 [95% CI, 1.03–1.05]; $P<0.001$), and increased discharge to home (OR, 1.03 [95% CI, 1.02–1.04]; $P<0.001$). Patient factors most strongly associated with shorter onset-to-treatment times include greater stroke severity, arrival by ambulance, and arrival during regular hours.[41] With respect to endovascular treatment, a pooled analysis of 5 randomized trials comparing endovascular therapy (EVT) with medical therapy alone in which the majority of the patients were treated within 6 hours found that the odds of improved disability outcomes at 90 days (as measured by the modified Rankin Scale [mRS] distribution) declined with longer time from symptom onset to arterial puncture.[42] The 6- to 16- and 6- to 24-hour treatment windows trials, which used advanced imaging to identify a relatively uniform patient group, showed limited variability of treatment effect with time in these highly selected patients.[51,52] The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure that the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible.			See Table VIII in online Data Supplement 1.
5. Establishing and monitoring target time goals for ED door-to-treatment IV fibrinolysis time can be beneficial to monitor and enhance system performance.	I	B-NR	New recommendation.
In AHA GWTG-Stroke hospitals, median DTN time for IV alteplase administration decreased from 77 minutes (interquartile range, 60–98 minutes) during the 2003 to 2009 preintervention period to 67 minutes (interquartile range, 51–87 minutes) during the 2010 to 2013 postintervention period ($P<0.001$). The percentage of alteplase-treated patients having DTN times of ≤60 minutes increased from 26.5% (95% CI, 26.0–27.1) to 41.3% (95% CI, 40.8–41.7; $P<0.001$). Comparing the quarter immediately before the intervention (quarter 4 of 2009) and the final postintervention quarter (quarter 3 of 2013) showed that DTN times of ≤60 minutes increased from 29.6% (95% CI, 27.8–31.5) to 53.3% (95% CI, 51.5–55.2; $P<0.001$).[53] In a subsequent study evaluating a cohort of hospitals from 2014 to 2015, 59.3% of patients received IV alteplase within a DTN time of 60 minutes.[54]			See Table 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 effective in supporting rapid imaging interpretation in time for IV alteplase administration decision making.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE revised. See Table XCV in online Data Supplement 1 for original wording.
Studies of teleradiology to read brain imaging in acute stroke have successfully assessed feasibility; agreement between telestroke neurologists, radiologists, and neuroradiologists over the presence or absence of radiological contraindications to IV alteplase; and reliability of telestroke radiological evaluations. Further support for this unchanged recommendation from the 2013 AIS Guidelines with LOE upgraded to A is provided by 3 additional studies published since the 2013 Guidelines.[55–57]			See Table X in online Data Supplement 1.
3. The use of telemedicine/telestroke resources and systems should be supported by healthcare institutions, governments, payers, and vendors as one method to ensure adequate 24/7 coverage and care of acute stroke patients in a variety of settings.	I	C-EO	Recommendation reworded for clarity from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
4. Telestroke/teleradiology evaluations of AIS patients can be effective for correct IV alteplase eligibility decision making.	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.[58]			See Table XI in online Data Supplement 1.

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

1.7. Organization and Integration of Components

1.7. Organization and Integration of Components	COR	LOE	New, Revised, or Unchanged
1. All hospitals caring for stroke patients within a stroke system of care should develop, adopt, and adhere to care protocols that reflect current care guidelines as established by national and international professional organizations and state and federal agencies and laws.	**I**	**C-EO**	Recommendation unchanged from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
2. Different services within a hospital that may be transferring patients through a continuum of care, as well as different hospitals that may be transferring patients to other facilities, should establish hand-off and transfer protocols and procedures that ensure safe and efficient patient care within and between facilities. Protocols for interhospital transfer of patients should be established and approved beforehand so that efficient patient transfers can be accomplished at all hours of the day and night.	**I**	**C-EO**	Recommendation unchanged from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
3. Mechanical thrombectomy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography, qualified neurointerventionalists, and a comprehensive periprocedural care team. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to consider preestablished criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures such as those agreed on by the Committee for Advanced Subspecialty Training of the Society of Neurological Surgeons in conjunction with other professional societies.[61a]	**I**	**C-EO**	Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
4. It may be useful for primary stroke centers and other healthcare facilities that provide initial emergency care, including administration of IV alteplase, to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for mechanical thrombectomy and to reduce the time to mechanical thrombectomy.	**IIb**	**C-LD**	Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
Between 2006 and 2010, the proportion of ischemic strokes undergoing computed tomographic angiography (CTA) increased from 3.8% to 9.1% ($P<0.0001$). Computed tomography perfusion (CTP) increased from 0.05% to 2.9% over the same period ($P<0.0001$). Reperfusion treatment was more common among those who were imaged with CTA (13.0%) and CTP (17.6%) compared with those with computed tomography (CT) of the head alone (4.0%; $P<0.0001$).[62] However, when considering implementation of multimodal CT imaging at small or remote-access hospitals, resource availability and realistic expectations for gains in efficiency should be taken into account.			

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

1.8. Establishment of Data Repositories

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

1.9. Stroke System Care Quality Improvement Process

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

2. Emergency Evaluation and Treatment

2.1. Stroke Scales

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

Table 4. National Institutes of Health Stroke Scale

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

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2.2. Head and Neck Imaging

2.2.1. Initial Imaging	COR	LOE	New, Revised, or Unchanged
1. All patients with suspected acute stroke should receive emergency brain imaging evaluation on first arrival to a hospital before initiating any specific therapy to treat AIS.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. Systems should be established so that brain imaging studies can be performed as quickly as possible in patients who may be candidates for IV fibrinolysis or mechanical thrombectomy or both.	I	B-NR	New recommendation.
The benefit of IV alteplase is time dependent, with earlier treatment within the therapeutic window leading to bigger proportional benefits.[42,78] A brain imaging study to exclude ICH is recommended as part of the initial evaluation of patients who are potentially eligible for these therapies. With respect to endovascular treatment, a pooled analysis of 5 randomized trials comparing EVT with medical therapy alone in which the majority of the patients were treated within 6 hours found that the odds of improved disability outcomes at 90 days (as measured by the mRS score distribution) declined with longer time from symptom onset to arterial puncture.[42] The 6- to 16- and 6- to 24-hour treatment windows trials, which used advanced imaging to identify a relatively uniform patient group, showed limited variability of treatment effect with time in these highly selected patients.[51,52] The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure that the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible. Reducing the time interval from ED presentation to initial brain imaging can help to reduce the time to treatment initiation. Studies have shown that median or mean door-to-imaging times of ≤20 minutes can be achieved in a variety of different hospital settings.[79–81]			See Tables XVI and XVII in online Data Supplement 1.
3. Noncontrast CT (NCCT) is effective to exclude ICH before IV alteplase administration.	I	A	Recommendation revised from 2013 AIS Guidelines.
4. Magnetic resonance (MR) imaging (MRI) is effective to exclude ICH before IV alteplase administration.	I	B-NR	Recommendation revised from 2013 AIS Guidelines.
5. CTA with CTP or MR angiography (MRA) with diffusion-weighted magnetic resonance imaging (DW-MRI) with or without MR perfusion is recommended for certain patients.	I	A	New recommendation.
In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention.[82,83] NCCT scanning of patients with acute stroke is effective for the rapid detection of acute ICH. NCCT was the only neuroimaging modality used in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA (Recombinant Tissue-Type Plasminogen Activator) trials and in ECASS (European Cooperative Acute Stroke Study) III and is therefore sufficient neuroimaging for decisions about IV alteplase in most patients.[48,49] Immediate CT scanning provides high value for patients with acute stroke.[84,85] MRI was as accurate as NCCT in detecting hyperacute intraparenchymal hemorrhage in patients presenting with stroke symptoms within 6 hours of onset when gradient echo sequences were used.[86,87] In patients who awake with stroke or have unclear time of onset >4.5 hours from baseline or last known well, MRI to identify diffusion-positive fluid-attenuated inversion recovery (FLAIR)–negative lesions can be useful for selecting those who can benefit from IV alteplase administration within 4.5 hours of stroke symptom recognition.[88] CTA with CTP or MRA with DW-MRI with or without MR perfusion is useful for selecting candidates for mechanical thrombectomy between 6 and 24 hours after last known well.[51,52] See specific recommendations below.			See Tables XVII through XX in online Data Supplement 1.

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

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

2.2.3. Mechanical Thrombectomy Eligibility–Vessel Imaging	COR	LOE	New, Revised, or Unchanged
1. For patients who otherwise meet criteria for mechanical thrombectomy, noninvasive vessel imaging of the intracranial arteries is recommended during the initial imaging evaluation.	I	A	Recommendation reworded for clarity from 2015 Endovascular. COR and LOE unchanged. See Table XCV in online Data Supplement 1 for original wording.
2. For patients with suspected LVO who have not had noninvasive vessel imaging as part of their initial imaging assessment for stroke, noninvasive vessel imaging should then be obtained as quickly as possible (eg, during alteplase infusion if feasible).	I	A	Recommendation revised from 2015 Endovascular. COR and LOE unchanged.
A recent systematic review evaluated the accuracy of prediction instruments for diagnosing LVO.[4] In the setting where confirmed ischemic stroke patients would be assessed by a neurologist or emergency physician in the ED, the authors suggested that the NIHSS score is the best of the LVO prediction instruments. According to their meta-analysis, a threshold of ≥10 would provide the optimal balance between sensitivity (73%) and specificity (74%). To maximize sensitivity (at the cost of lower specificity), a threshold of ≥6 would have 87% sensitivity and 52% specificity. However, even this low threshold misses some cases with LVO, whereas the low specificity indicates that false-positives will be common. The sensitivity of CTA and MRA compared with the gold standard of catheter angiography ranges from 87% to 100%, with CTA having greater accuracy than MRA.[95,96] Pivotal trials of mechanical thrombectomy all required noninvasive CTA or MRA diagnosis of LVO as an inclusion criterion.			See Tables XVII and XXII in online Data Supplement 1.
3. In patients with suspected intracranial LVO and no history of renal impairment, who otherwise meet criteria for mechanical thrombectomy, it is reasonable to proceed with CTA if indicated before obtaining a serum creatinine concentration.	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.[97–102]			See Table XXIII in online Data Supplement 1.
4. In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, may be reasonable to provide useful information on patient eligibility and endovascular procedural planning.	IIb	C-EO	New recommendation.
Knowledge of vessel anatomy and presence of extracranial vessel dissections, stenoses, and occlusions may assist in planning endovascular procedures or identifying patients ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature.			

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

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

2.3. Other Diagnostic Tests

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

3. General Supportive Care and Emergency Treatment

3.1. Airway, Breathing, and Oxygenation

3.1. Airway, Breathing, and Oxygenation	COR	LOE	New, Revised, or Unchanged
1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway.	I	C-EO	Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Supplemental oxygen should be provided to maintain oxygen saturation >94%.	I	C-LD	Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. Supplemental oxygen is not recommended in nonhypoxic patients with AIS.	III: No Benefit	B-R	Recommendation unchanged from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of oxygen by nasal cannula at 2 L/min (baseline O_2 saturation >93%) or 3 L/min (baseline O_2 saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights.[112]			See Table XXVII in online Data Supplement 1.

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

3.2. Blood Pressure

3.2. Blood Pressure	COR	LOE	New, Revised, or Unchanged
1. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.	**I**	**C-EO**	New recommendation.
The blood pressure (BP) level that should be maintained in patients with AIS to ensure the best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others have not.[116–123] No studies have addressed the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing the use of IV colloids and crystalloids, the odds of death or dependence were similar. Clinically important benefits or harms could not be excluded. There are no data to guide volume and duration of parenteral fluid delivery.[124] No studies have compared different isotonic fluids.			See Table XXIX in online Data Supplement 1.
2. Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their SBP is <185 mm Hg and their diastolic BP is <110 mm Hg before IV fibrinolytic therapy is initiated.	**I**	**B-NR**	Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
The RCTs of IV alteplase required the BP to be <185 mm Hg systolic and <110 mm Hg diastolic before treatment and <180/105 mm Hg for the first 24 hours after treatment. Options to treat arterial hypertension in patients with AIS who are candidates for immediate reperfusion therapy are given in Table 5. Some observational studies suggest that the risk of hemorrhage after administration of alteplase is greater in patients with higher BPs[125–131] and in patients with more BP variability.[132] The exact BP at which the risk of hemorrhage after IV alteplase increases is unknown. It is thus reasonable to target the BPs used in the RCTs of IV alteplase.			See Tables XX and XXX in online Data Supplement 1.
3. In patients for whom mechanical thrombectomy is planned and who have not received IV fibrinolytic therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure.	**IIa**	**B-NR**	Recommendation revised from 2013 AIS Guidelines.
Of the 6 RCTs that each independently demonstrated clinical benefit of mechanical thrombectomy with stent retrievers when performed <6 hours from stroke onset, 5 (REVASCAT, SWIFT PRIME, EXTEND-IA, THRACE, and MR CLEAN)[106–110] had eligibility exclusions for BP >185/110 mm Hg. The sixth, ESCAPE,[105] had no BP eligibility exclusion. DAWN also used an exclusion for BP >185/110 mm Hg.[51] RCT data for optimal BP management approaches in this setting are not available. Because the vast majority of patients enrolled in these RCTs had preprocedural BP managed below 185/110 mm Hg, it is reasonable to use this level as a guideline until additional data become available.			See Table XVII in online Data Supplement 1.
4. The usefulness of drug-induced hypertension in patients with AIS is not well established.	**IIb**	**B-R**	Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

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

COR IIb	LOE C-EO
Patient otherwise eligible for emergency reperfusion therapy except that BP is >185/110 mm Hg:	
Labetalol 10–20 mg IV over 1–2 min, may repeat 1 time; or	
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 min, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or	
Clevidipine 1–2 mg/h IV, titrate by doubling the dose every 2–5 min until desired BP reached; maximum 21 mg/h	
Other agents (eg, hydralazine, enalaprilat) may also be considered	
If BP is not maintained ≤185/110 mm Hg, do not administer alteplase	
Management of BP during and after alteplase or other emergency 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; COR, class of recommendation; IV, intravenous; and LOE, Level of Evidence.

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

Data derived from Jauch et al.[1]

3.3. Temperature

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

3.4. Blood Glucose

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

3.5. IV Alteplase

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

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

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

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

3.5.4. Other Specific Circumstances	COR	LOE	New, Revised, or Unchanged
1. IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial.	**IIa**	**B-NR**	New recommendation.
A case-control analysis using the population from the AHA GWTG-Stroke registry, including 832 cases with sickle cell disease (all adults) and 3328 age-, sex-, and race-matched controls without sickle cell disease with similar severity of neurological deficits at presentation, showed that sickle cell disease did not have a significant impact on the safety or the outcome at discharge of treatment with IV alteplase.[169]			See Table XXXVII in online Data Supplement 1.
2. In patients with a hyperdense MCA sign, IV alteplase can be beneficial.	**IIa**	**B-NR**	New recommendation.
Analyses of data from RCTs of IV alteplase for AIS have shown no statistically significant deleterious interaction on clinical outcomes between alteplase treatment and the hyperdense MCA sign on baseline CT. In the NINDS rt-PA trial, there was no interaction between hyperdense MCA sign and treatment for outcomes at 3 months measured by any of the 4 clinical scales (mRS score 0–1, NIHSS score 0–1, Barthel Index score ≥95, Glasgow Outcome Scale score 0–1) or for death.[170] In IST-3, no significant interaction of the hyperdense MCA sign with benefit of alteplase measured by the Oxford Handicap Score at 6 months was observed.[171,172]			See Table XXXVIII in online Data Supplement 1.

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

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

3.5.6. Post-alteplase Treatment	COR	LOE	New, Revised, or Unchanged
1. BP should be maintained at <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment.	**I**	**B-R**	Recommendation reworded for clarity from 2013 AIS Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
Main elements of postthrombolysis care are listed in Table 9. ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) randomized 2196 alteplase-eligible patients with AIS and systolic BP (SBP) ≥150 mm Hg to receive intensive target SBP of 130 to 140 mm Hg within 1 hour versus guideline target SBP <180 mm Hg; 1081 were in the intensive group, and 1115 were in the guideline group.[176] Median time from stroke onset to randomization was 3.3 hours. Mean SBP in the intensive group was 144.3 mm Hg, and mean SBP in the guideline group was 149.8 mm Hg. Primary outcome mRS score at 90 days did not differ between the 2 groups. Although fewer patients in the intensive group had ICH, the number of patients with serious adverse events did not differ between the 2 groups. Although intensive BP lowering was observed to be safe, the observed reduction in ICH did not lead to improved clinical outcome compared with guideline treatment.			See Table XLI in online Data Supplement 1.
2. The risk of antithrombotic therapy (other than IV aspirin) within the first 24 hours after treatment with IV alteplase (with or without mechanical thrombectomy) is uncertain. Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.	**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 and benefit.[177]			See Table XLII in online Data Supplement 1.

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

COR 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 <150 mg/dL	
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h) (Potential for benefit in all patients, but particularly when blood products are contraindicated or declined by patient/family or if cryoprecipitate is not available in a timely manner.)	
Hematology and neurosurgery consultations	
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control	

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

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

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

COR 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 after IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.	
Discontinue IV alteplase infusion and hold ACE inhibitors	
Administer IV methylprednisolone 125 mg	
Administer IV diphenhydramine 50 mg	
Administer ranitidine 50 mg IV or famotidine 20 mg IV	
If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL	
Icatibant, a selective bradykinin B_2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed a total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACE inhibitor-related angioedema	
Supportive care	

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

Sources: Foster-Goldman and McCarthy,[147] Gorski and Schmidt,[148] Lewis,[149] Lin et al,[150] Correia et al,[151] O'Carroll and Aguilar,[152] Myslimi et al,[153] and Pahs et al.[154]

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

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

(*Continued*)

Table 8. Continued

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

(*Continued*)

Table 8. Continued

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

(*Continued*)

Table 8. Continued

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

(*Continued*)

Table 8. Continued

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

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

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

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

AC indicates anticoagulants; AIS, acute ischemic stroke; aPTT, activated partial thromboplastin time; BP, blood pressure; CMB, cerebral microbleed; COR, class of recommendation; CT, computed tomography; DW-MRI, diffusion-weighted magnetic resonance imaging; FLAIR, fluid-attenuated inversion recovery; GI, gastrointestinal; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; LOE, level of evidence; MCA, middle cerebral artery; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; PT, 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 XCV in online Data Supplement 1 for original wording.

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

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

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

Table 9. Treatment of AIS: IV Administration of Alteplase

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 min, with 10% of the dose given as a bolus over 1 min.
Admit the patient to an intensive care or stroke unit for monitoring.
If the patient develops severe headache, acute hypertension, nausea, or vomiting or has a worsening neurological examination, discontinue the infusion (if IV alteplase is being administered) and obtain emergency head CT scan.
Measure BP and perform neurological assessments every 15 min during and after IV alteplase infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase treatment.
Increase the frequency of BP measurements if SBP is >180 mm Hg or if DBP is >105 mm Hg; administer antihypertensive medications to maintain BP at or below these levels (Table 5).
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters if the patient can be safely managed without them.
Obtain a follow-up CT or MRI scan at 24 h after IV alteplase before starting anticoagulants or antiplatelet agents.

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

3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	**IIb**	**B-R**	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (*P*=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; *P*=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (*P*=0.23) or 0 to 2 (*P*=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	**IIb**	**B-R**	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.
3. The administration of IV defibrinogenating agents or IV fibrinolytic agents other than alteplase and tenecteplase is not recommended.	**III: No Benefit**	**B-R**	Recommendation revised from 2013 AIS Guidelines.
Randomized placebo-controlled trials have not shown benefit from the administration of IV streptokinase within 6 hours or desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra, large intracranial artery occlusion, or severe stenosis.[155,183–186]			See Table XLIII in online Data Supplement 1.
4. The use of sonothrombolysis as adjuvant therapy with IV fibrinolysis is not recommended.	**III: No Benefit**	**A**	New recommendation.
Since the publication of the 2013 AIS Guidelines, 2 RCTs of sonothrombolysis as adjuvant therapy for IV thrombolysis have shown no clinical benefit. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis (93 patients) or sham (90 patients). Neurological improvement at 24 hours and functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of sICH.[187] CLOTBUST-ER (Combined Lysis of Thrombus With Ultrasound and Systemic Tissue Plasminogen Activator [tPA] for Emergent Revascularization in Acute Ischemic Stroke) randomized 676 patients with AIS (NIHSS score ≥10) who received IV alteplase within 3 or 4.5 hours of symptom onset and randomly allocated to operator independent sonothrombolysis (335) or sham ultrasound (341).[188] Compared with the control arm, the neurological improvement, death, and serious adverse events in the intervention arm were not statistically different. At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV fibrinolysis.			See Table XLIV in online Data Supplement 1.

3.7. Mechanical Thrombectomy

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

3.7.1. Concomitant With IV Alteplase (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed.	**III: Harm**	**B-R**	Recommendation revised from 2015 Endovascular.
In pooled patient-level data from 5 trials (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials], which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS score distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; and cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes.[42] Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76–0.93]; ARD, −6.7%) and less functional independence (OR, 0.81 [95% CI, 0.71–0.92]; ARD, −5.2% [95% CI, −8.3 to −2.1]) but no change in mortality (OR, 1.12 [95% CI, 0.93–1.34]; ARD, 1.5% [95% CI, −0.9 to 4.2]).[42] The REVASCAT trial included a 30-minute period of observation before undertaking EVT. Available data do not directly address the question of whether patients should be observed after IV alteplase to assess for clinical response before pursuing mechanical thrombectomy. However, one can infer that because disability outcomes at 90 days were directly associated with time from symptom onset to arterial puncture, any cause for delay to mechanical thrombectomy, including observing for a clinical response after IV alteplase, should be avoided. Therefore, the recommendation is slightly modified from the 2015 Endovascular Update.			See Tables XVII and XLV in online Data Supplement 1.

3.7.2. 0 to 6 Hours From Onset	COR	LOE	New, Revised, or Unchanged
1. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	**I**	**A**	Recommendation revised from 2015 Endovascular.
Results from 6 recent randomized trials of mechanical thrombectomy using predominantly stent retriever devices (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE) support COR I, LOE A recommendations for a defined group of patients as described in the 2015 Guidelines.[105–110] A pooled, patient-level analysis from 5 of these studies reported by the HERMES Collaboration showed treatment effect in the subgroup of 188 patients not treated with IV alteplase (cOR, 2.43 [95% CI, 1.30–4.55]); therefore, pretreatment with IV alteplase has been removed from the prior recommendation. The HERMES pooled patient-level data also showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years of age (cOR, 3.68 [95% CI, 1.95–6.92]).[189] In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration [Safety and Efficacy of Solitaire Stent Thrombectomy–Individual Patient Data Meta-Analysis of Randomized Trials]: SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT) showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years of age (3.46 [95% CI, 1.58–7.60]).[190] In a meta-analysis of 5 RCTs (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT), there was favorable effect with mechanical thrombectomy over standard care without heterogeneity of effect across patient age subgroups (for patients <70 and ≥70 years of age: OR, 2.41 [95% CI, 1.51–3.84] and 2.26 [95% CI, 1.20–4.26], respectively).[191] However, the number of patients in these trials who were ≥90 years of age was very small, and the benefit of mechanical thrombectomy over standard care in patients ≥90 years of age is not clear. As with any treatment decision in an elderly patient, consideration of comorbidities and risks should factor into the decision-making for mechanical thrombectomy.			See Tables XVII and XLV in online Data Supplement 1.

3.7.2. 0 to 6 Hours From Onset (Continued)	COR	LOE	New, Revised, or Unchanged
2. Direct aspiration thrombectomy as first-pass mechanical thrombectomy is recommended as noninferior to stent retriever for patients who meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS ≥6; and (6) treatment initiation (groin puncture) within 6 hours of symptom onset.	I	B-R	Recommendation revised from 2015 Endovascular.
Comparative available randomized data has assessed patients primarily in the therapeutic window within 6 hours of onset. The COMPASS (Comparison of Direct Aspiration Versus Stent Retriever as a First Approach) trial randomized patients with (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or M1; (3) age ≥18 years; (4) NIHSS score of ≥5; (5) ASPECTS ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset to aspiration thrombectomy or stentriever thrombectomy as first-line technique. Primary outcome was noninferiority of mRS score at 90 days. An mRS score of 0 to 2 was achieved in 69 of 134 (52%) of patients in the aspiration group and 67 of 136 (50%) in the stentriever group, demonstrating noninferiority of aspiration thrombectomy compared with stentriever thrombectomy ($P_{noninferiority}$=0.0014). No difference in recanalization rates or intracranial hemorrhage was found.[192] The ASTER trial (Contact Aspiration vs Stent Retriever for Successful Revascularization) compared the contact aspiration technique and the standard stent retriever technique as first-line mechanical thrombectomy for successful revascularization within 6 hours among patients with acute anterior circulation ischemic stroke and LVO. Eligibility criteria were different from COMPASS, lacking specification of NIHSS or ASPECTS. Primary outcome was successful revascularization. The proportion of patients with successful revascularization at the end of all interventions was 85.4% (n=164) in the contact aspiration group versus 83.1% (n=157) in the stent retriever group (OR, 1.20 [95% CI, 0.68–2.10]; *P*=0.53; difference, 2.4% [95% CI, −5.4 to 9.7]). The secondary clinical end point of mRS score of 0 to 2 at 90 days was achieved by 82 of 181 (45.3%) in the contact aspiration group versus 91 of 182 (50.0%) in the stent retriever group (OR, 0.83 [95% CI, 0.54–1.26]; *P*=0.38). Given its superiority design to detect a 15% difference in the primary end point, this trial was not designed to establish noninferiority.[193] The Penumbra Separator 3D Trial compared a 3-D stent retriever combined with aspiration to aspiration alone as first-line intracranial mechanical thrombectomy for successful revascularization within 8 hours among patients with AIS (NIHSS score of at least 8) and LVO refractory to or ineligible for IV alteplase in a 1:1 randomized, noninferiority trial with a 15% noninferiority margin. The primary end point of mTICI grade 2 to 3 occurred in 87.2% of the combination group versus 82.3% in the aspiration alone group, meeting the noninferiority criterion of lower 90% confidence bound less than −15%. A 90-day mRS score of aspiration alone group.[194] The trial demonstrated noninferiority of 3-D stent retriever with aspiration versus aspiration alone, using older-generation aspiration technology. The trial was not powered to demonstrate noninferiority in the secondary outcome of 90-day functional independence.			See Table XVII in online Data Supplement 1.
3. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.	IIb	B-R	Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE revised. See Table XCV in online Data Supplement 1 for original wording.
In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the direction of treatment effect for mechanical thrombectomy over standard care was favorable in M2 occlusions, but the adjusted cOR was not significant (1.28 [95% CI, 0.51–3.21]).[189] In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration: SWIFT PRIME, ESCAPE, EXTEND-IA, and REVASCAT) showed that the direction of treatment effect was favorable for mechanical thrombectomy over standard care in M2 occlusions, but the OR and 95% CI were not significant.[190] In an analysis of pooled data from SWIFT (Solitaire With the Intention for Thrombectomy), STAR (Solitaire Flow Restoration Thrombectomy for Acute Revascularization), DEFUSE 2, and IMS III, among patients with M2 occlusions, reperfusion was associated with excellent functional outcomes (mRS score 0–1; OR, 2.2 [95% CI, 1.0–4.7]).[195] Therefore, the recommendation for mechanical thrombectomy for M2/M3 occlusions does not change substantively from the 2015 AHA/ASA focused update.			See Tables XVII and XLV in online Data Supplement 1.
4. 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).	IIb	B-R	Recommendation unchanged from 2015 Endovascular.
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-LD	Recommendation reworded for clarity from 2015 Endovascular. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.

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

3.7.4. Technique	COR	LOE	New, Revised, or Unchanged
1. Use of stent retrievers is indicated in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device.	I	A	Recommendation unchanged from 2015 Endovascular.
2. The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome.	I	A	Recommendation reworded for clarity from 2015 Endovascular. See Table XCV in online Data Supplement 1 for original wording.
Mechanical thrombectomy aims to achieve reperfusion, not simply recanalization. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.[196,197] All recent endovascular trials used the mTICI grade 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to mTICI grade 2b/3.[189] Earlier trials with less efficient devices showed lower recanalization rates, a factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%). The additional benefit of pursuing mTICI of grade 3 rather than grade 2b deserves further investigation.			
3. To ensure benefit, reperfusion to mTICI grade 2b/3 should be achieved as early as possible within the therapeutic window.	I	A	Recommendation revised from 2015 Endovascular.
4. In the 6- to 24-hour thombectomy window evaluation and treatment should proceed as rapidly as possible to ensure access to treatment for the greatest proportion of patients.	I	B-R	New recommendation.
In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), ARD for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), and ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes.[42] Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84 [95% CI, 0.76–0.93]; ARD, −6.7%) and less functional independence (OR, 0.81 [95% CI, 0.71–0.92]; ARD, −5.2% [95% CI, −8.3 to −2.1]).[42] The 6- to 16- and 6- to 24-hour treatment windows trials, which utilized advanced imaging to identify a relatively uniform patient group, showed limited variability of treatment effect with time in these highly selected patients.[51,52] The absence of detailed screening logs in these trials limits estimations of the true impact of time in this population. To ensure the highest proportion of eligible patients presenting in the 6- to 24-hour window have access to mechanical thrombectomy, evaluation and treatment should be as rapid as possible. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.[128,129] All recent endovascular trials used the mTICI 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to TICI 2b/3.[189] Earlier trials with less efficient devices showed lower recanalization rates, 1 factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%).			See Tables XVII and XLV in online Data Supplement 1.

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

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

3.8. Other Endovascular Therapies

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

3.9. Antiplatelet Treatment

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

3.9. Antiplatelet Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
2. In patients presenting with minor noncardioembolic ischemic stroke (NIHSS score ≤3) who did not receive IV alteplase, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset.	I	A	New recommendation.
Two independent multicenter, randomized, double-blind, placebo-controlled trials have established the efficacy of short-term dual antiplatelet therapy to prevent recurrent ischemic stroke in patients with minor stroke or high-risk TIA. The CHANCE trial (Clopidogrel in High Risk Patients With Acute Nondisabling Cerebrovascular Events; N=5170) conducted in China studied the efficacy of short-term dual antiplatelet therapy begun within 24 hours in patients with minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD2 [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). The dosing regimen was clopidogrel at an initial dose of 300 mg followed by 75 mg/d for 90 days plus aspirin at a dose of 75 mg/d for the first 21 days or placebo plus aspirin (75 mg/d for 90 days). All participants received open-label aspirin at a clinician-determined dose of 75 to 300 mg on day 1. The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone: hazard ratio (HR), 0.68 (95% CI, 0.57–0.81; *P*<0.001).[210] Post hoc analysis found a small but measurable reduction in poor functional outcome (mRS score 2–6) on dual antiplatelet therapy compared with aspirin alone (absolute RR, 1.7% [95% CI, 0.03%–3.42%]; *P*=0.046).[211] However, a post hoc time-course analysis showed that the benefit in reducing recurrent ischemic stroke compared with the risk of bleeding on dual antiplatelet therapy dissipated after ≈10 days of treatment.[212] A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days.[213] In addition, subgroup analyses found no benefit of clopidogrel plus aspirin in carriers of a CYP2C19 loss-of-function allele[214] or those with a single acute infarction or no infarction compared with those with multiple acute infarctions,[215] although these subgroup analyses were likely underpowered. The POINT trial (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke; N=4881) was conducted in North America, Europe, Australia, and New Zealand, with the majority (83%) enrolled in the United States (75% white, 20% black).[216] Similar to CHANCE, the target enrollment population included minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD2 score ≥4) within 12 hours of symptom onset. Patients were randomized to either clopidogrel plus aspirin (600-mg loading dose of clopidogrel followed by 75 mg/d from day 2–90) plus open-label aspirin (50–325 mg/d) versus aspirin alone (50–325 mg/d) for 90 days. The primary outcome was a composite of ischemic stroke, myocardial infarction (MI), or death resulting from an ischemic vascular event up to 90 days, with a secondary safety end point of major hemorrhage during the same time period. Compared with aspirin alone, aspirin plus clopidogrel resulted in fewer ischemic events (5% versus 6.5%; HR, 0.75 [95% CI, 0.59–0.95]; *P*=0.02) but more major hemorrhages (0.9% versus 0.4%; HR, 2.32 [95% CI, 1.10–4.87]; *P*=0.02). Overall, the beneficial effect of aspirin plus clopidogrel was driven by a reduction in ischemic stroke (HR, 0.72 [95% CI, 0.56–0.92]; *P*=0.01) and greatest in the first 30 days of treatment from symptom onset (HR, 0.73 [95% CI, 0.56–0.95]; *P*=0.02). However, the risk of major hemorrhage was greatest after the first 7 days of treatment (HR, 2.69 [95% CI, 1.05–6.86]; *P*=0.04). There was no significant added benefit of aspirin plus clopidogrel after 30 days of treatment. In addition, in a prespecified analysis of functional outcomes determined by 90-day mRS score ≥2 for new disability, there was no difference between groups (HR, 0.97 [95% CI, 0.82–1.14]; *P*=0.71).			See Table XLVIII in online Data Supplement 1.
3. The efficacy of the IV glycoprotein IIb/IIIa inhibitors tirofiban and eptifibatide in the treatment of AIS is not well established.	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.
Prospective, randomized, open-label phase II trials of tirofiban[217] and eptifibatide[218] have suggested safety for treatment in patients with AIS. Single-arm studies of eptifibatide as adjunctive therapy to IV alteplase support ongoing RCTs to establish safety and efficacy.[173,174] Further trials are necessary to clarify the safety and efficacy of this intervention.			See Tables XXXIX and XLVIII in online Data Supplement 1.
4. Ticagrelor is not recommended over aspirin for treatment of patients with minor acute stroke.	III: No Benefit	B-R	New recommendation.
The recently completed SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA (ABCD2 score ≥4). With a primary outcome of time to the composite end point of stroke, MI, or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89 [95% CI, 0.78–1.01]; *P*=0.07).[219] However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin.			See Table XLVIII in online Data Supplement 1.
5. The administration of the IV glycoprotein IIb/IIIa inhibitor abciximab as medical treatment for AIS is potentially harmful and should not be performed.	III: Harm	B-R	Recommendation revised from 2013 AIS Guidelines.
A recent Cochrane review of IV glycoprotein IIb/IIIa receptor antagonists in the treatment of AIS found that these agents are associated with a significant risk of ICH without a measurable improvement in death or disability.[220] The majority of trial data apply to abciximab, which was studied in the AbESTT trial (A Study of Effectiveness and Safety of Abciximab in Patients With Acute Ischemic Stroke). The phase III trial was terminated early because of an unfavorable risk-benefit analysis.[221]			See Table XLVIII in online Data Supplement 1.
6. Aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy.	III: Harm	B-R	Recommendation revised from 2013 AIS Guidelines.
Recommendation was modified to eliminate wording about "acute interventions," which are broadly defined, and to specify that aspirin is a less effective substitute for the treatment of AIS in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy.			

3.10. Anticoagulants

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

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

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

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

3.12. Neuroprotective Agents

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

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

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

3.14. Other

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

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

4.1. Stroke Units

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

4.2 Head Positioning

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

4.3. Supplemental Oxygen

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

4.3. Supplemental Oxygen	COR	LOE	New, Revised, or Unchanged
1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway.	I	C-EO	Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Supplemental oxygen should be provided to maintain oxygen saturation >94%.	I	C-LD	Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. Supplemental oxygen is not recommended in nonhypoxic patients hospitalized with AIS.	III: No Benefit	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of oxygen by nasal cannula at 2 L/min (baseline O_2 saturation >93%) or 3 L/min (baseline O_2 saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights.[112]			See Table XXVII in online Data Supplement 1.

4.4. Blood Pressure

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

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

4.5. Temperature

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

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

4.6. Glucose

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

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

4.7. Dysphagia

4.7. Dysphagia	COR	LOE	New, Revised, or Unchanged
1.Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is effective to identify patients at increased risk for aspiration.	I	C-LD	New recommendation.
Dysphagia, a common (37%–78%) complication of acute stroke, is a risk factor for aspiration pneumonia and is associated with higher mortality and worse patient outcomes. The Evidence Review Committee completed a systematic review to determine whether dysphagia screening, compared with no screening or usual care, decreased outcomes of pneumonia, death, or dependency.[3,259–261] There were insufficient data to determine whether implementation of a dysphagia screening protocol reduces the risk of death or dependency. However, insufficient evidence does not mean that dysphagia screening is ineffective. Joundi et al[262] determined that patients who failed dysphagia screening were older, had a higher rate of multiple comorbidities (including prior stroke and dementia), more often came from a long-term care facility, more often presented with weakness and speech deficits, had a lower level of consciousness, and had a higher stroke severity. Patients who failed dysphagia screening were more likely to develop pneumonia (13.1% versus 1.9%), to have more severe disability (52.4% versus 18.0%), and to be discharged to a long-term care institution (14.0% versus 4.3%). Early dysphagia screening can be effective to identify patients at higher risk for aspiration, which is associated with greater risk of pneumonia, even if dysphagia screening was not associated with reduced rates of pneumonia or improvements in death or disability when tested in RCTs.[259–261]			See Tables LVII and LVIII in online Data Supplement 1.
2. An endoscopic evaluation is reasonable for those patients suspected of aspiration to verify the presence/absence of aspiration and to determine the physiological reasons for the dysphagia to guide the treatment plan.	IIa	B-NR	Recommendation wording modified from 2016 Rehab Guidelines to match COR IIa stratifications. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. It is reasonable for dysphagia screening to be performed by a speech-language pathologist or other trained healthcare provider.	IIa	C-LD	Recommendation reworded for clarity from 2016 Rehab Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.
4. It is not well established which instrument to choose for evaluation of swallowing with sensory testing, but the choice may be based on instrument availability or other considerations (ie, fiberoptic endoscopic evaluation of swallowing, videofluoroscopy, fiberoptic endoscopic evaluation with sensory testing).	IIb	C-LD	Recommendation reworded for clarity from 2016 Rehab Guidelines. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.

4.7. Dysphagia (Continued)	COR	LOE	New, Revised, or Unchanged
5. Implementing oral hygiene protocols to reduce the risk of pneumonia after stroke may be reasonable.	**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[263] showed that intervention with standardized dysphagia screening and diet and standardized oral hygiene with antibacterial mouth rinse with chlorhexidine reduced pneumonia (7% versus 28%) compared with a historical control group in which patients were unsystematically screened for dysphagia within 24 hours and received unsystematic and arbitrary oral hygiene without chlorhexidine. In this experimental design, the efficacy of the standardized oral hygiene portion in the intervention group could not be separated from the standardized dysphagia screening and diet. Furthermore, because of the historic nature of the control group, it is possible that other changes in care that could have occurred between the historical control subjects and the intervention group might have affected the risk for development of pneumonia. A Cochrane review that included 3 studies found that oral care and decontamination gel versus oral care and placebo gel reduced the incidence of pneumonia in the intervention group (P=0.03).[264] Wagner et al[265] 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 LIX and LX in online Data Supplement 1.

4.8. Nutrition

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

4.9. Deep Vein Thrombosis Prophylaxis

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

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

4.10. Depression Screening

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

4.11. Other

4.11. Other	COR	LOE	New, Revised, or Unchanged
1. During hospitalization and inpatient rehabilitation, regular skin assessments are recommended with objective scales of risk such as the Braden scale.	I	C-LD	Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. It is recommended to minimize or eliminate skin friction, to minimize skin pressure, to provide appropriate support surfaces, to avoid excessive moisture, and to maintain adequate nutrition and hydration to prevent skin breakdown. Regular turning, good skin hygiene, and use of specialized mattresses, wheelchair cushions, and seating are recommended until mobility returns.	I	C-LD	Recommendation and COR unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. It is reasonable for patients and families with stroke to be directed to palliative care resources as appropriate.	IIa	C-EO	New recommendation.
It is reasonable for healthcare providers to ascertain and include patient-centered preferences in decision-making, especially during prognosis formation and considering interventions or limitations in care. Healthcare providers should ascertain and include patient-centered preferences in decision-making, especially during prognosis formation and considering interventions or limitations in care. See 2014 Palliative Care for additional information.[9]			
4. Routine use of prophylactic antibiotics has not been shown to be beneficial.	III: No Benefit	A	Recommendation revised from 2013 AIS Guidelines.
Two large RCTs demonstrated no effect of preventive antimicrobial therapy on functional outcome. PASS (Preventive Antibiotics in Stroke Study) showed no difference in the primary end point of distribution of functional outcome scores on the mRS score at 3 months (adjusted common OR, 0.95 [95% CI, 0.82–1.09]; *P*=0.46) despite an overall reduction in the incidence of infection (OR, 0.57 [95% CI, 0.38–0.85]; *P*=0.005), including reducing the number of urinary tract infections (OR, 0.34 [95% CI, 0.26–0.46]; *P*<0.001), but no significant decrease in the rate of poststroke pneumonia (OR, 0.91 [95% CI, 0.73–1.13]; *P*=0.385).[274] In STROKE-INF (Antibiotics to Prevent Infection in Stroke), prophylactic antibiotics did not affect the incidence of the primary end point of poststroke pneumonia (adjusted OR,1.21 [95% CI, 0.71–2.08]; *P*=0.489) or the secondary end point of mRS score of 0 to 2 at 90 days (adjusted OR, 0.87 [95% CI, 0.6–1.24]; *P*=0.448).[275] Three meta-analyses including these trials and other smaller RCTs all demonstrated a reduction in infection but no change in functional outcome.[276–278]			See Table LXVII in online Data Supplement 1.
5. Routine placement of indwelling bladder catheters should not be performed because of the associated risk of catheter-associated urinary tract infections.	III: Harm	C-LD	Recommendation wording modified from 2013 AIS Guidelines to match COR III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.12. Rehabilitation

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

4.12. Rehabilitation (Continued)	COR	LOE	New, Revised, or Unchanged
6. High-dose, very early mobilization within 24 hours of stroke onset should not be performed because it can reduce the odds of a favorable outcome at 3 months.	**III: Harm**	**B-R**	Recommendation wording modified from 2016 Rehab Guidelines to match COR III stratifications. LOE revised. COR amended to conform with ACC/AHA 2015 Recommendation Classification System.
The AVERT RCT (A Very Early Rehabilitation Trial) compared high-dose, very early mobilization with standard-of-care mobility.[279] High-dose mobilization protocol interventions included the following: Mobilization was begun within 24 hours of stroke onset, whereas usual care typically was 24 hours after the onset of stroke; there was a focus on sitting, standing, and walking activity; and there were at least 3 additional out-of-bed sessions compared with usual care. Favorable outcome at 3 months after stroke was defined as an mRS score of 0 to 2. A total of 2104 patients were randomly assigned (1:1). The results of this RCT showed that patients in the high-dose, very early mobilization group had less favorable outcomes (46% versus 50%) than those in the usual care group: 8% versus 7% of patients died in the very early mobilization group, and 19% versus 20% had a nonfatal serious adverse event with high-dose, very early mobilization.			See Table LXVIII in online Data Supplement 1.

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

5.1. Brain Swelling

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

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

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

5.1.3. Surgical Management-Supratentorial Infarction	COR	LOE	New, Revised, or Unchanged
1. Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness attributed to brain swelling as selection criteria.	**IIa**	**A**	Recommendation, COR, and LOE unchanged from 2014 Brain Swelling.
2. In patients ≤60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion is reasonable.	**IIa**	**A**	Recommendation revised from 2014 Brain Swelling.
The pooled results of RCTs demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction in patients <60 years of age, with an absolute risk reduction in mortality of 50% (95% CI, 34–66) at 12 months.[280] These findings were noted despite differences in the clinical trials in terms of inclusion and exclusion criteria, percent of MCA territory involved, and surgical timing.[287,288] At 12 months, moderate disability (ability to walk) or better (mRS score 2 or 3) was achieved in 43% (22 of 51) of the total surgical group and 55% (22 of 40) of survivors compared with 21% (9 of 42; *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.[280,287–290]			See Tables LXIX and LXX in online Data Supplement 1.
3. In patients >60 years of age who deteriorate neurologically within 48 hours from brain swelling associated with unilateral MCA infarctions despite medical therapy, decompressive craniectomy with dural expansion may be considered.	**IIb**	**B-R**	Recommendation revised from 2014 Brain Swelling
There is evidence that patients >60 years of age can have a reduction in mortality of ≈50% (76% in the nonsurgical group versus 42% in the surgical group in DESTINY [Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery] II) when decompressive craniectomy for malignant MCA infarction is performed within 48 hours of stroke onset.[287,288,291–295] However, functional outcomes in elderly patients seem to be worse than those in patients <60 years of age. At 12 months, moderate disability (able to walk; mRS score 3) was achieved in 6% (3 of 47) of the total surgical group and 11% (3 of 27) of survivors compared with 5% (3 of 22) of the total nonsurgical group and 20% (3 of 15) of the nonsurgical survivors. At 12 months, independence (mRS score ≤2) was not achieved by any survivors in either group.			See Tables LXIX and LXX in online Data Supplement 1.

5.1.4. Surgical Management-Cerebellar Infarction	COR	LOE	New, Revised, or Unchanged
1. Ventriculostomy is recommended in the treatment of obstructive hydrocephalus after cerebellar infarction. Concomitant or subsequent decompressive craniectomy may or may not be necessary on the basis of factors such as the size of the infarction, neurological condition, degree of brainstem compression, and effectiveness of medical management.	**I**	**C-LD**	Recommendation revised from 2014 Brain Swelling.
Ventriculostomy is a well-recognized effective treatment for the management of acute obstructive hydrocephalus and is often effective in isolation in relieving symptoms, even among patients with acute cerebellar infarction.[289,296] Thus, in patients who develop symptoms of obstructive hydrocephalus from cerebellar infarction, emergency ventriculostomy is a reasonable first step in the surgical management paradigm. If cerebrospinal fluid diversion by ventriculostomy fails to improve neurological function, decompressive suboccipital craniectomy should be performed.[289,296,297] Although a risk of upward herniation exists with ventriculostomy alone, it can be minimized with conservative cerebrospinal fluid drainage or subsequent decompression if the cerebellar infarction causes significant swelling and mass effect.[289,296]			See Table LXIX in online Data Supplement 1.
2. Decompressive suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarction causing neurological deterioration from brainstem compression despite maximal medical therapy. When deemed safe and indicated, obstructive hydrocephalus should be treated concurrently with ventriculostomy.	**I**	**B-NR**	Recommendation revised from 2014 Brain Swelling.
The data support decompressive cerebellar craniectomy for the management of acute ischemic cerebellar stroke with mass effect.[289,296,297] This surgery is indicated as a therapeutic intervention in cases of neurological deterioration caused by swelling as a result of cerebellar infarction that cannot be otherwise managed with medical therapy or ventriculostomy in the setting of obstructive hydrocephalus.[289,296]			See Table LXIX in online Data Supplement 1.

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

5.2. Seizures

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

6. In-Hospital Institution of Secondary Stroke Prevention

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

Table 10. Guidelines Relevant to Secondary Stroke Prevention

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

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

6.1. Brain Imaging

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

6.2. Vascular Imaging

6.2. Vascular Imaging	COR	LOE	New, Revised, or Unchanged
1. For patients with nondisabling (mRS score 0–2) AIS in the carotid territory who are candidates for CEA or stenting, noninvasive imaging of the cervical carotid arteries should be performed routinely within 24 hours of admission.	I	B-NR	New recommendation.
Past data have indicated that the risk of recurrent stroke caused by symptomatic carotid stenosis is highest early after the initial event.[325–329] Although there is evidence that early or emergency revascularization via either CEA or carotid angioplasty and stenting may be safe in selected cases,[330–332] there are no high-quality prospective data supporting early versus late carotid revascularization in all cases.[333] In cases of nondisabling stroke, a meta-analysis by De Rango et al[326] demonstrates high rates of complications when treated <48 hours after the initial event and no difference in risks when treated between 0 and 7 days and 0 and 15 days. Revascularization between 48 hours and 7 days after initial stroke is supported by the data in cases of nondisabling stroke (mRS score 0–2).[334] Imaging within 24 hours of admission is feasible and recommended to facilitate CEA/carotid angioplasty and stenting in eligible patients in the 48- to 72-hour window.			See Table LXXVIII in online Data Supplement 1.

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

6.3. Cardiac Evaluation

6.3.1. Electrocardiographic Monitoring	COR	LOE	New, Revised, or Unchanged
1. Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours.	**I**	**B-NR**	Recommendation and COR unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Further support for this unchanged recommendation from the 2013 AIS Guidelines is provided by 2 additional studies published since the 2013 guidelines. Kallmünzer et al[340] prospectively monitored by cardiac telemetry 501 patients with acute stroke (92% with cerebral ischemia) for a median of 73 hours after admission to a dedicated stroke unit. A total of 139 serious arrhythmias were detected in 126 patients (25.1%). Atrial fibrillation accounted for 24 of 139 (17%) of the arrhythmias. Detection of arrhythmia led to direct antiarrhythmic treatment in 77.7%. In that study, 52.2% of all detected arrhythmias occurred within 12 hours and 74.4% within 24 hours after admission. Fernández-Menéndez et al[341] prospectively monitored by cardiac telemetry for a minimum of 48 hours 332 patients admitted to the stroke unit with a diagnosis of ischemic stroke, TIA, or intraparenchymal hemorrhage (90% with cerebral ischemia) admitted within 48 hours of symptom onset. One hundred seventy-four significant cardiac arrhythmias occurred in 98 patients (29.5%). Atrial fibrillation/flutter accounted for 23 of 174 (13%) of the arrhythmias. Thirty-three of 98 (34%) patients were directly treated for the arrhythmia (excluding anticoagulation for atrial fibrillation). Thirty-seven percent of all detected arrhythmias occurred on day 1, 29% on day 2, and 15% on day 3.[341]			See Table LXXXI in online Data Supplement 1.

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

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

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

6.4. Glucose

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

6.5. Other Tests for Secondary Prevention

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

6.6. Antithrombotic Treatment

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

6.6.2. Atrial Fibrillation	COR	LOE	New, Revised, or Unchanged
1. For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation between 4 and 14 days after the onset of neurological symptoms.	**IIa**	**B-NR**	Recommendation revised from 2014 Secondary Prevention.
A multicenter prospective cohort of 1029 patients with AIS and newly diagnosed atrial fibrillation showed a better composite outcome of stroke, TIA, systemic embolism, sICH, and major extracranial bleeding within 90 days when anticoagulant was initiated 4 to 14 days from stroke onset (HR 0.53 [95% CI, 0.30–0.93] for starting anticoagulation at 4–14 days compared with <4 days); high CHA_2DS_2-VASc score, high NIHSS score, large ischemic lesions, and type of anticoagulation were associated with poorer outcomes.[378] In a prospective, open-label study of 60 patients with atrial fibrillation and either mild to moderate AIS with NIHSS score <9 (n=49) or TIA (n=11) who were treated with rivaroxaban within14 days of onset, 50 were available for follow-up at 7 days after drug initiation. None developed symptomatic hemorrhagic transformation (HT). Of the 23 with AIS who had HT at baseline, 5 demonstrated asymptomatic radiographic progression, and 18 showed neither clinical nor radiographic progression. Of the remaining 27 who did not have HT at baseline, 3 developed asymptomatic HT.[227]			See Table LI in online Data Supplement 1.
2. For patients with a history of ischemic stroke, atrial fibrillation, and coronary artery disease, the usefulness of adding antiplatelet therapy to oral anticoagulants is uncertain for purposes of reducing the risk of ischemic cardiovascular and cerebrovascular events. Unstable angina and coronary artery stenting represent special circumstances in which management may warrant dual antiplatelet/oral anticoagulation.	**IIb**	**C-LD**	Recommendation reworded for clarity from 2014 Secondary Prevention. COR unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table XCV in online Data Supplement 1 for original wording.

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

6.6.4. Hemorrhagic Transformation	COR	LOE	New, Revised, or Unchanged
1. For patients with AIS and HT, initiation or continuation of antiplatelet or anticoagulation therapy may be considered, depending on the specific clinical scenario and underlying indication.	**IIb**	**C-LD**	Recommendation revised from 2014 Secondary Prevention.
Several observational studies suggest that antithrombotics can be safely initiated or continued in patients with AIS and HT. In a prospective, open-label study of 60 patients with atrial fibrillation and either mild to moderate AIS with an NIHSS score <9 (n=49) or TIA (n=11) who were treated with rivaroxaban within 14 days of onset, 50 were available for follow-up at 7 days after drug initiation. None developed symptomatic HT. Of the 23 with AIS who had HT at baseline, 5 demonstrated asymptomatic radiographic progression, and 18 showed neither clinical nor radiographic progression. Of the remaining 27 who did not have HT at baseline, 3 developed asymptomatic HT.[227] A retrospective stroke registry analysis identified 222 patients with AIS and HT. The frequency of composite events (neurological deterioration, vascular events, and death) at 1 month was significantly lower in patients treated with antithrombotics compared with those who were not (1.6% versus 11.1%; *P*=0.041). Neither antiplatelet (n=72) nor anticoagulant (n=28) treatment after HT was associated with enlargement of the original HT or development of new HT or neurological deterioration.[382] Individual assessment of the clinical indication, benefits, and associated risks is warranted.[10,382,383]			See Table LI in online Data Supplement 1.

6.7. Carotid Revascularization

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

6.8. Treatment of Hyperlipidemia

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

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

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

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

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

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

Major ASCVD Events:

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

High-Risk Conditions:

Age ≥65 years
Heterozygous familial hypercholesterolemia
History of prior coronary artery bypass surgery or percutaneous coronary intervention outside of the major ASCVD events
Diabetes mellitus
Hypertension
Chronic kidney disease (estimated glomerular filtration rate 15–59 mL·min^{-1}·1.73 m^2)
Current smoking

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

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

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

6.9. Institution of Antihypertensive Medications

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

6.10. Smoking Cessation Intervention

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

6.11. Stroke Education

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

Additional reference support for this guideline is provided in online Data Supplement 1.[394–544]

Disclosures

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This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all reviewers are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

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