AHA/ASA Guideline

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

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

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

Endorsed by the Society for Academic Emergency Medicine

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

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

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

This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on November 29, 2017, and the American Heart Association Executive Committee on December 11, 2017. A copy of the document is available at http://professional.heart.org/statements by using either "Search for Guidelines & Statements" or the "Browse by Topic" area. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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

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

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

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

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

An independent evidence review committee was commissioned to perform a systematic review of a limited number of clinical questions identified in conjunction with the writing group, the results of which were considered by the writing group for incorporation into this guideline. The systematic reviews "Accuracy of Prediction Instruments for Diagnosing Large Vessel Occlusion in Individuals With Suspected Stroke: A Systematic Review for the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke"[3] and "Effect of Dysphagia Screening Strategies on Clinical Outcomes After Stroke: A Systematic Review for the 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke"[4] are published in conjunction with this guideline.

These guidelines use the American College of Cardiology (ACC)/AHA 2015 Class of Recommendations (COR) and Levels of Evidence (LOE) (Table 1) and the new AHA guidelines format. New or revised recommendations that supersede previous guideline recommendations are accompanied by 250-word knowledge bytes and data supplement tables summarizing the key studies supporting the recommendations in place of extensive text. Existing recommendations that are unchanged are reiterated with reference to the previous publication. These previous publications and their abbreviations used in this document are listed in Table 2. When there is no new pertinent evidence, for these unchanged recommendations, no knowledge byte or data supplement is provided. For some unchanged recommendations, there are new pertinent data that support the existing recommendation, and these are provided. Additional abbreviations used in this guideline are listed in Table 3.

Members of the writing group were appointed by the AHA Stroke Council's Scientific Statements Oversight Committee, representing various areas of medical expertise. Strict adherence to the AHA conflict of interest policy was maintained throughout the writing and consensus process. Members were not allowed to participate in discussions or to vote on topics relevant to their relationships with industry. Writing group members accepted topics relevant to their areas of expertise, reviewed the stroke literature with emphasis on publications since the prior guidelines, and drafted recommendations. Draft recommendations and supporting evidence were discussed by the writing group, and the revised recommendations for each topic were reviewed by a designated writing group member. The full writing group then evaluated the complete guidelines. The members of the writing group unanimously approved all recommendations except when relationships with industry precluded members voting. Prerelease review of the draft guideline was performed by 4 expert peer reviewers and by the members of the Stroke Council's Scientific Statements Oversight Committee and Stroke Council Leadership Committee.

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

CLASS (STRENGTH) OF RECOMMENDATION

CLASS I (STRONG) — Benefit >>> Risk

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

CLASS IIa (MODERATE) — Benefit >> Risk

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

CLASS IIb (WEAK) — Benefit ≥ Risk

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

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

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

CLASS III: Harm (STRONG) — Risk > Benefit

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

LEVEL (QUALITY) OF EVIDENCE‡

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

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

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

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

LEVEL C-EO (Expert Opinion)

Consensus of expert opinion based on clinical experience

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

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

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

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

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

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

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

Document Title	Publication Year	Abbreviation Used in This Document
"Recommendations for the Implementation of Telemedicine Within Stroke Systems of Care: A Policy Statement From the American Heart Association"[5]	2009	N/A
"Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association"[1]	2013	2013 AIS Guidelines
"Interactions Within Stroke Systems of Care: A Policy Statement From the American Heart Association/American Stroke Association"[6]	2013	2013 Stroke Systems of Care
"2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines"[7]	2013	2013 Cholesterol Guidelines
"2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society"[8]	2014	N/A
"Recommendations for the Management of Cerebral and Cerebellar Infarction With Swelling: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association"[9]	2014	2014 Cerebral Edema
"Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association"[10]	2014	2014 Palliative Care
"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"[11]	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"[12]	2014	N/A
"Part 15: First Aid: 2015 American Heart Association and American Red Cross Guidelines Update for First Aid"[13]	2015	2015 CPR/ECC
"2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association"[14]	2015	2015 Endovascular
"Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association"[15]	2015	2015 IV Alteplase
"Guidelines for Adult Stroke Rehabilitation and Recovery: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association"[16]	2016	2016 Rehab Guidelines

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

Table 3. Abbreviations in This Guideline

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

(*Continued*)

Table 3. Continued

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

1. Prehospital Stroke Management and Systems of Care

1.1. Prehospital Systems

1.1. Prehospital Systems	COR	LOE	New, Revised, or Unchanged
1. Public health leaders, along with medical professionals and others, should design and implement public education programs focused on stroke systems and the need to seek emergency care (by calling 9-1-1) in a rapid manner. These programs should be sustained over time and designed to reach racially/ethnically, age, and sex diverse populations.	I	B-R	Recommendation revised from 2013 Stroke Systems of Care. COR and LOE added.
Early stroke symptom recognition is essential for seeking timely care. Unfortunately, knowledge of stroke warning signs and risk factors in the United States remains poor. Blacks and Hispanics particularly have lower stroke awareness than the general population and are at increased risk of prehospital delays in seeking care.[17] These factors may contribute to the disparities in stroke outcomes. Available evidence suggests that public awareness interventions are variably effective by age, sex, and racial/ethnic minority status.[18] Thus, stroke education campaigns should be designed in a targeted manner to optimize their effectiveness.[18]			See Tables I and II in online Data Supplement 1.
2. Activation of the 9-1-1 system by patients or other members of the public is strongly recommended. 9-1-1 dispatchers should make stroke a priority dispatch, and transport times should be minimized.	I	B-NR	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Emergency medical services (EMS) use by stroke patients has been independently associated with earlier emergency department (ED) arrival (onset-to-door time ≤3 hours; adjusted odds ratio [OR], 2.00; 95% confidence interval [CI], 1.93–2.08), quicker ED evaluation (more patients with door-to-imaging time ≤25 minutes; OR, 1.89; 95% CI, 1.78–2.00), more rapid treatment (more patients with door-to-needle [DTN] time ≤60 minutes; OR, 1.44; 95% CI, 1.28–1.63), and more eligible patients being treated with alteplase if onset is ≤2 hours (67% versus 44%; OR, 1.47; 95% CI, 1.33–1.64),[18] yet only ≈60% of all stroke patients use EMS.[19] Men, blacks, and Hispanics are less likely to use EMS.[17,19] Thus, persistent efforts to ensure activation of the 9-1-1 or similar emergency system by patients or other members of the public in the case of a suspected stroke are warranted.			See Table I in online Data Supplement 1.
3. To increase both the number of patients who are treated and the quality of care, educational stroke programs for physicians, hospital personnel, and EMS personnel are recommended.	I	B-NR	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
On 9-1-1 activation, EMS dispatch and clinical personnel should prioritize the potential stroke case, minimize on-scene times, and transport the patient as quickly as possible to the most appropriate hospital. A recent US-based analysis of EMS response times found that median EMS response time (9-1-1 call to ED arrival) in 184 179 cases in which EMS provider impression was stroke was 36 minutes (interquartile range, 28.7–48.0 minutes).[20] On-scene time (median, 15 minutes) was the largest component of this time, and longer times were noted for patients 65 to 74 years of age, whites, and women and in nonurban areas. Dispatch designation of stroke was associated with minimally faster response times (36.0 versus 36.7 minutes; $P<0.01$). Notably, only 52% of cases were identified by dispatch as stroke.			See Table I in online Data Supplement 1.

1.2. EMS Assessment and Management

1.2. EMS Assessment and Management	COR	LOE	New, Revised, or Unchanged
1. The use of a stroke assessment system by first aid providers, including EMS dispatch personnel, is recommended.	I	B-NR	Recommendation reworded for clarity from 2015 CPR/ECC. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
2. EMS personnel should begin the initial management of stroke in the field. Implementation of a stroke protocol to be used by EMS personnel is strongly encouraged.	I	B-NR	Recommendation revised from 2013 AIS Guidelines.
In 1 study, the positive predictive value for a hospital discharge diagnosis of stroke/transient ischemic attack (TIA) among 900 cases for which EMS dispatch suspected stroke was 51% (95% CI, 47–54), and the positive predictive value for ambulance personnel impression of stroke was 58% (95% CI, 52–64).[21] In another study of 21 760 dispatches for stroke, the positive predictive value of the dispatch stroke/TIA symptoms identification was 34.3% (95% CI, 33.7–35.0), and the sensitivity was 64.0% (95% CI, 63.0–64.9).[22] In both cases, use of a prehospital stroke scale improved stroke identification, but better stroke identification tools are needed in the prehospital setting.			See Table III in online Data Supplement 1.

1.2. EMS Assessment and Management (Continued)	COR	LOE	New, Revised, or Unchanged
3. EMS personnel should provide prehospital notification to the receiving hospital that a suspected stroke patient is en route so that the appropriate hospital resources may be mobilized before patient arrival.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
In the Get With The Guidelines (GWTG) registry, EMS personnel provided prearrival notification to the destination ED for 67% of transported stroke patients. EMS prenotification was associated with increased likelihood of alteplase treatment within 3 hours (82.8% versus 79.2%), shorter door-to-imaging times (26 versus 31 minutes), shorter DTN times (78 versus 80 minutes), and shorter symptom onset-to-needle times (141 versus 145 minutes).[23]			See Table I in online Data Supplement 1.

1.3. EMS Systems

1.3. EMS Systems	COR	LOE	New, Revised, or Unchanged
1. EMS leaders, in coordination with local, regional, and state agencies and in consultation with medical authorities and local experts, should develop triage paradigms and protocols to ensure that patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized instrument for stroke screening, such as the FAST (face, arm, speech test) scale, Los Angeles Prehospital Stroke Screen, or Cincinnati Prehospital Stroke Scale.	I	B-NR	Recommendation reworded for clarity from 2013 Stroke Systems of Care. Class and LOE added to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
			See Table IV in online Data Supplement 1.
2. Regional systems of stroke care should be developed. These should consist of the following: (a) Healthcare facilities that provide initial emergency care, including administration of IV alteplase, and, (b) Centers capable of performing endovascular stroke treatment with comprehensive periprocedural care to which rapid transport can be arranged when appropriate.	I	A	Recommendation reworded for clarity from 2015 Endovascular. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
3. Patients with a positive stroke screen and/or a strong suspicion of stroke should be transported rapidly to the closest healthcare facilities that can capably administer IV alteplase.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. See Table LXXXIII in online Data Supplement 1 for original wording.
The 2013 recommendation referred to initial emergency care as described elsewhere in the guidelines, which specified administration of IV alteplase as part of this care. The current recommendation is unchanged in intent but reworded to make this clear.			
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. Further research is needed.	IIb	B-NR	New recommendation.
At least 6 stroke severity scales targeted at recognition of large vessel occlusion (LVO) in the prehospital setting to facilitate transfer to endovascular centers have been published.[24–29] The performance of all available scales based on published literature was recently compared.[3] 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. For prehospital patients with suspected LVO by a stroke severity scale, the Mission: Lifeline Severity–based Stroke Triage Algorithm for EMS[30] 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,[31] the known impact of delays to mechanical thrombectomy on outcome,[32] 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.			See Table V 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 a state health department, is recommended. Additional medical centers should seek such certification. ***AHA has a cobranded, revenue-generating stroke certification with TJC**.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Data support the development of stroke centers to improve patient care and outcomes.[33] 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 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.[34]			See Table VI 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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. It is recommended that DTN time goals be established. A primary goal of achieving DTN times within 60 minutes in ≥50% of AIS patients treated with IV alteplase should be established.	I	B-NR	Recommendation revised from 2013 AIS Guidelines.
In GWTG-Stroke hospitals, median DTN time for alteplase administration decreased from 77 minutes (interquartile range, 60–98 minutes) during the 2003 to 2009 preintervention period to 67 minutes (interquartile range, 51–87 minutes) during the 2010 to 2013 postintervention period (P<0.001). The percentage of alteplase-treated patients having DTN times of ≤60 minutes increased from 26.5% (95% CI, 26.0–27.1) to 41.3% (95% CI, 40.8–41.7) (P<0.001). Comparing the quarter immediately before the intervention (quarter 4 of 2009) to the final postintervention quarter (quarter 3 of 2013) showed that DTN times of ≤60 minutes increased from 29.6% (95% CI, 27.8–31.5) to 53.3% (95% CI, 51.5–55.2) (P<0.001).[35] In a subsequent study evaluating a cohort of hospitals from 2014 to 2015, 59.3% of patients received IV alteplase within a DTN time of 60 minutes.[36]			See Table VII in online Data Supplement 1.
3. It may be reasonable to establish a secondary DTN time goal of achieving DTN times within 45 minutes in ≥50% of patients with AIS who were treated with IV alteplase.	IIb	C-EO	New recommendation.
In a cohort of 888 GWTG-Stroke hospitals surveyed between June 2014 and April 2015, 16 901 patients with ischemic stroke were treated with IV alteplase within 4.5 hours of symptom onset. The patient-level median DTN time was 56 minutes (interquartile range, 42–75 minutes), with 30.4% treated within 45 minutes after hospital arrival.[36] This recommendation mirrors Target: Stroke phase II objectives.[37]			See Table VII in online Data Supplement 1.
4. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is recommended. Patients with stroke should have a careful clinical assessment, including neurological examination.	I	B-NR	Recommendation wording modified from 2013 AIS Guidelines to match Class I stratifications. Class unchanged. LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
5. Multicomponent quality improvement initiatives, which include ED education and multidisciplinary teams with access to neurological expertise, are recommended to safely increase IV thrombolytic treatment.	I	A	New recommendation.
Multicomponent quality improvement programs to improve stroke care have demonstrated utility in safely increasing alteplase use in the community hospital setting. The US cluster-randomized INSTINCT trial (Increasing Stroke Treatment Through Interventional Change Tactics) demonstrated increased rates of alteplase use among all stroke patients. In the intervention group hospitals, alteplase use increased from 59 of 5882 (1.00%) before intervention to 191 of 7288 (2.62%) after intervention. This compared favorably with the change in the control group hospitals from 65 of 5957 (1.09%) to 120 of 6989 (1.72%), with a relative risk (RR) of 1.68 (95% CI, 1.09–2.57; P=0.02). Safety was also demonstrated with symptomatic intracranial hemorrhage (within 36 hours) in 24 of 404 (5.9%) treated strokes.[38] In the PRACTISE trial (Penumbra and Recanalisation Acute Computed Tomography in Ischaemic Stroke Evaluation), a multilevel intervention was conducted in a sample of 12 Dutch hospitals. After implementation of an intensive stroke treatment strategy, intervention hospitals treated 393 patients with IV thrombolysis (13.1% of all patients with acute stroke) versus 308 (12.2%) at control hospitals (adjusted OR, 1.25; 95% CI, 0.93–1.68).[39]			See Tables VIII and IX in online Data Supplement 1.

1.6. Telemedicine

1.6. Telemedicine	COR	LOE	New, Revised, or Unchanged
1. For sites without in-house imaging interpretation expertise, teleradiology systems approved by the US Food and Drug Administration are recommended for timely review of brain imaging in patients with suspected acute stroke.	I	A	Recommendation revised from 2013 AIS Guidelines.
2. When implemented within a telestroke network, teleradiology systems approved by the US Food and Drug Administration are useful in supporting rapid imaging interpretation in time for IV alteplase administration decision making.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE revised. See Table LXXXIII in online Data Supplement 1 for original wording.
Studies of teleradiology to read brain imaging in acute stroke have successfully assessed feasibility; agreement between telestroke neurologists, radiologists, and neuroradiologists over the presence or absence of radiological contraindications to IV alteplase; and reliability of telestroke radiological evaluations.[40–45]			See Table X in online Data Supplement 1.
3. Because of the limited distribution and availability of neurological, neurosurgical, and radiological expertise, the use of telemedicine/telestroke resources and systems can be beneficial and 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.	IIa	C-EO	Recommendation wording modified from 2013 Stroke Systems of Care to match Class IIa stratifications. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
4. Telestroke/teleradiology evaluations of AIS patients can be effective for correct IV alteplase eligibility decision making.	IIa	B-R	New recommendation.
The STRokEDOC (Stroke Team Remote Evaluation Using a Digital Observation Camera) pooled analysis supported the hypothesis that telemedicine consultations, which included teleradiology, compared with telephone-only resulted in statistically significantly more accurate IV alteplase eligibility decision making for patients exhibiting symptoms and signs of an acute stroke syndrome in EDs.[46]			See Table XI in online Data Supplement 1.
5. Administration of IV alteplase guided by telestroke consultation for patients with AIS may be as safe and as beneficial as that of stroke centers.	IIb	B-NR	New recommendation.
A systematic review and meta-analysis was performed to evaluate the safety and efficacy of IV alteplase delivered through telestroke networks in patients with AIS. Symptomatic intracerebral hemorrhage (sICH) rates were similar between patients subjected to telemedicine-guided IV alteplase and those receiving IV alteplase at stroke centers. There was no difference in mortality or in functional independence at 3 months between telestroke-guided and stroke center–managed patients. The findings indicate that IV alteplase delivery through telestroke networks is safe and effective in the 3-hour time window.[47]			See Table XII in online Data Supplement 1.
6. Providing alteplase decision-making support via telephone consultation to community physicians is feasible and safe and may be considered when a hospital has access to neither an in-person stroke team nor a telestroke system.	IIb	C-LD	New recommendation.
The advantages of telephone consultations for patients with acute stroke syndromes are feasibility, history of use, simplicity, availability, portability, short consultation time, and facile implementation.[48]			See Table XIII in online Data Supplement 1.
7. Telestroke networks may be reasonable for triaging patients with AIS who may be eligible for interfacility transfer in order to be considered for acute mechanical thrombectomy.	IIb	B-NR	New recommendation.
An observational study compared clinical outcomes of endovascular treatment (EVT) between patients with anterior circulation stroke transferred after teleconsultation and those directly admitted to a tertiary stroke center. The study evaluated 151 patients who underwent emergency EVT for anterior circulation stroke. Of these, 48 patients (31.8%) were transferred after teleconsultation, and 103 (68.2%) were admitted primarily through an ED. Transferred patients were younger, received IV alteplase more frequently, had prolonged time from stroke onset to EVT initiation, and tended to have lower rates of symptomatic intracranial hemorrhage and mortality than directly admitted patients. Similar rates of reperfusion and favorable functional outcomes were observed in patients treated by telestroke and those who were directly admitted. Telestroke networks may enable the triage and the delivery of EVT to selected ischemic stroke patients transferred from remote hospitals.[49]			See Table XII in online Data Supplement 1.

1.7. Organization and Integration of Components

1.7. Organization and Integration of Components	COR	LOE	New, Revised, or Unchanged
1. It may be useful for primary stroke centers and other healthcare facilities that provide initial emergency care, including administration of IV alteplase, to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for endovascular intervention and to reduce the time to EVT.	IIb	C-LD	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Between 2006 and 2010, the proportion of ischemic strokes undergoing computed tomography (CT) angiography (CTA) increased from 3.8% to 9.1% (*P*<0.0001). CT perfusion (CTP) increased from 0.05% to 2.9% over the same period (*P*<0.0001). Reperfusion treatment was more common among those who were imaged with CTA (13.0%) and CTP (17.6%) compared with those with CT of the head alone (4.0%; *P*<0.0001).[50] However, when considering implementation of multimodal CT imaging at small or remote access hospitals, resource availability and realistic expectations for gains in efficiency should be taken into account.			
2. Mechanical thrombectomy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography, qualified neurointerventionalists, and a comprehensive periprocedural care team. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures.	I	C-EO	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. All hospitals caring for stroke patients within a stroke system of care should develop, adopt, and adhere to care protocols that reflect current care guidelines as established by national and international professional organizations and state and federal agencies and laws.	I	C-EO	Recommendation unchanged from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
4. Different services within a hospital that may be transferring patients through a continuum of care, as well as different hospitals that may be transferring patients to other facilities, should establish hand-off and transfer protocols and procedures that ensure safe and efficient patient care within and between facilities. Protocols for interhospital transfer of patients should be established and approved beforehand so that efficient patient transfers can be accomplished at all hours of the day and night.	I	C-EO	Recommendation unchanged from 2013 Stroke Systems of Care. COR and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
5. It may be beneficial for government agencies and third-party payers to develop and implement reimbursement schedules for patients with acute stroke that reflect the demanding care and expertise that such patients require to achieve an optimal outcome, regardless of whether they receive a specific medication or procedure.	IIb	C-EO	Recommendation revised from 2013 Stroke Systems of Care.
Multiple studies evaluating fibrinolytic therapy and mechanical thrombectomy, alone or in combination, have demonstrated substantial cost-effectiveness of acute stroke treatment across multiple countries. Pre–mechanical thrombectomy era data demonstrate that, in the United States, cost savings of approximately US $30 million would be realized if the proportion of all ischemic stroke patients receiving thrombolysis was increased to 8%. This excludes any gain from increased quality-adjusted life-years gained, a source of tremendous additional economic and patient value. Before the implementation of Centers for Medicare & Medicaid Services diagnosis-related group 559 payment in 2005, treatment of acute stroke was economically discouraged at a hospital level because of a high hospital cost-reimbursement ratio. Diagnosis-related group 559 favorably altered the cost-reimbursement ratio for stroke care. In a single-hospital study, this ratio decreased from 1.41 (95% CI, 0.98–2.28) before diagnosis-related group 559 to 0.82 (95% CI, 0.66–0.97) after diagnosis-related group 559. The subsequent years corresponded to a period of rapid growth in the number of primary stroke centers and increasing total stroke treatment cases. Addressing emerging economic barriers to treatment is important as acute stroke care complexity evolves.[51–56]			

1.8. Establishment of Data Repositories

1.8. Establishment of Data Repositories	COR	LOE	New, Revised, or Unchanged
1. Participation in a stroke data repository is recommended to promote consistent adherence to current treatment guidelines, to allow continuous quality improvement, and to improve patient outcomes.	I	B-NR	New recommendation.
In GWTG-Stroke hospitals, participation in a stroke data repository as 1 part of a quality improvement process was associated with improved timeliness of IV alteplase administration after AIS, lower in-hospital mortality and intracranial hemorrhage rates, and an increase in the percentage of patients discharged home.[35,57]			See Table XIV in online Data Supplement 1.

1.9. Stroke System Care Quality Improvement Process

1.9. Stroke System Care Quality Improvement Process	COR	LOE	New, Revised, or Unchanged
1. Healthcare institutions should organize a multidisciplinary quality improvement committee to review and monitor stroke care quality benchmarks, indicators, evidence-based practices, and outcomes. The formation of a clinical process improvement team and the establishment of a stroke care data bank are helpful for such quality of care assurances. The data repository can be used to identify the gaps or disparities in quality stroke care. Once the gaps have been identified, specific interventions can be initiated to address these gaps or disparities.	I	B-NR	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
In GWTG-Stroke hospitals, a multidisciplinary quality improvement committee, as 1 part of a quality improvement process, was associated with improved timeliness of IV alteplase administration after AIS, lower in-hospital mortality and intracranial hemorrhage rates, and an increase in the percentage of patients discharged home.[35,57] Identification of stroke treatment barriers with targeted interventions has demonstrated benefit in improving stroke treatment in community hospitals.[38]			See Tables VIII and IX in online Data Supplement 1.
2. Continuous quality improvement processes, implemented by each major element of a stroke system of care and the system as a whole, can be useful in improving patient care or outcomes.	IIa	B-NR	Recommendation revised from 2013 Stroke Systems of Care. Class and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
3. Stroke outcome measures should include adjustments for baseline severity.	I	B-NR	Recommendation revised from 2013 Stroke Systems of Care. Class and LOE added to conform with ACC/AHA 2015 Recommendation Classification System.
Data indicate continuous quality improvement efforts along the stroke spectrum of care, from initial patient identification to EMS activation, ED evaluation, stroke team activation, and poststroke care, can be useful in improving outcomes.[35,38,57] Stroke outcome measures are strongly influenced by baseline stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS).[58–61] Other identified predictors of poor outcomes include age, blood glucose, and infarct on imaging.[61] Quality improvement efforts should recognize these predictors in order to have meaningful comparisons between stroke care systems.			See Tables VIII, IX, and XIV in online Data Supplement 1.

2. Emergency Evaluation and Treatment

2.1. Stroke Scales

2.1. Stroke Scales	COR	LOE	New, Revised, or Unchanged
1. The use of a stroke severity rating scale, preferably the NIHSS, is recommended.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Formal stroke scores or scales such as the NIHSS (Table 4) may be performed rapidly, have demonstrated utility, and may be administered by a broad spectrum of healthcare providers with accuracy and reliability.[63,64] Use of a standardized scale quantifies the degree of neurological deficit, facilitates communication, helps identify patients for thrombolytic or mechanical intervention, allows objective measurement of changing clinical status, and identifies those at higher risk for complications such as intracerebral hemorrhage (ICH).[59–61,65]			See Table III in online Data Supplement 1.

Table 4. National Institutes of Health Stroke Scale

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—Alert
		1—Drowsy
		2—Obtunded
		3—Coma/unresponsive
1B	Orientation questions (2)	0—Answers both correctly
		1—Answers 1 correctly
		2—Answers neither correctly
1C	Response to commands (2)	0—Performs both tasks correctly
		1—Performs 1 task correctly
		2—Performs neither
2	Gaze	0—Normal horizontal movements
		1—Partial gaze palsy
		2—Complete gaze palsy
3	Visual fields	0—No visual field defect
		1—Partial hemianopia
		2—Complete hemianopia
		3—Bilateral hemianopia
4	Facial movement	0—Normal
		1—Minor facial weakness
		2—Partial facial weakness
		3—Complete unilateral palsy
5	Motor function (arm)	0—No drift
	a. Left	1—Drift before 10 s
	b. Right	2—Falls before 10 s
		3—No effort against gravity
		4—No movement
6	Motor function (leg)	0—No drift
	a. Left	1—Drift before 5 s
	b. Right	2—Falls before 5 s
		3—No effort against gravity
		4—No movement
7	Limb ataxia	0—No ataxia
		1—Ataxia in 1 limb
		2—Ataxia in 2 limbs
8	Sensory	0—No sensory loss
		1—Mild sensory loss
		2—Severe sensory loss
9	Language	0—Normal
		1—Mild aphasia
		2—Severe aphasia
		3—Mute or global aphasia
10	Articulation	0—Normal
		1—Mild dysarthria
		2—Severe dysarthria
11	Extinction or inattention	0—Absent
		1—Mild loss (1 sensory modality lost)
		2—Severe loss (2 modalities lost)

Adapted from Lyden et al.[62] Copyright © 1994, American Heart Association, Inc.

2.2. Brain Imaging

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

2.2. Brain Imaging (Continued)	COR	LOE	New, Revised, or Unchanged
6. Use of imaging criteria to select ischemic stroke patients who awoke with stroke or have unclear time of symptom onset for treatment with IV alteplase is not recommended outside a clinical trial.	III: No Benefit	B-NR	Recommendation unchanged from 2015 IV Alteplase. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
7. Multimodal CT and MRI, including perfusion imaging, should not delay administration of IV alteplase.	III: Harm	B-NR	New recommendation.
Analysis of trials using advanced, multimodal pretreatment imaging (including CTP measures of penumbral imaging, diffusion-perfusion mismatch, or vessel imaging) for IV fibrinolytics has failed to demonstrate clinical efficacy in patients with various pretreatment imaging biomarkers compared with those without those markers.[88–95]			See Table XX and XXI in online Data Supplement 1.
8. For patients who otherwise meet criteria for EVT, a noninvasive intracranial vascular study is recommended during the initial imaging evaluation of the acute stroke patient, but should not delay IV alteplase if indicated. For patients who qualify for IV alteplase according to guidelines from professional medical societies, initiating IV alteplase before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should then be obtained as quickly as possible.	I	A	Recommendation reworded for clarity from 2015 Endovascular. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
A recent systematic review evaluated the accuracy of prediction instruments for diagnosing LVO.[3] In the setting where confirmed ischemic stroke patients would be assessed by a neurologist or emergency physician in the ED, the authors suggested that the NIHSS is the best of the LVO prediction instruments. According to their meta-analysis, a threshold of ≥10 would provide the optimal balance between sensitivity (73%) and specificity (74%). To maximize sensitivity (at the cost of lower specificity), a threshold of ≥6 would have 87% sensitivity and 52% specificity. However, even this low threshold misses some cases with LVO, whereas the low specificity indicates that false-positives will be common.			
9. For patients who otherwise meet criteria for EVT, it is reasonable to proceed with CTA if indicated in patients with suspected intracranial LVO before obtaining a serum creatinine concentration in patients without a history of renal impairment.	IIa	B-NR	New recommendation.
Analyses from a number of observational studies suggest that the risk of contrast-induced nephropathy secondary to CTA imaging is relatively low, particularly in patients without a history of renal impairment. Moreover, waiting for these laboratory results may lead to delays in mechanical thrombectomy.[96–101]			See Table XXII in online Data Supplement 1.
10. In patients who are potential candidates for mechanical thrombectomy, imaging of the extracranial carotid and vertebral arteries, in addition to the intracranial circulation, is reasonable to provide useful information on patient eligibility and endovascular procedural planning.	IIa	C-EO	New recommendation.
Knowledge of vessel anatomy and presence of extracranial vessel dissections, stenoses, and occlusions may assist in planning endovascular procedures or identifying patients ineligible for treatment because of vessel tortuosity or inability to access the intracranial vasculature.			
11. Additional imaging beyond CT and CTA or MRI and magnetic resonance angiography (MRA) such as perfusion studies for selecting patients for mechanical thrombectomy in <6 hours is not recommended.	III: No Benefit	B-R	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 [Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times])[102–105] 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 [Multicenter Randomized Clinical Trial of Endovascular Treatment for AIS in the Netherlands])[106,107] required only NCCT and demonstration of LVO. Because the last 2 studies independently demonstrated benefit in the treated group, additional imaging-based eligibility criteria 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, collateral flow status, and penumbra, are beneficial for selecting patients for acute reperfusion therapy who are within 6 hours of symptom onset and have an ASPECTS score <6.			See Table XXIII in online Data Supplement 1.

2.2. Brain Imaging (Continued)	COR	LOE	New, Revised, or Unchanged
12. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP, DW-MRI, or MRI perfusion is recommended to aid in patient selection for mechanical thrombectomy, but only when imaging and other eligibility criteria from RCTs showing benefit are being strictly applied in selecting patients for mechanical thrombectomy.	I	A	New recommendation.
The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical imaging mismatch (a combination of NIHSS and imaging findings on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33%; 95% CI, 21–44; posterior probability of superiority >0.999).[108] The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67; 95% CI, 1.60–4.48; *P*<0.0001).[109] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from 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 and DEFUSE 3 eligibility should be strictly adhered to in clinical practice.			See Table XXIII in online Data Supplement 1.
13. It may be reasonable to incorporate collateral flow status into clinical decision making in some candidates to determine eligibility for mechanical thrombectomy.	IIb	C-LD	Recommendation revised from 2015 Endovascular.
Several studies, including secondary analyses from MR CLEAN and IMS (Interventional Management of Stroke) III, provide data supporting the role of collateral assessments in identifying patients likely or unlikely to benefit from mechanical thrombectomy.[110,111]			See Table XXIV in online Data Supplement 1.

2.3. Other Diagnostic Tests

2.3. Other Diagnostic Tests	COR	LOE	New, Revised, or Unchanged
1. Only the assessment of blood glucose must precede the initiation of IV alteplase in all patients.	I	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Recommendation was modified to clarify that it is only blood glucose that must be measured in all patients. Other tests, for example, international normalized ratio, activated partial thromboplastin time, and platelet count, may be necessary in some circumstances if there is suspicion of coagulopathy. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, IV alteplase treatment should not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.			
2. Baseline ECG assessment is recommended in patients presenting with AIS, but should not delay initiation of IV alteplase.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. Baseline troponin assessment is recommended in patients presenting with AIS, but should not delay initiation of IV alteplase.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE revised. See Table LXXXIII in online Data Supplement 1 for original wording.

2.3. Other Diagnostic Tests (Continued)	COR	LOE	New, Revised, or Unchanged
4. Usefulness of chest radiographs in the hyperacute stroke setting in the absence of evidence of acute pulmonary, cardiac, or pulmonary vascular disease is unclear. If obtained, they should not unnecessarily delay administration of IV alteplase.	IIb	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Additional support for this reworded recommendation from the 2013 AIS Guidelines comes from a cohort study of 615 patients, 243 of whom had chest x-ray done before IV thrombolytics. Cardiopulmonary adverse events in the first 24 hours of admission, endotracheal intubation in the first 7 hours, and in-hospital mortality were not different between the 2 groups. Patients with chest x-ray done before treatment had longer mean DTN times than those who did not (75.8 versus 58.3 minutes; P=0.0001).[112]			See Table XXV in online Data Supplement 1.

3. General Supportive Care and Emergency Treatment

3.1. Airway, Breathing, and Oxygenation

3.1. Airway, Breathing, and Oxygenation	COR	LOE	New, Revised, or Unchanged
1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway.	I	C-EO	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Supplemental oxygen should be provided to maintain oxygen saturation >94%.	I	C-LD	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. Supplemental oxygen is not recommended in nonhypoxic patients with AIS.	III: No Benefit	B-R	Recommendation unchanged from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of oxygen by nasal cannula at 2 L/min (baseline O_2 saturation >93%) or 3 L/min (baseline O_2 saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights.[113]			See Table XXVI in online Data Supplement 1.
4. Hyperbaric oxygen (HBO) is not recommended for patients with AIS except when caused by air embolization.	III: No Benefit	B-NR	Recommendation revised from 2013 AIS Guidelines.
The limited data available on the utility of HBO therapy for AIS (not related to cerebral air embolism) show no benefit.[114] HBO therapy is associated with claustrophobia and middle ear barotrauma,[115] as well as an increased risk of seizures.[116] Given the confines of HBO chambers, the ability to closely/adequately monitor patients may also be compromised. HBO thus should be offered only in the context of a clinical trial or to individuals with cerebral air embolism.			See Table XXVII in online Data Supplement 1.

3.2. Blood Pressure

3.2. Blood Pressure	COR	LOE	New, Revised, or Unchanged
1. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.	I	C-EO	New recommendation.
The blood pressure (BP) level that should be maintained in patients with AIS to ensure best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others have not.[117–124] No studies have addressed the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing colloids with crystalloids, the odds of death or dependence were similar. Clinically important benefits or harms could not be excluded. There are no data to guide volume and duration of parenteral fluid delivery.[125] No studies have compared different isotonic fluids.			See Table XXVIII in online Data Supplement 1.

3.2. Blood Pressure (Continued)	COR	LOE	New, Revised, or Unchanged
2. Patients who have elevated BP and are otherwise eligible for treatment with IV alteplase should have their BP carefully lowered so that their systolic BP is <185 mm Hg and their diastolic BP is <110 mm Hg before IV fibrinolytic therapy is initiated.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
The RCTs of IV alteplase required the BP to be <185 mm Hg systolic and <110 mm Hg diastolic before treatment and <180/105 mm Hg for the first 24 hours after treatment. Options to treat arterial hypertension in patients with AIS who are candidates for acute reperfusion therapy are given in Table 5. Some observational studies suggest that the risk of hemorrhage after administration of alteplase is greater in patients with higher BPs[126–132] and in patients with more BP variability.[133] The exact BP at which the risk of hemorrhage after thrombolysis increases is unknown. It is thus reasonable to target the BPs used in the RCTs of IV thrombolysis.			See Table XXIX in online Data Supplement 1.
3. Until additional data become available, in patients for whom intra-arterial therapy is planned and who have not received IV thrombolytic therapy, it is reasonable to maintain BP ≤185/110 mm Hg before the procedure.	IIa	B-R	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[102–104,106,107]) 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.[108] 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.			See Table XXIII in online Data Supplement 1.
4. The usefulness of drug-induced hypertension in patients with AIS is not well established.	IIb	C-LD	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE revised.

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

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

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

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

Data derived from Jauch et al.[1]

3.3. Temperature

3.3. Temperature	COR	LOE	New, Revised, or Unchanged
1. Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke.	I	C-EO	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Additional support for this recommendation unchanged from the 2013 AIS Guidelines is provided by a large retrospective cohort study conducted from 2005 to 2013 of patients admitted to intensive care units in Australia, New Zealand, and the United Kingdom. Peak temperature in the first 24 hours <37°C and >39°C was associated with an increased risk of in-hospital death compared with normothermia in 9366 patients with AIS.[134]			See Tables XXX and XXXI in online Data Supplement 1.
2. The benefit of induced hypothermia for treating patients with ischemic stroke is not well established. Hypothermia should be offered only in the context of ongoing clinical trials.	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.
Hypothermia is a promising neuroprotective strategy, but its benefit in patients with AIS has not been proven. Most studies suggest that induction of hypothermia is associated with an increase in the risk of infection, including pneumonia.[135–138] Therapeutic hypothermia should be undertaken only in the context of a clinical trial.			See Tables XXXII and XXXIII in online Data Supplement 1.

3.4. Blood Glucose

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

3.5. IV Alteplase

3.5. IV Alteplase	COR	LOE	New, Revised, or Unchanged
1. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is recommended for selected patients who may be treated within 3 hours of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in Table 6 to determine patient eligibility.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
The safety and efficacy of this treatment when administered within the first 3 hours after stroke onset are solidly supported by combined data from multiple RCTs[90,139,140] and confirmed by extensive community experience in many countries.[141] The eligibility criteria for IV alteplase have evolved over time as its usefulness and true risks have become clearer. A recent AHA statement provides a detailed discussion of this topic.[15] Eligibility recommendations for IV alteplase in patients with AIS are summarized in Table 6. The benefit of IV alteplase is well established for adult patients with disabling stroke symptoms regardless of age and stroke severity.[73,142] Because of this proven benefit and the need to expedite treatment, when a patient cannot provide consent (eg, aphasia, confusion) and a legally authorized representative is not immediately available to provide proxy consent, it is justified to proceed with IV thrombolysis in an otherwise eligible adult patient with a disabling AIS. In a recent trial, a lower dose of IV alteplase (0.6 mg/kg) was not shown to be equivalent to standard-dose IV alteplase for the reduction of death and disability at 90 days.[143] Main elements of postthrombolysis care are listed in Table 7.			See Table XXXIV in online Data Supplement 1.
2. IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 minutes with initial 10% of dose given as bolus over 1 minute) is also recommended for selected patients who can be treated within 3 and 4.5 hours of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in Table 6 determine patient eligibility.	I	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
One trial (ECASS-III) specifically evaluating the efficacy of IV alteplase within 3 and 4.5 hours after symptom onset[144] and pooled analysis of multiple trials testing IV alteplase within various time windows[90,139,140] support the value of IV thrombolysis up to 4.5 hours after symptom onset. ECASS-III excluded octogenarians, patients taking warfarin regardless of international normalized ratio, patients with combined history of diabetes mellitus and previous ischemic stroke, and patients with very severe strokes (NIHSS score >25) because of a perceived excessive risk of intracranial hemorrhage in those cases. However, careful analysis of available published data summarized in an AHA/American Stroke Association scientific statement indicates that these exclusion criteria from the trial may not be justified in practice (Table 6).[15]			See Table XXXIV in online Data Supplement 1.

3.5. IV Alteplase (Continued)	COR	LOE	New, Revised, or Unchanged
3. For otherwise eligible patients with mild stroke presenting in the 3- to 4.5-hour window, treatment with IV alteplase may be reasonable. Treatment risks should be weighed against possible benefits.	IIb	B-NR	New recommendation.
In ECASS III, there was no significant interaction of benefit (mRS score 0–1 at 90 days) or safety (sICH or death) with stroke severity when patients were categorized by baseline NIHSS score of 0 to 9, 10 to 19, and >20.[144] Patients with a minor neurological deficit were excluded. Only 128 patients with an NIHSS score of 0 to 5 were included, and they were not analyzed separately.[145] In SITS-ISTR (Safe Implementation of Treatments in Stroke–International Stroke Thrombolysis Registry), good functional outcomes (mRS score 0–1 at 90 days) and risk of sICH were similar or the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours.[146] Similarly, in the GWTG registry, good functional outcomes, mortality, and risk of sICH were the same in mild stroke treated in 0 to 3 and 3 to 4.5 hours.[147]			See Tables XXXV and XXXVI in online Data Supplement 1.
4. In otherwise eligible patients who have had a previously demonstrated small number (1–10) of CMBs on MRI, administration of IV alteplase is reasonable.	IIa	B-NR	New recommendation.
5. In otherwise eligible patients who have had a previously demonstrated high burden of CMBs (>10) on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit.	IIb	B-NR	New recommendation.
MRI with hemosiderin-sensitive sequences has shown that clinically silent CMBs occur in approximately one fourth of patients who have received IV alteplase. No RCTs of IV alteplase in AIS with baseline MRI to identify CMBs have been conducted, so no determination of the effect of baseline CMB on the treatment effect of alteplase with CMB is available. Two meta-analyses of the association of baseline CMBs on the risk of sICH after IV alteplase have shown that sICH is more common in patients with baseline CMBs (OR, 2.18; 95% CI, 1.12–4.22; OR, 2.36; 95% CI, 1.21–4.61).[85,86] However, sICH in patients with baseline CMBs is not more common (6.1%, 6.5%)[85,86] than in the NINDS rtPA trial (6.4%).[87] In patients with >10 CMBs, the sICH rate was 40%, but this is based on only 6 events in 15 patients, and patients with >10 CMBs constituted only 0.8% of the sample.[86] Meta-analysis of the 4 studies that provided information on 3- to 6-month functional outcomes showed that the presence of CMBs was associated with worse outcomes after IV alteplase compared with patients without CMBs (OR, 1.58; 95% CI, 1.18–2.14; *P*=0.002).[85] Thus, the presence of CMBs increases the risk of ICH and the chances of poor outcomes after IV alteplase, but it is unclear whether these negative effects fully negate the benefit of thrombolysis. It is also unknown whether the location and number of CMBs may differentially influence outcomes. These questions deserve further investigation.			See Table XIX in online Data Supplement 1.
6. IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial.	IIa	B-NR	New recommendation.
A case-control analysis using the population from the AHA GWTG-Stroke registry, including 832 cases with sickle cell disease (all adults) and 3328 age-, sex-, and race-matched controls without sickle cell disease with similar severity of neurological deficits at presentation, showed that sickle cell disease did not have a significant impact on the safety or the outcome at discharge of treatment with IV alteplase.[148]			See Table XXXVII in online Data Supplement 1.
7. Abciximab should not be administered concurrently with IV alteplase.	III: Harm	B-R	Recommendation revised from 2013 AIS Guidelines.
8. IV alteplase should not be administered to patients who have received a treatment dose of low-molecular-weight heparin (LMWH) within the previous 24 hours.	III: Harm	B-NR	Recommendation reworded for clarity from 2015 IV Alteplase. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
The recommendation refers to full treatment doses and not to prophylactic doses. The 2015 "Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke" stated, "Intravenous alteplase in patients who have received a dose of LMWH within the previous 24 hours is not recommended. This applies to both prophylactic doses and treatment doses (*Class III; Level of Evidence B*)."[15] This statement was updated in a subsequently published erratum to specify that the contraindication does not apply to prophylactic doses.			
9. The potential risks should be discussed during thrombolysis eligibility deliberation and weighed against the anticipated benefits during decision making.	I	C-EO	Recommendation and Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
10. Given the extremely low risk of unsuspected abnormal platelet counts or coagulation studies in a population, it is reasonable that urgent IV alteplase treatment not be delayed while waiting for hematologic or coagulation testing if there is no reason to suspect an abnormal test.	IIa	B-NR	Recommendation and Class unchanged from 2015 IV Alteplase. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

3.5. IV Alteplase (Continued)	COR	LOE	New, Revised, or Unchanged
11. Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and determine blood glucose levels before IV alteplase initiation. IV alteplase is not indicated for nonvascular conditions.	III: No Benefit	B-NR	Recommendation reworded for clarity from 2015 IV Alteplase. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
12. Because time from onset of symptoms to treatment has such a powerful impact on outcomes, treatment with IV alteplase should not be delayed to monitor for further improvement.	III: Harm	C-EO	Recommendation wording modified from 2015 IV Alteplase to match Class III stratifications and reworded for clarity. Class and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
13. In patients undergoing fibrinolytic therapy, physicians should be prepared to treat potential emergent adverse effects, including bleeding complications and angioedema that may cause partial airway obstruction.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
See Table 8 for options for management of symptomatic intracranial bleeding occurring within 24 hours after administration of IV alteplase for treatment of AIS and Table 9 for options for management of orolingual angioedema associated with IV alteplase administration for AIS.			
14. BP should be maintained <180/105 mm Hg for at least the first 24 hours after IV alteplase treatment.	I	B-NR	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
15. The risk of antithrombotic therapy within the first 24 hours after treatment with IV alteplase (with or without EVT) is uncertain. Use might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.	IIb	B-NR	New recommendation.
A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or EVT compared with initiation >24 hours. However, this study may have been subject to selection bias, and the timing of the initiation of antiplatelet therapy or anticoagulation should be based on an individual level, balancing risk versus benefit.[166]			See Table XXXVIII in online Data Supplement 1.
16. In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible.	I	A	Recommendation reworded for clarity from 2013 AIS Guidelines. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.

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

Indications (Class I)	
Within 3 h*	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is recommended for selected patients who may be treated within 3 h of ischemic stroke symptom onset or patient last known well or at baseline state. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*Class I; LOE A*)
Age	For otherwise medically eligible patients ≥18 y of age, IV alteplase administration within 3 h is equally recommended for patients <80 and >80 y of age.† (*Class I; LOE A*)
Severity	For severe stroke symptoms, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. Despite increased risk of hemorrhagic transformation, there is still proven clinical benefit for patients with severe stroke symptoms.† (*Class I; LOE A*)
	For patients with mild but disabling stroke symptoms, IV alteplase is indicated within 3 h from symptom onset of ischemic stroke. There should be no exclusion for patients with mild but nonetheless disabling stroke symptoms, in the opinion of the treating physician, from treatment with IV alteplase because there is proven clinical benefit for those patients.† (*Class I; LOE B-R*)‡
3–4.5 h*	IV alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) is also recommended for selected patients who can be treated within 3 and 4.5 h of ischemic stroke symptom onset or patient last known well. Physicians should review the criteria outlined in this table to determine patient eligibility.† (*Class I; LOE B-R*)‡
Age Diabetes mellitus Prior stroke Severity OACs Imaging	IV alteplase treatment in the 3- to 4.5-h time window is recommended for those patients ≤80 y of age, without a history of both diabetes mellitus and prior stroke, NIHSS score ≤25, not taking any OACs, and without imaging evidence of ischemic injury involving more than one third of the MCA territory.† (*Class I; LOE B-R*)‡
Urgency	Treatment should be initiated as quickly as possible within the above listed time frames because time to treatment is strongly associated with outcomes.† (*Class I; LOE A*)
BP	IV alteplase is recommended in patients whose BP can be lowered safely (to <185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the BP before starting IV alteplase.† (*Class I; LOE B-NR*)‡
Blood glucose	IV alteplase is recommended in otherwise eligible patients with initial glucose levels >50 mg/dL.† (*Class I; LOE A*)
CT	IV alteplase administration is recommended in the setting of early ischemic changes on NCCT of mild to moderate extent (other than frank hypodensity).† (*Class I; LOE A*)
Prior antiplatelet therapy	IV alteplase is recommended for patients taking antiplatelet drug monotherapy before stroke on the basis of evidence that the benefit of alteplase outweighs a possible small increased risk of sICH.† (*Class I; LOE A*)
	IV alteplase is recommended for patients taking antiplatelet drug combination therapy (eg, aspirin and clopidogrel) before stroke on the basis of evidence that the benefit of alteplase outweighs a probable increased risk of sICH.† (*Class I; LOE B-NR*)‡
End-stage renal disease	In patients with end-stage renal disease on hemodialysis and normal aPTT, IV alteplase is recommended.† (*Class I; LOE C-LD*)‡ However, those with elevated aPTT may have elevated risk for hemorrhagic complications.
Contraindications (Class III)	
Time of onset	IV alteplase is not recommended in ischemic stroke patients who have an unclear time and/ or unwitnessed symptom onset and in whom the time last known to be at baseline state is >3 or 4.5 h.† (*Class III: No Benefit; LOE B-NR*)‡§
	IV alteplase is not recommended in ischemic stroke patients who awoke with stroke with time last known to be at baseline state >3 or 4.5 h.† (*Class III: No Benefit; LOE B-NR*)‡§
CT	IV alteplase should not be administered to a patient whose CT reveals an acute intracranial hemorrhage.† (*Class III: Harm; LOE C-EO*)‡§
	There remains insufficient evidence to identify a threshold of hypoattenuation severity or extent that affects treatment response to alteplase. However, administering IV alteplase to patients whose CT brain imaging exhibits extensive regions of clear hypoattenuation is not recommended. These patients have a poor prognosis despite IV alteplase, and severe hypoattenuation defined as obvious hypodensity represents irreversible injury.† (*Class III: No Benefit; LOE* A)§
Ischemic stroke within 3 mo	Use of IV alteplase in patients presenting with AIS who have had a prior ischemic stroke within 3 mo may be harmful.† (*Class III: Harm; LOE B-NR*)‡§
Severe head trauma within 3 mo	In AIS patients with recent severe head trauma (within 3 mo), IV alteplase is contraindicated.† (*Class III: Harm; LOE C-EO*)‡§
	Given the possibility of bleeding complications from the underlying severe head trauma, IV alteplase should not be administered in posttraumatic infarction that occurs during the acute in-hospital phase.† (*Class III: Harm; LOE C-EO*)‡§ (Recommendation wording modified to match Class III stratifications.)
Intracranial/intraspinal surgery within 3 mo	For patients with AIS and a history of intracranial/spinal surgery within the prior 3 mo, IV alteplase is potentially harmful.† (*Class III: Harm; LOE C-EO*)‡§

(*Continued*)

Table 6. Continued

History of intracranial hemorrhage	IV alteplase administration in patients who have a history of intracranial hemorrhage is potentially harmful.† (*Class III: Harm; LOE C-EO*)‡§
Subarachnoid hemorrhage	IV alteplase is contraindicated in patients presenting with symptoms and signs most consistent with an SAH.† (*Class III: Harm; LOE C-EO*)‡§
GI malignancy or GI bleed within 21 d	Patients with a structural GI malignancy or recent bleeding event within 21 d of their stroke event should be considered high risk, and IV alteplase administration is potentially harmful.† (*Class III: Harm; LOE C-EO*)‡§
Coagulopathy	The safety and efficacy of IV alteplase for acute stroke patients with platelets <100 000/mm^3, INR >1.7, aPTT >40 s, or PT >15 s are unknown, and IV alteplase should not be administered.† (*Class III: Harm; LOE C-EO*)‡§ (In patients without history of thrombocytopenia, treatment with IV alteplase can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm^3. In patients without recent use of OACs or heparin, treatment with IV alteplase can be initiated before availability of coagulation test results but should be discontinued if INR is >1.7 or PT is abnormally elevated by local laboratory standards.) (Recommendation wording modified to match Class III stratifications.)
LMWH	IV alteplase should not be administered to patients who have received a treatment dose of LMWH within the previous 24 h.† (*Class III: Harm; LOE B-NR*)‖ (Recommendation wording modified to match Class III stratifications.)
Thrombin inhibitors or factor Xa inhibitors	The use of IV alteplase in patients taking direct thrombin inhibitors or direct factor Xa inhibitors has not been firmly established but may be harmful.† (*Class III: Harm; LOE C-EO*)‡§ IV alteplase should not be administered to patients taking direct thrombin inhibitors or direct factor Xa inhibitors unless laboratory tests such as aPTT, INR, platelet count, ecarin clotting time, thrombin time, or appropriate direct factor Xa activity assays are normal or the patient has not received a dose of these agents for >48 h (assuming normal renal metabolizing function). (Alteplase could be considered when appropriate laboratory tests such as aPTT, INR, ecarin clotting time, thrombin time, or direct factor Xa activity assays are normal or when the patient has not taken a dose of these ACs for >48 h and renal function is normal.) (Recommendation wording modified to match Class III stratifications.)
Glycoprotein IIb/IIIa receptor inhibitors	Antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor should not be administered concurrently with IV alteplase outside a clinical trial.† (*Class III: Harm; LOE B-R*)‡§ (Recommendation wording modified to match Class III stratifications.)
Infective endocarditis	For patients with AIS and symptoms consistent with infective endocarditis, treatment with IV alteplase should not be administered because of the increased risk of intracranial hemorrhage.† (*Class III: Harm; LOE C-LD*)‡§ (Recommendation wording modified to match Class III stratifications.)
Aortic arch dissection	IV alteplase in AIS known or suspected to be associated with aortic arch dissection is potentially harmful and should not be administered.† (*Class III: Harm; LOE C-EO*)‡§ (Recommendation wording modified to match Class III stratifications.)
Intra-axial intracranial neoplasm	IV alteplase treatment for patients with AIS who harbor an intra-axial intracranial neoplasm is potentially harmful.† (*Class III: Harm; LOE C-EO*)‡§
Additional recommendations for treatment with IV alteplase for patients with AIS (Class II)	
Extended 3- to 4.5-h window	For patients >80 y of age presenting in the 3- to 4.5-h window, IV alteplase is safe and can be as effective as in younger patients.† (*Class IIa; LOE B-NR*)‡
	For patients taking warfarin and with an INR ≤1.7 who present in the 3- to 4.5-h window, IV alteplase appears safe and may be beneficial.† (*Class IIb; LOE B-NR*)‡
	In AIS patients with prior stroke and diabetes mellitus presenting in the 3- to 4.5- h window, IV alteplase may be as effective as treatment in the 0- to 3-h window and may be a reasonable option.† (*Class IIb; LOE B-NR*)‡
Severity 0- to 3-h window	Within 3 h from symptom onset, treatment of patients with mild ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio.† (*Class IIb; LOE C-LD*)‡
Severity 3- to 4.5-h window	For otherwise eligible patients with mild stroke presenting in the 3- to 4.5-h window, IV alteplase may be as effective as treatment in the 0- to 3-h window and may be a reasonable option. Treatment risks should be weighed against possible benefits. (*Class IIb; LOE B-NR*)‖
	The benefit of IV alteplase between 3 and 4.5 h from symptom onset for patients with very severe stroke symptoms (NIHSS > 25) is uncertain.† (*Class IIb; LOE C-LD*)
Preexisting disability	Preexisting disability does not seem to independently increase the risk of sICH after IV alteplase, but it may be associated with less neurological improvement and higher mortality. Thrombolytic therapy with IV alteplase for acute stroke patients with preexisting disability (mRS score ≥2) may be reasonable, but decisions should take into account relevant factors, including quality of life, social support, place of residence, need for a caregiver, patients' and families' preferences, and goals of care.† (*Class IIb; LOE B-NR*)‡

(*Continued*)

Table 6. Continued

	Patients with preexisting dementia may benefit from IV alteplase. Individual considerations such as life expectancy and premorbid level of function are important to determine whether alteplase may offer a clinically meaningful benefit.† (*Class IIb; LOE B-NR*)‡
Early improvement	IV alteplase treatment is reasonable for patients who present with moderate to severe ischemic stroke and demonstrate early improvement but remain moderately impaired and potentially disabled in the judgment of the examiner.† (*Class IIa; LOE A*)
Seizure at onset	IV alteplase is reasonable in patients with a seizure at the time of onset of acute stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon.† (*Class IIa; LOE C-LD*)‡
Blood glucose	Treatment with IV alteplase in patients with AIS who present with initial glucose levels <50 or >400 mg/dL that are subsequently normalized and who are otherwise eligible may be reasonable. (Recommendation modified from 2015 IV Alteplase to conform to text of 2015 IV Alteplase. [*Class IIb; LOE C-LD*])‡
Coagulopathy	The safety and efficacy of IV alteplase for acute stroke patients with a clinical history of potential bleeding diathesis or coagulopathy are unknown. IV alteplase may be considered on a case-by-case basis.† (*Class IIb; LOE C-EO*)‡
	IV alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤1.7 and/or a PT <15 s.† (*Class IIb; LOE B-NR*)‡
Dural puncture	IV alteplase may be considered for patients who present with AIS, even in instances when they may have undergone a lumbar dural puncture in the preceding 7 d.† (*Class IIb; LOE C-EO*)‡
Arterial puncture	The safety and efficacy of administering IV alteplase to acute stroke patients who have had an arterial puncture of a noncompressible blood vessel in the 7 d preceding stroke symptoms are uncertain.† (*Class IIb; LOE C-LD*)‡
Recent major trauma	In AIS patients with recent major trauma (within 14 d) not involving the head, IV alteplase may be carefully considered, with the risks of bleeding from injuries related to the trauma weighed against the severity and potential disability from the ischemic stroke. (Recommendation modified from 2015 IV Alteplase to specify that it does not apply to head trauma. [*Class IIb; LOE C-LD*])‡
Recent major surgery	Use of IV alteplase in carefully selected patients presenting with AIS who have undergone a major surgery in the preceding 14 d may be considered, but the potential increased risk of surgical-site hemorrhage should be weighed against the anticipated benefits of reduced stroke related neurological deficits.† (*Class IIb; LOE C-LD*)‡
GI and genitourinary bleeding	Reported literature details a low bleeding risk with IV alteplase administration in the setting of past GI/genitourinary bleeding. Administration of IV alteplase in this patient population may be reasonable.† (*Class IIb; LOE C-LD*)‡ (Note: Alteplase administration within 21 d of a GI bleeding event is not recommended; see Contraindications.)
Menstruation	IV alteplase is probably indicated in women who are menstruating who present with AIS and do not have a history of menorrhagia. However, women should be warned that alteplase treatment could increase the degree of menstrual flow.† (*Class IIa; LOE C-EO*)
	Because the potential benefits of IV alteplase probably outweigh the risks of serious bleeding in patients with recent or active history of menorrhagia without clinically significant anemia or hypotension, IV alteplase administration may be considered.† (*Class IIb; LOE C-LD*)‡
	When there is a history of recent or active vaginal bleeding causing clinically significant anemia, then emergency consultation with a gynecologist is probably indicated before a decision about IV alteplase is made.† (*Class IIa; LOE C-EO*)‡
Extracranial cervical dissections	IV alteplase in AIS known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 h and probably recommended.† (*Class IIa; LOE C-LD*)‡
Intracranial arterial dissection	IV alteplase usefulness and hemorrhagic risk in AIS known or suspected to be associated with intracranial arterial dissection remain unknown, uncertain, and not well established.† (*Class IIb; LOE C-LD*)‡
Unruptured intracranial aneurysm	For patients presenting with AIS who are known to harbor a small or moderate-sized (<10 mm) unruptured and unsecured intracranial aneurysm, administration of IV alteplase is reasonable and probably recommended.† (*Class IIa; LOE C-LD*)‡
	Usefulness and risk of IV alteplase in patients with AIS who harbor a giant unruptured and unsecured intracranial aneurysm are not well established.† (*Class IIb; LOE C-LD*)‡
Intracranial vascular malformations	For patients presenting with AIS who are known to harbor an unruptured and untreated intracranial vascular malformation the usefulness and risks of administration of IV alteplase are not well established.† (*Class IIb; LOE C-LD*)‡
	Because of the increased risk of ICH in this population of patients, IV alteplase may be considered in patients with stroke with severe neurological deficits and a high likelihood of morbidity and mortality to outweigh the anticipated risk of ICH secondary to thrombolysis.† (*Class IIb; LOE C-LD*)‡
CMBs	In otherwise eligible patients who have previously had a small number (1–10) of CMBs demonstrated on MRI, administration of IV alteplase is reasonable. (*Class IIa; Level B-NR*)‖
	In otherwise eligible patients who have previously had a high burden of CMBs (>10) demonstrated on MRI, treatment with IV alteplase may be associated with an increased risk of sICH, and the benefits of treatment are uncertain. Treatment may be reasonable if there is the potential for substantial benefit. (*Class IIb; Level B-NR*)‖

(*Continued*)

Table 6. Continued

Extra-axial intracranial neoplasms	IV alteplase treatment is probably recommended for patients with AIS who harbor an extra-axial intracranial neoplasm.† (*Class IIa; LOE C-EO*)‡
Acute MI	For patients presenting with concurrent AIS and acute MI, treatment with IV alteplase at the dose appropriate for cerebral ischemia, followed by percutaneous coronary angioplasty and stenting if indicated, is reasonable.† (*Class IIa; LOE C-EO*)‡
Recent MI	For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase is reasonable if the recent MI was non-STEMI.† (*Class IIa; LOE C-LD*)‡
	For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase is reasonable if the recent MI was a STEMI involving the right or inferior myocardium.† (*Class IIa; LOE C-LD*)‡
	For patients presenting with AIS and a history of recent MI in the past 3 mo, treating the ischemic stroke with IV alteplase may reasonable if the recent MI was a STEMI involving the left anterior myocardium.† (*Class IIb; LOE C-LD*)‡
Other cardiac diseases	For patients with major AIS likely to produce severe disability and acute pericarditis, treatment with IV alteplase may be reasonable† (*Class IIb; LOE C-EO*)‡; urgent consultation with a cardiologist is recommended in this situation.
	For patients presenting with moderate AIS likely to produce mild disability and acute pericarditis, treatment with IV alteplase is of uncertain net benefit.† (*Class IIb; LOE C-EO*)‡
	For patients with major AIS likely to produce severe disability and known left atrial or ventricular thrombus, treatment with IV alteplase may be reasonable.† (*Class IIb; LOE C-LD*)‡
	For patients presenting with moderate AIS likely to produce mild disability and known left atrial or ventricular thrombus, treatment with IV alteplase is of uncertain net benefit.† (*Class IIb; LOE C-LD*)‡
	For patients with major AIS likely to produce severe disability and cardiac myxoma, treatment with IV alteplase may be reasonable.† (*Class IIb; LOE C-LD*)‡
	For patients presenting with major AIS likely to produce severe disability and papillary fibroelastoma, treatment with IV alteplase may be reasonable.† (*Class IIb; LOE C-LD*)‡
Procedural stroke	IV alteplase is reasonable for the treatment of AIS complications of cardiac or cerebral angiographic procedures, depending on the usual eligibility criteria.† (*Class IIa; LOE A*)‡
Systemic malignancy	The safety and efficacy of alteplase in patients with current malignancy are not well established.† (*Class IIb; LOE C-LD*)‡ Patients with systemic malignancy and reasonable (>6 mo) life expectancy may benefit from IV alteplase if other contraindications such as coagulation abnormalities, recent surgery, or systemic bleeding do not coexist.
Pregnancy	IV alteplase administration may be considered in pregnancy when the anticipated benefits of treating moderate or severe stroke outweigh the anticipated increased risks of uterine bleeding.† (*Class IIb; LOE C-LD*)‡
	The safety and efficacy of IV alteplase in the early postpartum period (<14 d after delivery) have not been well established.† (*Class IIb; LOE C-LD*)‡
Ophthalmological conditions	Use of IV alteplase in patients presenting with AIS who have a history of diabetic hemorrhagic retinopathy or other hemorrhagic ophthalmic conditions is reasonable to recommend, but the potential increased risk of visual loss should be weighed against the anticipated benefits of reduced stroke-related neurological deficits.† (*Class IIa; LOE B-NR*)‡
Sickle cell disease	IV alteplase for adults presenting with an AIS with known sickle cell disease can be beneficial. (*Class IIa; LOE B-NR*)‖
Illicit drug use	Treating clinicians should be aware that illicit drug use may be a contributing factor to incident stroke. IV alteplase is reasonable in instances of illicit drug use–associated AIS in patients with no other exclusions.† (*Class IIa; LOE C-LD*)‡
Stroke mimics	The risk of symptomatic intracranial hemorrhage in the stroke mimic population is quite low; thus, starting IV alteplase is probably recommended in preference over delaying treatment to pursue additional diagnostic studies.† (*Class IIa; LOE B-NR*)

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

For a detailed discussion of this topic and evidence supporting these recommendations, refer to the American Heart Association (AHA) scientific statement on the rationale for inclusion and exclusion criteria for IV alteplase in AIS.[15]

AC indicates anticoagulants; ACC, American College of Cardiology; AIS, acute ischemic stroke; AHA, American Heart Association; aPTT, activated partial thromboplastin time; BP, blood pressure; CMB, cerebral microbleed; CT, computed tomography; GI, gastrointestinal; ICH, intracerebral hemorrhage; INR, international normalized ratio; IV, intravenous; LMWH, low-molecular-weight heparin; LOE, level of evidence; MCA, middle cerebral artery; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NCCT, noncontrast computed tomography; NIHSS, National Institutes of Health Stroke Scale; OAC, oral anticoagulant; PT, prothromboplastin time; sICH, symptomatic intracerebral hemorrhage; and STEMI, ST-segment–elevation myocardial infarction.

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

†Recommendation unchanged or reworded for clarity from 2015 IV Alteplase. See Table LXXXIII in online Data Supplement 1 for original wording.

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

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

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

Table 7. Treatment of AIS: IV Administration of Alteplase

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

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

Reprinted from Jauch et al.[1]

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

Class IIb, LOE C-EO
Stop alteplase infusion
CBC, PT (INR), aPTT, fibrinogen level, and type and cross-match
Emergent nonenhanced head CT
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <200 mg/dL
Tranexamic acid 1000 mg IV infused over 10 min OR ε-aminocaproic acid 4–5 g over 1 h, followed by 1 g IV until bleeding is controlled (peak onset in 3 h)
Hematology and neurosurgery consultations
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control

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

Sources: Sloan et al,[149] Mahaffey et al,[150] Goldstein et al,[151] French et al,[152] Yaghi et al,[153–155] Stone et al,[156] and Frontera et al.[157]

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

Class IIb, LOE C-EO
Maintain airway
Endotracheal intubation may not be necessary if edema is limited to anterior tongue and lips.
Edema involving larynx, palate, floor of mouth, or oropharynx with rapid progression (within 30 min) poses higher risk of requiring intubation.
Awake fiberoptic intubation is optimal. Nasal-tracheal intubation may be required but poses risk of epistaxis post-IV alteplase. Cricothyroidotomy is rarely needed and also problematic after IV alteplase.
Discontinue IV alteplase infusion and hold ACEIs
Administer IV methylprednisolone 125 mg
Administer IV diphenhydramine 50 mg
Administer ranitidine 50 mg IV or famotidine 20 mg IV
If there is further increase in angioedema, administer epinephrine (0.1%) 0.3 mL subcutaneously or by nebulizer 0.5 mL
Icatibant, a selective bradykinin B_2 receptor antagonist, 3 mL (30 mg) subcutaneously in abdominal area; additional injection of 30 mg may be administered at intervals of 6 h not to exceed total of 3 injections in 24 h; and plasma-derived C1 esterase inhibitor (20 IU/kg) has been successfully used in hereditary angioedema and ACEI-related angioedema
Supportive care

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

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

3.6. Other IV Thrombolytics and Sonothrombolysis

3.6. Other IV Thrombolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. The benefit of IV defibrinogenating agents and of IV fibrinolytic agents other than alteplase and tenecteplase is unproven; therefore, their administration is not recommended outside a clinical trial.	III: No Benefit	B-R	Recommendation revised from 2013 AIS Guidelines.
Randomized placebo-controlled trials have not shown benefit from the administration of IV streptokinase within 6 hours or desmoteplase within 3 to 9 hours after stroke onset in patients with ischemic penumbra or large intracranial artery occlusion or severe stenosis.[92,95,167,168]			See Table XXXIX in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	IIb	B-R	New recommendation.
IV tenecteplase has been compared to IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[89,91,169,170] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[170] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XXXIX in online Data Supplement 1.
3. The use of sonothrombolysis as adjuvant therapy with IV thrombolysis is not recommended.	III: No Benefit	B-R	New recommendation.
Since the publication of the 2013 AIS Guidelines, a further RCT of sonothrombolysis as adjuvant therapy for IV thrombolysis has shown no clinical benefit. NOR-SASS (Norwegian Sonothrombolysis in Acute Stroke Study) randomized 183 patients who had received either alteplase or tenecteplase for AIS within 4.5 hours of onset to either contrast-enhanced sonothrombolysis (93 patients) or sham (90 patients). Neurological improvement at 24 hours and functional outcome at 90 days were not statistically significantly different in the 2 groups, nor were the rates of sICH.[171] At this time, there are no RCT data to support additional clinical benefit of sonothrombolysis as adjuvant therapy for IV thrombolysis.			See Table XL in online Data Supplement 1.

3.7. Mechanical Thrombectomy

3.7. Mechanical Thrombectomy	COR	LOE	New, Revised, or Unchanged
1. Patients eligible for IV alteplase should receive IV alteplase even if EVTs are being considered.	I	A	Recommendation reworded for clarity from 2015 Endovascular. See Table LXXXIII in online Data Supplement 1 for original wording.
2. In patients under consideration for mechanical thrombectomy, observation after IV alteplase to assess for clinical response should not be performed.	III: Harm	B-R	Recommendation revised from 2015 Endovascular.
In pooled patient-level data from 5 trials (HERMES [Highly Effective Reperfusion Evaluated in Multiple Endovascular Stroke Trials], which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: common odds ratio (cOR) at 3 hours, 2.79 (95% CI, 1.96–3.98), absolute risk difference (ARD) for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; and cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes.[32] Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84; 95% CI, 0.76–0.93; ARD, −6.7%) and less functional independence (OR, 0.81; 95% CI, 0.71–0.92; ARD, −5.2%; 95% CI, −8.3 to −2.1) but no change in mortality (OR, 1.12; 95% CI, 0.93–1.34; ARD, 1.5%; 95% CI, −0.9 to 4.2).[32] These data do not directly address the question of whether patients should be observed after IV alteplase to assess for clinical response before pursuing mechanical thrombectomy. However, one can infer that because disability outcomes at 90 days were directly associated with time from symptom onset to arterial puncture, any cause for delay to mechanical thrombectomy, including observing for a clinical response after IV alteplase, should be avoided. Therefore, the recommendation is slightly modified from the 2015 Endovascular Update.			See Tables XXIII and XLI in online Data Supplement 1.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
3. Patients should receive mechanical thrombectomy with a stent retriever if they meet all the following criteria: (1) prestroke mRS score of 0 to 1; (2) causative occlusion of the internal carotid artery or MCA segment 1 (M1); (3) age ≥18 years; (4) NIHSS score of ≥6; (5) ASPECTS of ≥6; and (6) treatment can be initiated (groin puncture) within 6 hours of symptom onset.	I	A	Recommendation revised from 2015 Endovascular.
Results from 6 recent randomized trials of mechanical thrombectomy using predominantly stent retriever devices (MR CLEAN, SWIFT PRIME, EXTEND-IA, ESCAPE, REVASCAT, THRACE) support Class I, LOE A recommendations for a defined group of patients as described in the 2015 guidelines.[102–107] A pooled, patient-level analysis from 5 of these studies reported by the HERMES collaboration showed treatment effect in the subgroup of 188 patients not treated with IV alteplase (cOR, 2.43; 95% CI, 1.30–4.55); therefore, pretreatment with IV alteplase has been removed from the prior recommendation. The HERMES pooled patient-level data also showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years old (cOR, 3.68; 95% CI, 1.95–6.92).[172] In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration [Safety and Efficacy of Solitaire Stent Thrombectomy–Individual Patient Data Meta-Analysis of Randomized Trials]: SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT) showed that mechanical thrombectomy had a favorable effect over standard care in patients ≥80 years old (3.46; 95% CI, 1.58–7.60).[173] In a meta-analysis of 5 RCTs (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT), there was favorable effect with mechanical thrombectomy over standard care without heterogeneity of effect across patient age subgroups (for patient age <70 and ≥70 years: OR, 2.41; 95% CI, 1.51–3.84; and OR, 2.26; 95% CI, 1.20–4.26, respectively).[174] However, the number of patients in these trials who were ≥90 years of age was very small, and the benefit of mechanical thrombectomy over standard care in patients ≥90 years of age is not clear. As with any treatment decision in an elderly patient, consideration of comorbidities and risks should factor into the decision making for mechanical thrombectomy.			See Tables XXIII and XLI in online Data Supplement 1.
4. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the MCA segment 2 (M2) or MCA segment 3 (M3) portion of the MCAs.	IIb	B-R	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE revised. See Table LXXXIII in online Data Supplement 1 for original wording.
In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the direction of treatment effect for mechanical thrombectomy over standard care was favorable in M2 occlusions, but the adjusted common OR was not significant (1.28; 95% CI, 0.51–3.21).[172] In patient-level data pooled from trials in which the Solitaire was the only or the predominant device used, a prespecified meta-analysis (SEER Collaboration: SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT) showed that the direction of treatment effect was favorable for mechanical thrombectomy over standard care in M2 occlusions, but the OR and 95% CI were not significant.[173] In an analysis of pooled data from SWIFT (Solitaire With the Intention for Thrombectomy), STAR (Solitaire Flow Restoration Thrombectomy for Acute Revascularization), DEFUSE 2, and IMS III, among patients with M2 occlusions, reperfusion was associated with excellent functional outcomes (mRS score 0–1; OR, 2.2; 95% CI, 1.0–4.7).[175] Therefore, the recommendation for mechanical thrombectomy for M2/M3 occlusions does not change substantively from the 2015 AHA/American Stroke Association focused update.			See Tables XXIII and XLI in online Data Supplement 1.
5. Although the benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for carefully selected patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.	IIb	C-EO	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
6. Although its benefits are uncertain, the use of mechanical thrombectomy with stent retrievers may be reasonable for patients with AIS in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have prestroke mRS score >1, ASPECTS <6, or NIHSS score <6, and causative occlusion of the internal carotid artery (ICA) or proximal MCA (M1). Additional randomized trial data are needed.	IIb	B-R	Recommendation unchanged from 2015 Endovascular.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
7. In selected patients with AIS within 6 to 16 hours of last known normal who have LVO in the anterior circulation and meet other DAWN or DEFUSE 3 eligibility criteria, mechanical thrombectomy is recommended.	I	A	New recommendation.
8. In selected patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation and meet other DAWN eligibility criteria, mechanical thrombectomy is reasonable.	IIa	B-R	New recommendation.
The DAWN trial used clinical imaging mismatch (a combination of NIHSS score and imaging findings on CTP or DW-MRI) as eligibility criteria to select patients with large anterior circulation vessel occlusion for treatment with mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in function outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33%; 95% CI, 21–44; posterior probability of superiority >0.999).[108] In DAWN, there were few strokes with witnessed onset (12%).The DEFUSE 3 trial used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67; 95% CI, 1.60–4.48; *P*<0.0001).[109] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from 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 and DEFUSE-3 eligibility should be strictly adhered to in clinical practice.			See Table XXIII in online Data Supplement 1.
9. The technical goal of the thrombectomy procedure should be reperfusion to a modified Thrombolysis in Cerebral Infarction (mTICI) 2b/3 angiographic result to maximize the probability of a good functional clinical outcome.	I	A	Recommendation reworded for clarity from 2015 Endovascular. See Table LXXXIII in online Data Supplement 1 for original wording.
Mechanical thrombectomy aims to achieve reperfusion, not simply recanalization. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.[176,177] All recent endovascular trials used the mTICI 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to mTICI 2b/3.[172] Earlier trials with less efficient devices showed lower recanalization rates, 1 factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%). The additional benefit of pursuing mTICI of 3 rather than 2b deserves further investigation.			
10. As with IV alteplase, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. To ensure benefit, reperfusion to TICI grade 2b/3 should be achieved as early as possible within the therapeutic window.	I	B-R	Recommendation revised from 2015 Endovascular.
In pooled patient-level data from 5 trials (HERMES, which included the 5 trials MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, and EXTEND-IA), the odds of better disability outcomes at 90 days (mRS scale distribution) with the mechanical thrombectomy group declined with longer time from symptom onset to expected arterial puncture: cOR at 3 hours, 2.79 (95% CI, 1.96–3.98), ARD for lower disability scores, 39.2%; cOR at 6 hours, 1.98 (95% CI, 1.30–3.00), ARD, 30.2%; cOR at 8 hours, 1.57 (95% CI, 0.86–2.88), and ARD, 15.7%, retaining statistical significance through 7 hours 18 minutes.[32] Among 390 patients who achieved substantial reperfusion with endovascular thrombectomy, each 1-hour delay to reperfusion was associated with a less favorable degree of disability (cOR, 0.84; 95% CI, 0.76–0.93; ARD, −6.7%) and less functional independence (OR, 0.81; 95% CI, 0.71–0.92; ARD, −5.2%; 95% CI, −8.3 to −2.1).[32] In the DAWN trial, the likelihood of achieving an mRS score of 0 to 2 at 90 days in the mechanical thrombectomy group declined with time since last known normal.[108] Therefore, reduced time from symptom onset to reperfusion with endovascular therapies is highly associated with better clinical outcomes. A variety of reperfusion scores exist, but the mTICI score is the current assessment tool of choice, with proven value in predicting clinical outcomes.[129,130] All recent endovascular trials used the mTICI 2b/3 threshold for adequate reperfusion, with high rates achieved. In HERMES, 402 of 570 patients (71%) were successfully reperfused to TICI 2b/3.[172] Earlier trials with less efficient devices showed lower recanalization rates, 1 factor in their inability to demonstrate benefit from the procedure (IMS III, 41%; MR RESCUE, 25%).			See Tables XXIII and XLI in online Data Supplement 1.
11. Use of stent retrievers is indicated in preference to the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) device.	I	A	Recommendation unchanged from 2015 Endovascular.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
12. The use of mechanical thrombectomy devices other than stent retrievers as first-line devices for mechanical thrombectomy may be reasonable in some circumstances, but stent retrievers remain the first choice.	IIb	B-R	Recommendation revised from 2015 Endovascular.
The ASTER trial (Contact Aspiration vs Stent Retriever for Successful Revascularization) compared the contact aspiration technique and the standard stent retriever technique as first-line EVT for successful revascularization within 6 hours among patients with acute anterior circulation ischemic stroke and LVO. The proportion of patients with successful revascularization at the end of all interventions was 85.4% (n=164) in the contact aspiration group versus 83.1% (n=157) in the stent retriever group (OR, 1.20; 95% CI, 0.68–2.10; *P*=0.53; difference, 2.4%; 95% CI, −5.4 to 9.7%). The secondary clinical end point of mRS score of 0 to 2 at 90 days was achieved by 82 of 181 (45.3%) in the contact aspiration group versus 91 of 182 (50.0%) in the stent retriever group (OR, 0.83; 95% CI, 0.54–1.26; *P*=0.38). The primary end point in ASTER was technical (successful revascularization after all interventions), and the trial was not powered to detect a smaller yet potentially clinically important difference between groups. Given its superiority design to detect a 15% difference in the primary end point, this trial was not designed to establish noninferiority.[178]			See Table XXIII in online Data Supplement 1.
13. The use of a proximal balloon guide catheter or a large-bore distal-access catheter, rather than a cervical guide catheter alone, in conjunction with stent retrievers may be beneficial. Future studies should examine which systems provide the highest recanalization rates with the lowest risk for nontarget embolization.	IIa	C-LD	Recommendation and Class unchanged from 2015 Endovascular. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
14. Use of salvage technical adjuncts including intra-arterial thrombolysis may be reasonable to achieve mTICI 2b/3 angiographic results.	IIb	C-LD	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Intra-arterial lytic therapy played a limited role in the recent endovascular trials but was used as rescue therapy, not initial treatment. In MR CLEAN, the EVT method was at the discretion of operator, with 40 of 233 treated with alternative stent retrievers to Trevo and Solitaire or intra-arterial alteplase. Details are not available, but no patients were treated with intra-arterial alteplase alone. Twenty-four of 233 (10.3%) had treatment with a second modality. Treatment method had no impact on outcomes in this trial.[179] In THRACE, an intra-arterial lytic was used to a maximum dose of 0.3 mg/kg and allowed to establish goal reperfusion, only after mechanical thrombectomy was attempted. A mean dose of 8.8 mg was administered in 15 of 141 patients receiving mechanical thrombectomy (11%). There was no effect on outcomes compared with mechanical thrombectomy alone.			
15. EVT of tandem occlusions (both extracranial and intracranial occlusions) at the time of thrombectomy may be reasonable.	IIb	B-R	Recommendation revised from 2015 Endovascular.
Tandem occlusions were considered in recent endovascular trials that showed benefit of mechanical thrombectomy over medical management alone. In the HERMES meta-analysis, 122 of 1254 tandem occlusions (RR, 1.81; 95% CI, 0.96–3.4) and 1132 of 1254 nontandem occlusions (RR, 1.71; 95% CI, 1.40–2.09) were reported compared with medical management.[172] In THRACE, 24 of 196 tandem occlusions (RR, 1.82; 95% CI, 0.55–6.07) and 172 of 196 nontandem occlusions (RR, 1.34; 95% CI, 0.87–2.07) were treated compared with IV alteplase alone.[106] In HERMES, there is heterogeneity of treatment methods directed to the proximal extracranial carotid occlusion (no revascularization of the proximal lesion versus angioplasty versus stenting). Multiple retrospective reports detail the technical success of EVT for tandem occlusions but do not provide specifics on comparative approaches. No conclusions about the optimum treatment approach for patients with tandem occlusions are therefore possible.			See Tables XXIII and XLI in online Data Supplement 1.
16. It is reasonable to select an anesthetic technique during endovascular therapy for AIS on the basis of individualized assessment of patient risk factors, technical performance of the procedure, and other clinical characteristics. Further randomized trial data are needed.	IIa	B-R	Recommendation revised from 2015 Endovascular.
Conscious sedation (CS) was widely used in the recent endovascular trials (90.9% of ESCAPE, 63% of SWIFT PRIME) with no clear positive or negative impact on outcome. In MR CLEAN, post hoc analysis showed a 51% (95% CI, 31–86) decrease in treatment effect of general anesthesia (GA) compared with CS.[180] In THRACE, 51 of 67 patients receiving GA and 43 of 69 patients receiving CS achieved TICI 2b/3 (*P*=0.059) with no impact on outcome.[106] Thirty-five of 67 patients with GA and 36 of 74 with CS had mRS scores of 0 to 2 at 90 days. Although several retrospective studies suggest that GA produces worsening of functional outcomes, there are limited prospective randomized data. Two small (≤150 participants) single-center RCTs have compared GA with CS. Both failed to show superiority of either treatment for the primary clinical end point.[181,182] Until further data are available, either method of procedural sedation is reasonable.			See Tables XLII and XLIII in online Data Supplement 1.

3.7. Mechanical Thrombectomy (Continued)	COR	LOE	New, Revised, or Unchanged
17. In patients who undergo mechanical thrombectomy, it is reasonable to maintain the BP ≤180/105 mm Hg during and for 24 hours after the procedure.	IIa	B-NR	New recommendation.
18. In patients who undergo mechanical thrombectomy with successful reperfusion, it might be reasonable to maintain BP at a level <180/105 mm Hg.	IIb	B-NR	New recommendation.
There are very limited data to guide BP therapy during and after the procedure in patients who undergo mechanical thrombectomy. RCT data on optimal BP management approaches in this setting are not available. The vast majority of patients enrolled in under 6-hour RCTs received IV alteplase and the trial protocols stipulated management according to local guidelines with BP ≤80/105 during and for 24 hours after the procedure for these participants. Two trial protocols provided additional recommendations. The ESCAPE protocol states that systolic BP ≥150 mm Hg is probably useful in promoting and keeping collateral flow adequate while the artery remains occluded and that controlling BP once reperfusion has been achieved and aiming for a normal BP for that individual is sensible. Labetalol or an IV β-blocker such as metoprolol in low doses is recommended.[104] The DAWN protocol recommends maintaining systolic BP <140 mm Hg in the first 24 hours in subjects who are reperfused after mechanical thrombectomy (defined as achieving more than two thirds MCA territory reperfusion).[183]			See Table XXIII in online Data Supplement 1.

3.8. Other EVTs

3.8. Other EVTs	COR	LOE	New, Revised, or Unchanged
1. Initial treatment with intra-arterial thrombolysis is beneficial for carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA.	I	B-R	Recommendation and Class unchanged from 2015 Endovascular. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System.
2. Regarding the previous recommendation about intra-arterial thrombolysis, these data are derived from clinical trials that no longer reflect current practice, including the use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial alteplase is not established, and alteplase does not have US Food and Drug Administration approval for intra-arterial use. As a consequence, mechanical thrombectomy with stent retrievers is recommended over intra-arterial thrombolysis as first-line therapy.	I	C-EO	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with the ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. Intra-arterial thrombolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of IV alteplase might be considered, but the consequences are unknown.	IIb	C-EO	Recommendation reworded for clarity from 2015 Endovascular. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

3.9. Antiplatelet Treatment

3.9. Antiplatelet Treatment	COR	LOE	New, Revised, or Unchanged
1. Administration of aspirin is recommended in patients with AIS within 24 to 48 hours after onset. For those treated with IV alteplase, aspirin administration is generally delayed until 24 hours later but might be considered in the presence of concomitant conditions for which such treatment given in the absence of IV alteplase is known to provide substantial benefit or withholding such treatment is known to cause substantial risk.	I	A	Recommendation revised from 2013 AIS Guidelines.
The safety and benefit of aspirin in the treatment of patients with AIS were established by 2 large clinical trials administering doses between 160 and 300 mg.[184,185] This has recently been confirmed by a large Cochrane review of aspirin trials.[186] In patients unsafe or unable to swallow, rectal or nasogastric administration is appropriate. Limited data exist on the use of alternative antiplatelet agents in the treatment of AIS. However, in patients with a contraindication to aspirin, administering alternative antiplatelet agents may be reasonable. A retrospective analysis of consecutive ischemic stroke patients admitted to a single center in Seoul, South Korea, found no increased risk of hemorrhage with early initiation of antiplatelet or anticoagulant therapy (<24 hours) after IV alteplase or EVT compared with initiation >24 hours. However, this study may have been subject to selection bias, and the timing of initiation of antiplatelet therapy or anticoagulation should be made on an individual level, balancing risk versus benefit. The recommendation was modified from the previous guideline to remove the specific dosing recommendation, "initial dose is 325 mg," because previous clinical trials supporting its use for AIS included doses of 160 to 300 mg.			See Table XXXVIII in online Data Supplement 1.

3.9. Antiplatelet Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
2. Aspirin is not recommended as a substitute for acute stroke treatment in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy.	III: No Benefit	B-R	Recommendation revised from 2013 AIS Guidelines.
Recommendation was modified to eliminate wording about "acute interventions," which are broadly defined, and to specify that aspirin is a less effective substitute for the treatment of AIS in patients who are otherwise eligible for IV alteplase or mechanical thrombectomy.			
3. The efficacy of IV tirofiban and eptifibatide is not well established. Further clinical trials are needed.	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.
Prospective, randomized, open-label phase II trials of tirofiban[187] and eptifibatide[188] have suggested safety for treatment in patients with AIS. Single-arm studies of eptifibatide as adjunctive therapy to IV alteplase support ongoing RCTs to establish safety and efficacy.[189,190]			See Table XLIV in online Data Supplement 1.
4. The administration of other glycoprotein IIb/IIIa receptor antagonists, including abciximab, in the treatment of AIS is potentially harmful and should not be performed. Further research testing the safety and efficacy of these medications in patients with AIS is required.	III: Harm	B-R	Recommendation revised from 2013 AIS Guidelines.
A recent Cochrane review of IV glycoprotein IIb/IIIa receptor antagonists in the treatment of AIS found that these agents are associated with a significant risk of ICH without a measurable improvement in death or disability.[191] The majority of trial data apply to abciximab, which was studied in the AbESTT trial (A Study of Effectiveness and Safety of Abciximab in Patients With Acute Ischemic Stroke). The phase III trial was terminated early because of an unfavorable risk-benefit analysis.[192]			See Table XLV in online Data Supplement 1.
5. In patients presenting with minor stroke, treatment for 21 days with dual antiplatelet therapy (aspirin and clopidogrel) begun within 24 hours can be beneficial for early secondary stroke prevention for a period of up to 90 days from symptom onset.	IIa	B-R	New recommendation.
The CHANCE trial (Clopidogrel in High-Risk Patients With Acute Nondisabling Cerebrovascular Events) was a randomized, double-blind, placebo-controlled trial conducted in China to study the efficacy of short-term dual antiplatelet therapy begun within 24 hours, clopidogrel plus aspirin for 21 days followed by clopidogrel alone to 90 days, in patients with minor stroke (NIHSS score ≤3) or high-risk TIA (ABCD² [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). The primary outcome of recurrent stroke at 90 days (ischemic or hemorrhagic) favored dual antiplatelet therapy over aspirin alone (hazard ratio [HR], 0.68; 95% CI, 0.57–0.81; *P*<0.001).[193] A subsequent report of 1-year outcomes found a durable treatment effect, but the HR for secondary stroke prevention was only significantly beneficial in the first 90 days.[194] The generalizability of this intervention in non-Asian populations remains to be established, and a large phase III multicenter trial in the United States, Canada, Europe, and Australia is ongoing.[195]			See Table XLV in online Data Supplement 1.
6. Ticagrelor is not recommended (over aspirin) in the acute treatment of patients with minor stroke.	III: No Benefit	B-R	New recommendation.
The recently completed SOCRATES trial (Acute Stroke or Transient Ischaemic Attack Treated With Aspirin or Ticagrelor and Patient Outcomes) was a randomized, double-blind, placebo-controlled trial of ticagrelor versus aspirin begun within 24 hours in patients with minor stroke (NIHSS score ≤5) or TIA (ABCD² [Age, Blood Pressure, Clinical Features, Duration, Diabetes] score ≥4). With a primary outcome of time to the composite end point of stroke, myocardial infarction (MI), or death up to 90 days, ticagrelor was not found to be superior to aspirin (HR, 0.89; 95% CI, 0.78–1.01; *P*=0.07).[196] However, because there were no significant safety differences in the 2 groups, ticagrelor may be a reasonable alternative in stroke patients who have a contraindication to aspirin.			See Table XLV in online Data Supplement 1.

3.10. Anticoagulants

3.10. Anticoagulants	COR	LOE	New, Revised, or Unchanged
1. Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after AIS, is not recommended for treatment of patients with AIS.	III: No Benefit	A	Recommendation and LOE unchanged from 2013 AIS Guidelines. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.
Further support for this unchanged recommendation from the 2013 AIS Guidelines is provided by 2 updated meta-analyses that confirm the lack of benefit of urgent anticoagulation.[197,198] An additional study, not included in these meta-analyses, investigated the efficacy of LMWH compared with aspirin in preventing early neurological deterioration in an unblinded RCT. Although there was a statistically significant difference in early neurological deterioration at 10 days after admission (LMWH, 27 [3.95%] versus aspirin, 81 [11.82%]; *P*<0.001), there was no difference in 6-month mRS score of 0 to 2 (LMWH, 64.2% versus aspirin, 6.52%; *P*=0.33).[199]			See Table XLV in online Data Supplement 1.

3.10. Anticoagulants (Continued)	COR	LOE	New, Revised, or Unchanged
2. The usefulness of urgent anticoagulation in patients with severe stenosis of an internal carotid artery ipsilateral to an ischemic stroke is not well established.	IIb	B-NR	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. The safety and usefulness of short-term anticoagulation for nonocclusive, extracranial intraluminal thrombus in the setting of AIS are not well established.	IIb	C-LD	New recommendation.
The optimal medical management of patients with AIS and radiologic evidence of nonocclusive, intraluminal thrombus (eg, cervical carotid, vertebrobasilar arteries) remains uncertain. Several small observational studies have suggested the safety of short-term IV heparin or LMWH in this setting,[203,204] but further research is required to establish safety and efficacy.			See Table XLVII in online Data Supplement 1.
4. At present, the usefulness of argatroban, dabigatran, or other thrombin inhibitors for the treatment of patients with AIS is not well established. Further clinical trials are needed.	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.
Several observational studies have demonstrated the safety and feasibility of treating AIS with thrombin inhibitors, as either a single or an adjunct therapy to alteplase. The oral direct thrombin inhibitor dabigatran was studied in 53 patients with TIA or minor stroke (NIHSS score ≤3) with no occurrences of sICH up to 30 days.[201] ARTSS (Argatroban With Recombinant Tissue Plasminogen Activator for Acute Stroke)-1 was an open label, pilot safety study of argatroban infusion plus IV alteplase in 65 patients with complete or partially occlusive thrombus diagnosed by transcranial Doppler.[205] In the ARTSS-2 phase II study, patients with AIS treated with alteplase (n=90) were randomized to receive placebo or argatroban (100-µg/kg bolus), followed by infusion of either 1 (low dose) or 3 (high dose) µg/kg per minute for 48 hours. Rates of sICH were similar among the control, low-dose, and high-dose arms: 3 of 29 (10%), 4 of 30 (13%), and 2 of 31 (7%), respectively.[206]			See Table XLVII in online Data Supplement 1.
5. The safety and usefulness of factor Xa inhibitors in the treatment of AIS are not well established. Further clinical trials are needed.	IIb	C-LD	New recommendation.
Limited data exist on the use of factor Xa inhibitors (eg, rivaroxaban, apixaban, edoxaban) in the acute treatment of patients with ischemic stroke.[207] Several prospective observational studies and early-phase trials are ongoing (NCT02279940, NCT02042534, NCT02283294).			See Table LXXVII in online Data Supplement 1.

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

3.11. Volume Expansion/Hemodilution, Vasodilators, and Hemodynamic Augmentation	COR	LOE	New, Revised, or Unchanged
1. Hemodilution by volume expansion is not recommended for treatment of patients with AIS.	III: No Benefit	A	Recommendation and LOE unchanged from 2013 AIS Guidelines. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.
A recent Cochrane review of 4174 participants from multiple RCTs confirmed the previous guideline recommendation that hemodilution therapy, including varying methods of volume expansion with or without venesection, demonstrates no significant benefit in patients with AIS.[208]			See Table XLVIII in online Data Supplement 1.
2. The administration of high-dose albumin is not recommended for the treatment of patients with AIS.	III: No Benefit	A	Recommendation revised from 2013 AIS Guidelines.
The ALIAS (Albumin in Acute Ischemic Stroke) part II trial of high-dose albumin infusion versus placebo in patients with AIS was terminated early for futility.[209] Combined analysis of the ALIAS parts I and II trials demonstrated no difference between groups in 90-day disability.[210]			See Table XLVIII in online Data Supplement 1.
3. The administration of vasodilatory agents, such as pentoxifylline, is not recommended for treatment of patients with AIS.	III: No Benefit	A	Recommendation and LOE unchanged from 2013 AIS Guidelines. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. At present, use of devices to augment cerebral blood flow for the treatment of patients with AIS is not well established. These devices should be used only in the setting of clinical trials.	IIb	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

3.12. Neuroprotective Agents

3.12. Neuroprotective Agents	COR	LOE	New, Revised, or Unchanged
1. At present, no pharmacological or non-pharmacological treatments with putative neuroprotective actions have demonstrated efficacy in improving outcomes after ischemic stroke, and therefore, other neuroprotective agents are not recommended.	III: No Benefit	A	Recommendation reworded for clarity from 2013 AIS Guidelines. LOE unchanged. COR amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Recent trials of both pharmacological and nonpharmacological neuroprotective treatments in AIS have been negative. The FAST-MAG trial (Field Administration of Stroke Therapy–Magnesium) of hyperacute magnesium infusion was the first acute stroke neuroprotection drug trial to enroll participants during ambulance transport, but no differences were seen between the intervention group and placebo control subjects.[103] A recent Cochrane review of neuroprotection trials in AIS further confirms the recommendation of no benefit with previously studied interventions to date.[114]			See Table XLVIII in online Data Supplement 1.

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

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

3.14. Other

3.14. Other	COR	LOE	New, Revised, or Unchanged
1. Transcranial near-infrared laser therapy is not recommended for the treatment of AIS.	III: No Benefit	B-R	Recommendation revised from 2013 AIS Guidelines.
Previous data suggested that transcranial near-infrared laser therapy for stroke held promise as a therapeutic intervention through data published in NEST (Neurothera Effectiveness and Safety Trial)-1 and NEST-2.[211–213] Such basic science and preclinical data culminated in the NEST-3 trial, which was a prospective RCT. This trial investigated the use of transcranial laser therapy for the treatment of ischemic stroke between 4.5 and 24 hours of stroke onset in patients with moderate stroke (NIHSS score 7–17) who did not receive IV alteplase.[214] This study was terminated because of futility after analysis of the first 566 patients found no benefit of transcranial laser therapy over sham treatment. There is currently no evidence that transcranial laser therapy is beneficial in the treatment of ischemic stroke.			See Table XLIX in online Data Supplement 1.

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

4.1. Stroke Units

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

4.2. Supplemental Oxygen

4.2. Supplemental Oxygen	COR	LOE	New, Revised, or Unchanged
1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction that causes compromise of the airway.	I	C-EO	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Supplemental oxygen should be provided to maintain oxygen saturation >94%.	I	C-LD	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. Supplemental oxygen is not recommended in nonhypoxic patients hospitalized with AIS.	III: No Benefit	B-R	Recommendation reworded for clarity from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
Additional support for this unchanged recommendation from the 2013 AIS Guidelines is provided by an RCT of 8003 participants randomized within 24 hours of admission. There was no benefit on functional outcome at 90 days of oxygen by nasal cannula at 2 L/min (baseline O_2 saturation >93%) or 3 L/min (baseline O_2 saturation ≤93%) continuously for 72 hours or nocturnally for 3 nights.[113]			See Table XXVI in online Data Supplement 1.

4.3. Blood Pressure

4.3. Blood Pressure	COR	LOE	New, Revised, or Unchanged
1. In patients with AIS, early treatment of hypertension is indicated when required by comorbid conditions (eg, concomitant acute coronary event, acute heart failure, aortic dissection, postthrombolysis sICH, or preeclampsia/eclampsia). Lowering BP initially by 15% is probably safe.	I	C-EO	New recommendation.
Patients with AIS can present with severe acute comorbidities that demand emergency BP reduction to prevent serious complications. However, it is important to keep in mind that excessive BP lowering can sometimes worsen cerebral ischemia.[215] Ideal management in these situations should be individualized, but in general, initial BP reduction by 15% is a reasonable goal.			
2. In patients with BP <220/120 mm Hg who did not receive IV alteplase or EVT and do not have a comorbid condition requiring acute 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[216–230] 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 acute BP reduction.			See Table L in online Data Supplement 1.
3. In patients with BP ≥220/120 mm Hg who did not receive IV alteplase or EVT and have no comorbid conditions requiring acute antihypertensive treatment, the benefit of initiating or reinitiating treatment of hypertension within the first 48 to 72 hours is uncertain. It might be reasonable to lower BP by 15% during the first 24 hours after onset of stroke.	IIb	C-EO	New recommendation.
Patients with severe hypertension (most commonly >220/120 mm Hg) were excluded from clinical trials evaluating BP lowering after AIS.[218,219,222,223,225,228] BP reduction has been traditionally advised for these cases, but the benefit of such treatment in the absence of comorbid conditions that may be acutely exacerbated by severe hypertension has not been formally studied.			See Table L in online Data Supplement 1.
4. Although no solid data are available to guide selection of medications for BP lowering after AIS, the antihypertensive medications and doses included in Table 5 are reasonable options.	IIa	C-EO	Recommendation/table revised from 2013 AIS Guidelines.
There are no data to show that 1 strategy to lower BP is better than another after AIS. The medications and doses in Table 5 are all reasonable options.			

4.3. Blood Pressure (Continued)	COR	LOE	New, Revised, or Unchanged
5. Starting or restarting antihypertensive therapy during hospitalization in patients with BP >140/90 mm Hg who are neurologically stable is safe and is reasonable to improve long-term BP control unless contraindicated.	IIa	B-R	New recommendation.
Starting or restarting antihypertensive medications has been shown to be associated with improved control of the BP after discharge in 2 trials.[223,225] Therefore, it is reasonable to start or restart antihypertensive medications in the hospital when the patient remains hypertensive and is neurologically stable. Studies evaluating this question included only patients with previous diagnosis of hypertension[223] or enrolled mostly patients with previous hypertension.[225] However, because hypertension is not uncommonly first diagnosed during the hospitalization for stroke, it is reasonable to apply this recommendation also to patients without preexistent hypertension.			See Table L in online Data Supplement 1.
6. Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function.	I	C-EO	New recommendation.
The BP level that should be maintained in patients with AIS to ensure the best outcome is not known. Some observational studies show an association between worse outcomes and lower BPs, whereas others do not.[117–124] No studies address the treatment of low BP in patients with stroke. In a systematic analysis of 12 studies comparing colloids with crystalloids, the odds of death or dependence were similar. Clinically important benefits or harms could not be excluded. There are no data to guide volume and duration of parenteral fluid delivery.[125] No studies have compared different isotonic fluids.			See Table XXVIII in online Data Supplement 1.

4.4. Temperature

4.4. Temperature	COR	LOE	New, Revised, or Unchanged
1. Sources of hyperthermia (temperature >38°C) should be identified and treated. Antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke.	I	C-EO	Recommendation and Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
Additional support for this recommendation unchanged from the 2013 AIS Guidelines is provided by a large retrospective cohort study conducted from 2005 to 2013 of patients admitted to intensive care units in Australia, New Zealand, and the United Kingdom. Peak temperature in the first 24 hours <37°C and >39°C was associated with an increased risk of in-hospital death compared with normothermia in 9366 patients with AIS.[134]			See Tables XXX and XXXI in online Data Supplement 1.
2. The benefit of induced hypothermia for treating patients with ischemic stroke is not well established. Hypothermia should be offered only in the context of ongoing clinical trials.	IIb	B-R	Recommendation revised from 2013 AIS Guidelines.
Hypothermia is a promising neuroprotective strategy, but its benefit in patients with AIS has not been proven. Most studies suggest that induction of hypothermia is associated with an increase in the risk of infection, including pneumonia.[135–138] Therapeutic hypothermia should be undertaken only in the context of a clinical trial.			See Tables XXXII and XXXIII in online Data Supplement 1.

4.5. Glucose

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

4.6. Dysphagia Screening

4.6. Dysphagia Screening	COR	LOE	New, Revised, or Unchanged
1. Dysphagia screening before the patient begins eating, drinking, or receiving oral medications is reasonable to identify patients at increased risk for aspiration.	IIa	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.[4,231–233] 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[234] 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 is reasonable to identify patients at higher risk for adverse outcomes.			See Tables LI and LII in online Data Supplement 1.
2. It is reasonable for dysphagia screening to be performed by a speech-language pathologist or other trained healthcare provider.	IIa	C-LD	Recommendation reworded for clarity from 2016 Rehab Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
3. An instrumental evaluation is reasonable for those patients suspected of aspiration to verify the presence/absence of aspiration and to determine the physiological reasons for the dysphagia to guide the treatment plan.	IIa	B-NR	Recommendation wording modified from 2016 Rehab Guidelines to match Class IIa stratifications. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. It is not well established which instrument to choose for evaluation of swallowing with sensory testing, but the choice may be based on instrument availability or other considerations (ie, fiberoptic endoscopic evaluation of swallowing, videofluoroscopy, fiberoptic endoscopic evaluation).	IIb	C-LD	Recommendation reworded for clarity from 2016 Rehab Guidelines. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

4.7. Nutrition

4.7. Nutrition	COR	LOE	New, Revised, or Unchanged
1. Enteral diet should be started within 7 days of admission after an acute stroke.	I	B-R	New recommendation.
2. For patients with dysphagia, it is reasonable to initially use nasogastric tubes for feeding in the early phase of stroke (starting within the first 7 days) and to place percutaneous gastrostomy tubes in patients with longer anticipated persistent inability to swallow safely (>2–3 weeks).	IIa	C-EO	New recommendation.
The FOOD RCTs (Feed Or Ordinary Diet; phases I–III), completed in 131 hospitals in 18 countries,[235] showed that supplemented diet was associated with an absolute reduction in risk of death of 0.7% and that early tube feeding (within 7 days of admission) was associated with an absolute reduction in risk of death of 5.8% and a reduction in death or poor outcomes of 1.2%. When nasogastric feeding and percutaneous endoscopic gastrostomy feeding were compared, percutaneous endoscopic gastrostomy feeding was associated with an increase in absolute risk of death of 1.0% and an increased risk of death or poor outcomes of 7.8%. The conclusion was that stroke patients should be started on enteral diet within the first 7 days of admission.[235] In 2012, a Cochrane review analyzed 33 RCTs involving 6779 patients to assess the intervention for dysphagia treatment, feeding strategies and timing (early [within 7 days] versus later), fluid supplementation, and the effects of nutritional supplementation on acute and subacute stroke patients.[236] The conclusion was that, although data remained insufficient to offer definitive answers, available information suggested that percutaneous endoscopic gastrostomy feeding and nasogastric tube feeding do not differ in terms of case fatality, death, or dependency, but percutaneous endoscopic gastrostomy is associated with fewer treatment failures (P=0.007), less gastrointestinal bleeding (P=0.007), and higher food delivery (P<.00001).			See Table LIII in online Data Supplement 1.

4.7. Nutrition (Continued)	COR	LOE	New, Revised, or Unchanged
3. Nutritional supplements are reasonable to consider for patients who are malnourished or at risk of malnourishment.	IIa	B-R	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. Implementing oral hygiene protocols to reduce the risk of pneumonia after stroke may be reasonable.	IIb	B-NR	New recommendation.
Limited studies suggest that intensive oral hygiene protocols might reduce the risk of aspiration pneumonia. In patients with acute stroke, Sørensen et al[237] showed that intervention with standardized dysphagia screening and diet and standardized oral hygiene with antibacterial mouth rinse with chlorhexidine reduced pneumonia (7% versus 28%) compared with a historical control group in which patients were unsystematically screened for dysphagia within 24 hours and received unsystematic and arbitrary oral hygiene without chlorhexidine. In this experimental design, the efficacy of the standardized oral hygiene portion in the intervention group could not be separated from the standardized dysphagia screening and diet. Furthermore, because of the historic nature of the control group, it is possible that other changes in care that could have occurred between the historical control subjects and the intervention group might have affected the risk for development of pneumonia. A Cochrane review that included 3 studies found that oral care and decontamination gel versus oral care and placebo gel reduced the incidence of pneumonia in the intervention group (P=0.03).[238] Wagner et al[239] conducted a cohort study comparing rates of pneumonia in hospitalized stroke patients before and after implementation of systematic oral hygiene care. The unadjusted incidence of hospital-acquired pneumonia was lower in the group assigned to oral hygiene care compared with control subjects (14% versus 10.33%; P=0.022), with an unadjusted OR of 0.68 (95% CI, 0.48–0.95; P=0.022). After adjustment for confounders, the OR of hospital-acquired pneumonia in the intervention group remained significantly lower at 0.71 (95% CI, 0.51–0.98; P=0.041).			See Tables LIV and LV in online Data Supplement 1.

4.8. Deep Vein Thrombosis Prophylaxis

4.8. Deep Vein Thrombosis Prophylaxis	COR	LOE	New, Revised, or Unchanged
1. In immobile stroke patients without contraindications, intermittent pneumatic compression (IPC) in addition to routine care (aspirin and hydration) is recommended over routine care to reduce the risk of deep vein thrombosis (DVT).	I	B-R	Recommendation revised from 2016 Rehab Guidelines.
CLOTS (Clots in Legs or stockings After Stroke) 3 was a multicenter trial enrolling 2867 patients in 94 centers in the United Kingdom and comparing the use of IPC with routine care to no IPC with routine care in immobile stroke patients for venous thromboembolism prophylaxis. Eligible patients were enrolled within 3 days of the acute stroke and could not mobilize to the toilet without the help of another person. Routine care was defined as the use of aspirin for nonhemorrhagic stroke, hydration, and possible compression stockings. A total of 31% of the patients received prophylactic or full-dose heparin or LMWH, but these patients were evenly distributed between both groups. After the exclusion of 323 patients who died before any primary outcome and 41 who had no screening, the primary outcome of DVT occurred in 122 of 1267 IPC participants (9.6%) compared with 174 of 1245 no-IPC participants (14.0%), giving an adjusted OR of 0.65 (95% CI, 0.51–0.84; P=0.001). Among patients treated with IPC, there was a statistically significant improvement in survival to 6 months (HR, 0.86; 95% CI, 0.73–0.99; P=0.042) but no improvement in disability. Skin breaks were more common in the IPC group (3.1% versus 1.4%; P=0.002). Contraindications to IPC include leg conditions such as dermatitis, gangrene, severe edema, venous stasis, severe peripheral vascular disease, postoperative vein ligation, or grafting, as well as existing swelling or other signs of an existing DVT.[403] A meta-analysis including this trial and 2 smaller trials confirmed these results.[240]			See Table LVI in online Data Supplement 1.
2. The benefit of prophylactic-dose subcutaneous heparin (unfractionated heparin [UFH] or LMWH) in immobile patients with AIS is not well established.	IIb	A	New recommendation.
The most recent and comprehensive meta-analysis of pharmacological interventions for venous thromboembolism prophylaxis in AIS included 1 very large trial (n=14 578) and 4 small trials of UFH, 8 small trials of LMWHs or heparinoids, and 1 trial of a heparinoid.[240] Prophylactic anticoagulants were not associated with any significant effect on mortality or functional status at final follow-up. There were statistically significant reductions in symptomatic pulmonary embolisms (OR, 0.69; 95% CI, 0.49–0.98) and in DVTs, most of which were asymptomatic (OR, 0.21; 95% CI, 0.15–0.29). There were statistically significant increases in symptomatic intracranial hemorrhage (OR, 1.68; 95% CI, 1.11–2.55) and symptomatic extracranial hemorrhages (OR, 1.65; 95% CI, 1.0–2.75). There may be a subgroup of patients in whom the benefits of reducing the risk of venous thromboembolism are high enough to offset the increased risks of intracranial and extracranial bleeding; however, no prediction tool to identify such a subgroup has been derived.[197,198,240]			See Table LVI in online Data Supplement 1.

4.8. Deep Vein Thrombosis Prophylaxis (Continued)	COR	LOE	New, Revised, or Unchanged
3. When prophylactic anticoagulation is used, the benefit of prophylactic-dose LMWH over prophylactic-dose UFH is uncertain.	IIb	B-R	New recommendation.
The most recent and comprehensive meta-analysis comparing LMWH or heparinoid with UFH for venous thromboembolism prophylaxis in AIS included 1 large trial (n=1762) and 2 smaller trials comparing LMWH with UFH and 4 small trials comparing heparinoids with UFH. There were no significant effects on death or disability for LMWH/heparinoids compared with UFH.[240] The use of LMWH/heparinoid was associated with a statistically significant reduction in DVTs (OR, 0.55; 95% CI, 0.44–0.70), which were mostly asymptomatic, at the expense of a greater risk of major extracranial hemorrhages (OR, 3.79; 95% CI, 1.30–11.03). LMWH can be administered once a day and thus is more convenient for nurses and comfortable for patients. Higher cost and increased bleeding risk in elderly patients with renal impairment are disadvantages of LMWH that should be kept in mind.			See Table LVI in online Data Supplement 1.
4. In ischemic stroke, elastic compression stockings should not be used.	III: Harm	B-R	Recommendation wording modified from 2016 Rehab Guidelines to match Class III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.9. Depression Screening

4.9. Depression Screening	COR	LOE	New, Revised, or Unchanged
1. Administration of a structured depression inventory is recommended to routinely screen for poststroke depression, but the optimal timing of screening is uncertain.	I	B-NR	Recommendation revised from 2016 Rehab Guidelines.
A meta-analysis of studies assessing poststroke depression screening tools (24 studies, n=2907) found several inventories with high sensitivity for detecting poststroke depression.[241] However, further research is needed to determine the optimal screening method and timing to diagnose and treat poststroke depression.[242]			See Table LVII in online Data Supplement 1.
2. Patients diagnosed with poststroke depression should be treated with antidepressants in the absence of contraindications and closely monitored to verify effectiveness.	I	B-R	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.

4.10. Other

4.10. Other	COR	LOE	New, Revised, or Unchanged
1. Routine use of prophylactic antibiotics has not been shown to be beneficial.	III: No Benefit	B-R	Recommendation unchanged from 2013 AIS Guidelines. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. Routine placement of indwelling bladder catheters should not be performed because of the associated risk of catheter-associated urinary tract infections.	III: Harm	C-LD	Recommendation wording modified from 2013 AIS Guidelines to match Class III stratifications. COR and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. During hospitalization and inpatient rehabilitation, regular skin assessments are recommended with objective scales of risk such as the Braden scale.	I	C-LD	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. It is recommended to minimize or eliminate skin friction, to minimize skin pressure, to provide appropriate support surfaces, to avoid excessive moisture, and to maintain adequate nutrition and hydration to prevent skin breakdown. Regular turning, good skin hygiene, and use of specialized mattresses, wheelchair cushions, and seating are recommended until mobility returns.	I	C-LD	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
5. It is reasonable for patients and families with stroke to be directed to palliative care resources as appropriate. Caregivers should ascertain and include patient-centered preferences in decision making, especially during prognosis formation and considering interventions or limitations in care.	IIa	C-EO	New recommendation.
The AHA scientific statement for palliative care in stroke[10] outlines, in detail, a number of palliative care considerations for patients with AIS. The consensus is that patient- and family-centered care, aimed at improving the well-being of survivors and family members while preserving the dignity of patients, is the cornerstone of care. Appropriate consultations, educational resources, and other aids should be identified in order to support patients and families.			

4.11. Rehabilitation

4.11. Rehabilitation	COR	LOE	New, Revised, or Unchanged
1. It is recommended that early rehabilitation for hospitalized stroke patients be provided in environments with organized, interprofessional stroke care.	I	A	Recommendation unchanged from 2016 Rehab Guidelines.
2. It is recommended that stroke survivors receive rehabilitation at an intensity commensurate with anticipated benefit and tolerance.	I	B-NR	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
3. High-dose, very early mobilization within 24 hours of stroke onset should not be performed because it can reduce the odds of a favorable outcome at 3 months.	III: Harm	B-R	Recommendation wording modified from 2016 Rehab Guidelines to match Class III stratifications. LOE revised. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.
The AVERT RCT (A Very Early Rehabilitation Trial) compared high-dose, very early mobilization with standard-of-care mobility.[243] High-dose mobilization protocol interventions included the following: Mobilization was begun within 24 hours of stroke onset whereas usual care typically was 24 hours after the onset of stroke; there was a focus on sitting, standing, and walking activity; and there were at least 3 additional out-of-bed sessions compared with usual care. Favorable outcome at 3 months after stroke was defined as an mRS score of 0 to 2. A total of 2104 patients were randomly assigned (1:1). The results of the RCT showed that patients in the high-dose, very early mobilization group had less favorable outcomes (46% versus 50%) than those in the usual care group: 8% versus 7% of patients died in the very early mobilization group and 19% versus 20% had a nonfatal serious adverse event with high-dose, very early mobilization.			See Table LVIII in online Data Supplement 1.
4. It is recommended that all individuals with stroke be provided a formal assessment of their activities of daily living and instrumental activities of daily living, communication abilities, and functional mobility before discharge from acute care hospitalization and the findings be incorporated into the care transition and the discharge planning process.	I	B-NR	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
5. A functional assessment by a clinician with expertise in rehabilitation is recommended for patients with an acute stroke with residual functional deficits.	I	C-LD	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
6. The effectiveness of fluoxetine or other selective serotonin reuptake inhibitors to enhance motor recovery is not well established.	IIb	C-LD	Recommendation and Class unchanged from 2016 Rehab Guidelines. LOE revised from 2016 Rehab Guidelines.

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

5.1. Cerebellar and Cerebral Edema

5.1. Cerebellar and Cerebral Edema	COR	LOE	New, Revised, or Unchanged
1. Ventriculostomy is recommended in the treatment of obstructive hydrocephalus after a cerebellar infarct. Concomitant or subsequent decompressive craniectomy may or may not be necessary on the basis of factors such as infarct size, neurological condition, degree of brainstem compression, and effectiveness of medical management.	I	C-LD	Recommendation revised from 2014 Cerebral Edema.
Ventriculostomy is a well-recognized effective treatment for the management of acute obstructive hydrocephalus and is often effective in isolation in relieving symptoms, even among patients with acute ischemic cerebellar stroke.[244,245] Thus, in patients who develop symptoms of obstructive hydrocephalus from a cerebellar stroke, emergency ventriculostomy is a reasonable first step in the surgical management paradigm. If cerebrospinal diversion by ventriculostomy fails to improve neurological function, decompressive suboccipital craniectomy should be performed.[244–246] Although a risk of upward herniation exists with ventriculostomy alone, it can be minimized with conservative cerebrospinal fluid drainage or subsequent decompression if the cerebellar infarct causes significant edema or mass effect.[244,245]			See Table LIX in online Data Supplement 1.

5.1. Cerebellar and Cerebral Edema (Continued)	COR	LOE	New, Revised, or Unchanged
2. Decompressive suboccipital craniectomy with dural expansion should be performed in patients with cerebellar infarction causing neurological deterioration from brainstem compression despite maximal medical therapy. When deemed safe and indicated, obstructive hydrocephalus should be treated concurrently with ventriculostomy.	I	B-NR	Recommendation revised from 2014 Cerebral Edema.
The data support decompressive cerebellar craniectomy for the management of acute ischemic cerebellar stroke with mass effect.[244–246] This surgery is indicated as a therapeutic intervention in cases of neurological deterioration caused by cerebral edema as a result of cerebellar infarction that cannot be otherwise managed with medical therapy or ventriculostomy in the setting of obstructive hydrocephalus.[244,245]			See Table LIX in online Data Supplement 1.
3. When considering decompressive suboccipital craniectomy for cerebellar infarction, it may be reasonable to inform family members that the outcome after cerebellar infarct can be good after sub-occipital craniectomy.	IIb	C-LD	Recommendation and Class unchanged from 2014 Cerebral Edema. Wording revised and LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
4. Patients with large territorial supratentorial infarctions are at high risk for complicating brain edema and increased intracranial pressure. Discussion of care options and possible outcomes should take place quickly with patients (if possible) and caregivers. Medical professionals and caregivers should ascertain and include patient-centered preferences in shared decision making, especially during prognosis formation and considering interventions or limitations in care.	I	C-EO	New recommendation.
Cerebral edema can cause serious and even life-threatening complications in patients with large territorial supratentorial infarctions. Although less severe edema can be managed medically, surgical treatment may be the only effective option for very severe cases; in such instances, timely decompressive surgery has been shown to reduce mortality.[247] Nevertheless, there is evidence that persistent morbidity is common and individual preexisting decisions about end-of-life and degree of treatment performed in the face of severe neurological injury must be considered.			
5. Patients with major infarctions are at high risk for complicating brain edema. Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first days after stroke are recommended. Early transfer of patients at risk for malignant brain edema to an institution with neurosurgical expertise should be considered.	I	C-LD	Recommendation revised from 2013 AIS Guidelines. LOE revised.
6. In patients ≤60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion is reasonable because it reduces mortality by close to 50%, with 55% of the surgical survivors achieving moderate disability (able to walk) or better (mRS score 2 or 3) and 18% achieving independence (mRS score 2) at 12 months.	IIa	A	Recommendation revised from 2014 Cerebral Edema.
The pooled results of RCTs demonstrated significant reduction in mortality when decompressive craniectomy was performed within 48 hours of malignant MCA infarction in patients <60 years of age, with an absolute risk reduction in mortality of 50% (95% CI, 34–66) at 12 months.[247] These findings were noted despite differences in the clinical trials in terms of inclusion and exclusion criteria, percent of MCA territory involved, and surgical timing.[248,249] At 12 months, moderate disability (ability to walk) or better (mRS score 2 or 3) was achieved in 43% (22 of 51) of the total surgical group and 55% (22 of 40) of survivors compared with 21% (9 of 42; *P*=0.045) of the total nonsurgical group and 75% (9 of 12; *P*=0.318) of the nonsurgical survivors. At 12 months, independence (mRS score 2) was achieved in 14% (7 of 51) of the total surgical group and 18% (7 of 40) of survivors compared with 2% (1 of 42) of the total nonsurgical group and 8% (1 of 12) of the nonsurgical survivors.[245,247–250]			See Tables LIX and LX in online Data Supplement 1.
7. In patients >60 years of age with unilateral MCA infarctions who deteriorate neurologically within 48 hours despite medical therapy, decompressive craniectomy with dural expansion may be considered because it reduces mortality by close to 50%, with 11% of the surgical survivors achieving moderate disability (able to walk [mRS score 3]) and none achieving independence (mRS score ≤2) at 12 months.	IIb	B-R	Recommendation revised from 2014 Cerebral Edema.
There is evidence that patients >60 years of age can have a reduction in mortality of ≈50% (76% in the nonsurgical group versus 42% in the surgical group in DESTINY [Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery] II) when decompressive craniectomy for malignant MCA infarction is performed within 48 hours of stroke onset.[248,249,251–255] However, functional outcomes in elderly patients seem to be worse than those in patients <60 years of age. At 12 months, moderate disability (able to walk; mRS score 3) was achieved in 6% (3 of 47) of the total surgical group and 11% (3 of 27) of survivors compared with 5% (3 of 22) of the total nonsurgical group and 20% (3 of 15) of the nonsurgical survivors. At 12 months, independence (mRS score ≤2) was not achieved by any survivors in either group.			See Tables LIX and LX in online Data Supplement 1.

5.1. Cerebellar and Cerebral Edema (Continued)	COR	LOE	New, Revised, or Unchanged
8. Although the optimal trigger for decompressive craniectomy is unknown, it is reasonable to use a decrease in level of consciousness attributed to brain swelling as selection criteria.	IIa	A	Recommendation, Class, and LOE unchanged from 2014 Cerebral Edema.
9. Use of osmotic therapy for patients with clinical deterioration from cerebral swelling associated with cerebral infarction is reasonable.	IIa	C-LD	Recommendation reworded for clarity from 2014 Cerebral Edema. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
10. Use of brief moderate hyperventilation (Pco_2 target 30–34 mm Hg) is a reasonable treatment for patients with acute severe neurological decline from brain swelling as a bridge to more definitive therapy.	IIa	C-EO	New recommendation.
Hyperventilation is a very effective treatment to rapidly improve brain swelling, but it works by inducing cerebral vasoconstriction, which can worsen ischemia if the hypocapnia is sustained or profound.[256] Thus, hyperventilation should be induced rapidly but should be used as briefly as possible and avoid excessive hypocapnia (<30 mm Hg).			
11. Hypothermia or barbiturates in the setting of ischemic cerebral or cerebellar swelling are not recommended.	III: No Benefit	B-R	Recommendation and LOE revised from 2014 Cerebral Edema. COR amended to conform with ACC/AHA 2015 Recommendation Classification System.
The data on the use of hypothermia and barbiturates for the management of AIS continue to be limited. Such data include only studies with small numbers of patients and unclear timing of intervention with respect to stroke onset. Hypothermia use has recently been shown to have no impact on stroke outcomes in a meta-analysis of 6 RCTs.[257] Further research is recommended.			See Tables LIX and LX in online Data Supplement 1.
12. Because of a lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) should not be administered for the treatment of cerebral edema and increased intracranial pressure complicating ischemic stroke.	III: Harm	A	Recommendation wording modified from 2013 AIS Guidelines to match Class III stratifications. LOE unchanged. Class amended to conform with ACC/AHA 2015 Recommendation Classification System.

5.2. Seizures

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

6. In-Hospital Institution of Secondary Prevention: Evaluation

6.1. Brain Imaging

6.1. Brain Imaging	COR	LOE	New, Revised, or Unchanged
1. Routine use of brain MRI in all patients with AIS is not cost-effective and is not recommended for initial diagnosis or to plan subsequent treatment.	III: No Benefit	B-NR	New recommendation.
2. In some patients with AIS, the use of MRI might be considered to provide additional information for initial diagnosis or to plan subsequent treatment, although the effect on outcomes is uncertain.	IIb	C-EO	New recommendation.
Diagnostic testing is cost-effective when it leads to a change in treatment that improves outcomes. NCCT scanning of all patients with acute stroke has been shown to be cost-effective primarily because of the detection of acute ICH and the avoidance of antithrombotic treatment in these patients.[70] In many patients, the diagnosis of ischemic stroke can be made accurately on the basis of the clinical presentation and either a negative NCCT or one showing early ischemic changes, which can be detected in the majority of patients with careful attention.[71] Although DW-MRI is more sensitive than CT for detecting AIS,[66,67] systematic reviews with meta-analyses and decision-analytic modeling have shown that routine use of MRI in all patients with AIS is not cost-effective.[68,69] Studies of patients with AIS have shown poor or no association between the pattern on ischemic lesions on brain MRI and etiologic classification.[258–266] Specifically, the pattern of acute multiple infarcts in multiple cerebral circulations has a positive likelihood ratio of 1.41 and a negative likelihood ratio of 0.96 for cardioembolic etiologic classification (combined data from 4 studies[263–265,267]) and a positive likelihood ratio of 1.18 and a negative likelihood ratio of 0.98 for subsequent detection of atrial fibrillation on long-term cardiac monitoring (combined data from 2 studies[258,260]). In some patients with negative NCCT such as those with uncertain clinical stroke localization who are candidates for early CEA or stenting for secondary prevention, demonstration of an area of restricted diffusion on DW-MRI may be helpful in selecting treatment that improves outcomes. However, there are inadequate data at this time to establish which patients will benefit from DW-MRI, and its routine use is not recommended. More research is needed to determine criteria for its cost-effective use.			See Tables XV, LXI, and LXII in online Data Supplement 1.

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 vessels 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.[268–272] Although there is evidence that early or emergency revascularization via either CEA or carotid angioplasty and stenting may be safe in selected cases,[273–275] there are no high-quality prospective data supporting early versus late carotid revascularization in all cases.[276] In cases of nondisabling stroke, a meta-analysis by De Rango et al[269] 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).[277] 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 LXIII in online Data Supplement 1.
2. In patients with AIS, routine noninvasive imaging by means of CTA or MRA of the intracranial vasculature to determine the presence of intracranial arterial stenosis or occlusion is not recommended to plan subsequent secondary preventive treatment.	III: No Benefit	A	New recommendation.
3. In some patients with AIS, noninvasive imaging by means of CTA or MRA of the intracranial vasculature to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain.	IIb	C-EO	New recommendation.
Intracranial atherosclerosis is associated with a high risk of recurrent stroke, often in the same arterial distribution.[278,279] 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.[280] The SAMMPRIS study (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.[281-283] Compared with pooled historical control subjects from similar patients 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.[282–284] Thus, the added utility and cost-effectiveness of noninvasive imaging CTA or MRA of the intracranial vessels to identify intracranial arterial steno-occlusive disease in guiding validated therapy that will ultimately improve outcomes are unproven. Moreover, MRA and CTA often overestimate the degree of stenosis,[285,286] so any data from the angiographically based WASID or SAMMPRIS RCTs cannot be reliably extrapolated.			See Tables LXIV and LXV in online Data Supplement 1.

6.3. Cardiac Evaluation

6.3. Cardiac Evaluation	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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. The clinical benefit of prolonged cardiac monitoring to detect atrial fibrillation after AIS is uncertain.	IIb	B-R	New recommendation.
3. In some patients with AIS, prolonged cardiac monitoring to provide additional information to plan subsequent secondary preventive treatment may be reasonable, although the effect on outcomes is uncertain.	IIb	C-EO	New recommendation.
In patients with TIA or ischemic stroke and atrial fibrillation detected by 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).[287] With prolonged cardiac monitoring by a variety of techniques, atrial fibrillation is newly detected in nearly a quarter of patients with stroke or TIA.[288] However, in the few RCTs of prolonged cardiac monitoring after stroke with clinical end points, no significant benefit of oral anticoagulation for stroke prevention in such patients has been demonstrated.[289–294] 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).[291,292] 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).[294] Other smaller studies have also failed to show a difference in outcomes.[290,293,295] All of these studies were underpowered for the secondary clinical end points. Thus, the appropriate patient selection criteria for prolonged cardiac monitoring and the clinical benefits of doing so remain uncertain at this time. Further randomized trials are planned or ongoing and are needed to clarify best practice.			See Tables LXVI through LXVIII in online Data Supplement 1.
4. Routine use of echocardiography in all patients with AIS to plan subsequent secondary preventive treatment is not cost-effective and is not recommended.	III: No Benefit	B-NR	New recommendation.
5. In selected patients with AIS, echocardiography to provide additional information to plan subsequent secondary preventive treatment may be reasonable.	IIb	B-R	New recommendation.
Current evidence on cost-effectiveness is insufficient to justify routine use of echocardiography in stroke patients. Those patients with known or newly discovered atrial fibrillation by ECG will benefit from oral anticoagulation regardless of echocardiographic findings. The risk of recurrent stroke associated with most echocardiographic lesions and the efficacy of treatment in reducing that risk are unclear. The estimated yield and accuracy of echocardiography in detecting intracardiac thrombus indicate that for unselected patients, transthoracic echocardiography and transesophageal echocardiography will produce at least as many false-positive as true-positive diagnoses. Intracardiac thrombus occurs almost exclusively in patients with clinical evidence of heart disease but is rare even in them.[296] Additional research on how to identify patients likely to harbor intracardiac thrombus, on recurrent stroke risk in patients with intracardiac thrombus, and on the efficacy of oral anticoagulation in reducing that risk is needed.[296–298] Five RCTs have evaluated mechanical closure of echocardiographically detected patent foramen ovale to prevent recurrent stroke in patients without obvious cause for their index stroke.[299–304] All 5 suffered from potential bias resulting from unblinded investigators determining which events should be referred for blinded end-point adjudication. Three had many more patients lost to follow-up than stroke end points, making their results unreliable.[299,301–303] Of 2 RCTs with 1% lost to follow-up, 1 showed no benefit of closure over antithrombotic therapy alone over a 2-year period of 12 strokes (2.9%) versus 13 strokes (3.1%; *P*=0.79),[304] and the other showed a reduction in all stroke versus antiplatelet therapy alone over a mean of 5.3 years of 0 versus 14 (*P*< 0.001) with rates at 5 years of 0% and 5%. There was, however, no change in disabling stroke, 0 versus 1 (*P*=0.63), over the duration of the trial.[300] These 2 trials had different highly restrictive eligibility criteria, used different closure devices, and had different guidelines for antithrombotic therapy.			See Tables LXIX and LXX in online Data Supplement 1.

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 A1c, 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 A1c may be more accurate than other screening tests in the immediate post-event period.	IIa	C-EO	Recommendation wording modified from 2014 Secondary Prevention to match Class IIa stratifications and reworded for clarity. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

6.5. Cholesterol

6.5. Cholesterol	COR	LOE	New, Revised, or Unchanged
1. Routine measurement of blood cholesterol levels in all patients with ischemic stroke presumed to be of atherosclerotic origin who are not already taking a high-intensity statin is not recommended.	III: No Benefit	B-R	New recommendation.
2. Measurement of blood cholesterol levels in patients with ischemic stroke presumed to be of atherosclerotic origin who are already taking an optimized regimen of statin therapy may be useful for identifying patients who would be candidates for outpatient proprotein convertase subtilisin/kexin type 9 inhibitor treatment to reduce the risk of subsequent cardiovascular death, MI, or stroke.	IIb	B-R	New recommendation.
The "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults" recommend statin therapy for secondary prevention for adults with clinical atherosclerotic cardiovascular disease (ASCVD), including stroke presumed to be of atherosclerotic origin. No data were identified for treatment or titration to a specific low-density lipoprotein cholesterol (LDL-C) goal.[7] The 2016 European Society of Cardiology/European Atherosclerosis Society guidelines for the management of dyslipidemias and the 2014 guidelines from the UK National Institute for Health Care Excellence also contain recommendations based on clinical factors and not blood cholesterol measurements.[305,306] Thus, statin therapy can be recommended in patients with stroke presumed to be of atherosclerotic origin without measurement of blood cholesterol. For patients with ischemic stroke that is presumed to be the result of nonatherosclerotic disease such as arterial dissection, measurement of blood cholesterol may be of value because the primary prevention guidelines are based on LDL-C levels.[7] It is of note that the 2012 Canadian Cardiovascular Society guidelines recommend a target LDL-C <2.0 mmol/L or >50% reduction of LDL-C for patients with cerebrovascular disease.[307] The FOURIER study (Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk) randomized 27 564 patients with clinically evident ASCVD and elevated fasting LDL-C level or non–high-density lipoprotein cholesterol who were taking an optimized regimen of lipid-lowering therapy to subcutaneous injections of evolocumab or placebo. Over a mean follow-up of 2.2 years, evolocumab treatment significantly reduced the risk of the composite primary end point of cardiovascular death, MI, stroke, hospitalization for unstable angina, or coronary revascularization (9.8% versus 11.3%; HR, 0.85; 95% CI, 0.79–0.92) and the composite secondary end point of cardiovascular death, MI, or stroke (5.9% versus 7.4%; HR, 0.80; 95% CI, 0.73–0.88). The number needed to treat to prevent 1 cardiovascular death, MI, or stroke over a period of 2 years was 74 with an estimated 2-year cost of $2.1 million.[308]			See Tables LXXI and LXXII in online Data Supplement 1.

6.6. Other Tests for Secondary Prevention

6.6. Other Tests for Secondary Prevention	COR	LOE	New, Revised, or Unchanged
1. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
2. 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 LXXXIII in online Data Supplement 1 for original wording.

6.6. Other Tests for Secondary Prevention (Continued)	COR	LOE	New, Revised, or Unchanged
3. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
A recent review article concludes that there is little, if any, contribution of the inherited thrombophilias to the development of arterial thrombotic events and therefore tests for inherited thrombophilia should not be ordered for the evaluation of stroke.[309]			
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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
5. 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 LXXXIII in online Data Supplement 1 for original wording.
6. 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 remains the most effective medical therapy for OSA.[310–314] However, secondary prevention RCTs showed no benefit of treating moderate to severe OSA with continuous positive airway pressure in preventing cardiovascular events or death in patients with previous stroke.[315,316] Thus, the routine screening for OSA of all patients with AIS is not beneficial for the secondary prevention of cardiovascular events or death.			See Table LXXIII in online Data Supplement 1.

6.7. Antithrombotic Treatment

6.7. Antithrombotic Treatment	COR	LOE	New, Revised, or Unchanged
1. For patients with non-cardioembolic 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. Class and LOE unchanged. See Table LXXXIII in online Data Supplement 1 for original wording.
2. 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 (Secondary Prevention of Small Subcortical Strokes) RCT 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 qualifying event to enrollment in the SPS3 trial was >40 days, so results may have underestimated benefit in the early poststroke period.[317] 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.[318]			See Tables LXXIV and LXXV in online Data Supplement 1.

6.7. Antithrombotic Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
3. For patients who have a noncardioembolic AIS while taking antiplatelet therapy, switching to warfarin is not beneficial for secondary stroke prevention.	III: No Benefit	B-R	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).[319,320] 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.[278,321]			See Table LXXVI in online Data Supplement 1.
4. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
5. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
6. For most patients with an AIS in the setting of atrial fibrillation, it is reasonable to initiate oral anticoagulation within 4 to 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 compared with <4 days); high $CHADS_2$-VASC score, high NIHSS score, large ischemic lesions, and type of anticoagulation were associated with poorer outcomes.[202] In addition, a prospective, open-label study of patients (n=60) with atrial fibrillation and mild to moderate AIS (NIHSS score <9) treated with rivaroxaban for ≤14 days found no symptomatic hemorrhagic transformation by 7 days from initiation.[207]			See Table LXXVII in online Data Supplement 1.
7. For patients with AIS and hemorrhagic transformation, initiation or continuation of antiplatelet or anticoagulation therapy may be considered, depending on the specific clinical scenario and underlying indication.	IIb	B-NR	Recommendation revised from 2014 Secondary Prevention.
Numerous observational studies suggest that antithrombotics can be safely initiated or continued in patients with AIS and hemorrhagic conversion. Individual assessment of the clinical indication, benefits, and associated risks is warranted.[322,323]			See Table LXXVII in online Data Supplement 1.
8. For patients with AIS and extracranial carotid or vertebral arterial dissection, treatment with either antiplatelet or anticoagulant therapy for 3 to 6 months may be reasonable.	IIb	B-R	Recommendation revised from 2014 Secondary Prevention.
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.[324] 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, driven primarily by 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 in 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 cervical artery dissection (CeAD). In addition, a follow-up CADISS analysis found no difference in the natural history of dissecting aneurysms or associated stroke risk by treatment allocation, suggesting an overall favorable prognosis in regard to recurrent events.[325]			See Table LXXVIII in online Data Supplement 1.

6.7. Antithrombotic Treatment (Continued)	COR	LOE	New, Revised, or Unchanged
9. For patients with AIS and extracranial carotid or vertebral arterial dissection who have definite recurrent cerebral ischemic events despite medical therapy, the value of 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.[326] 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 bias. A retrospective analysis of patients with CeAD (n=161) comparing 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 dissecting aneurysms, are favorable.[324,325] Therefore, the benefit of EVT and stenting in patients with CeAD is not well established, and consideration of EVT should be reserved for patients with definite recurrent cerebral ischemic events despite medical therapy.			See Table LXXVII in online Data Supplement 1.

6.8. Statins

6.8. Statins	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 Class unchanged from 2013 AIS Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
2. High-intensity statin therapy should be initiated or continued as first-line therapy in women and men ≤75 years of age who have clinical ASCVD*, unless contraindicated.	I	A	Recommendation and Class unchanged from 2013 Cholesterol Guidelines.
3. In individuals with clinical ASCVD* in whom high-intensity statin therapy would otherwise be used, when high-intensity statin therapy is contraindicated or when characteristics predisposing to statin-associated adverse effects are present, moderate-intensity statin should be used as the second option if tolerated.	I	A	Recommendation and Class unchanged from 2013 Cholesterol Guidelines.
4. In individuals with clinical ASCVD* >75 years of age, it is reasonable to evaluate the potential for ASCVD risk-reduction benefits and for adverse effects and drug–drug interactions and to consider patient preferences when initiating a moderate- or high-intensity statin. It is reasonable to continue statin therapy in those who are tolerating it.	IIb	C-EO	Recommendation and Class unchanged from 2013 Cholesterol Guidelines. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System.
*Clinical ASCVD includes acute coronary syndromes, history of MI, stable or unstable angina, coronary or other arterial revascularization, stroke, TIA, or peripheral arterial disease presumed to be of atherosclerotic origin. For high-intensity statin therapy, the 2013 ACC/AHA guidelines on the treatment of blood cholesterol to reduce atherosclerotic risk recommend atorvastatin 80 mg daily or rosuvastatin 20 mg daily.[7] Please refer to these guidelines for contraindications to high-intensity statin therapy and recommendations for moderate-intensity statin therapy.			See Table LXXI in online Data Supplement 1.
5. Patients with ischemic stroke and other comorbid ASCVD should be otherwise managed according to the 2013 ACC/AHA cholesterol guidelines, which include lifestyle modification, dietary recommendations, and medication recommendations.	I	A	Recommendation, Class, and LOE unchanged from 2014 Secondary Prevention.
6. For patients with an 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.[1,11] 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.[327] A meta-analysis of primarily observational studies found that in-hospital statin use was associated with good functional outcomes.[328] 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.[329] 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.[330]			See Tables LXXIX and LXXX in online Data Supplement 1.

6.9. Carotid Revascularization

6.9. 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.[268–272] Although there is evidence that early or emergency revascularization via either CEA or carotid angioplasty and stenting may be safe in selected cases,[273–275] there are no high-quality prospective data supporting early versus late carotid revascularization in all cases.[276] In cases of minor, nondisabling stroke, a meta-analysis by De Rango et al[269] 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).[277]			See Table LXIII in online Data Supplement 1.

6.10. Smoking Cessation Intervention

6.10. Smoking Cessation Intervention	COR	LOE	New, Revised, or Unchanged
1. 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. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.
2. Counseling, nicotine products, and oral smoking cessation medications are effective in helping smokers to quit.	I	A	Recommendation, Class, and LOE unchanged from 2014 Secondary Prevention.
3. For smokers with an AIS, in-hospital initiation of high-intensity behavioral therapies is reasonable.	IIa	B-R	New recommendation.
4. For smokers with an AIS, in-hospital initiation of varenicline might be considered.	IIb	B-R	New recommendation.
5. For smokers with an AIS, in-hospital initiation of interventions that incorporate both pharmacotherapy and behavioral support might be considered.	IIb	B-R	New recommendation.
A meta-analysis by the Cochrane group indicates that (1) high-intensity behavioral interventions that begin during an index hospitalization and include at least 1 month of supportive contact after discharge promote smoking cessation among hospitalized patients, regardless of the patients' admitting diagnoses,[331] and (2) interventions that incorporate both pharmacotherapy and behavioral support enhance smoking cessation success compared with minimal intervention or usual care.[332,333] There are limited data on the efficacy of the various smoking cessation strategies and when they should be implemented after the occurrence of an acute atherosclerotic event. A 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 and continuous abstinence rates were 35.8% in the varenicline group versus 25.8% in the placebo group.[334] Patients in both groups received low-intensity counseling. A study of Korean smokers with AIS assessed a timely intervention strategy versus conventional counseling.[335] 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 LXXXI and LXXXII in online Data Supplement 1.
6. It is reasonable to advise patients after ischemic stroke to avoid second-hand (passive) tobacco smoke.	IIa	B-NR	Recommendation reworded for clarity from 2014 Secondary Prevention. Class unchanged. LOE amended to conform with ACC/AHA 2015 Recommendation Classification System. See Table LXXXIII in online Data Supplement 1 for original wording.

6.11. 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 Class unchanged from 2016 Rehab Guidelines. LOE revised.

Additional reference support for this guideline is provided in online Data Supplement 1.[200,336-402,404-421]

Disclosures

Writing Group 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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*Modest.

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2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

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CORRECTION

Correction to: 2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

Based on recent feedback received from the clinical stroke community related to the article by Powers et al, "2018 Guidelines for the Early Management of Patients With Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association," which published ahead of print January 24, 2018, and appeared in the March 2018 issue of the journal (*Stroke*. 2018;49:e46–e110. DOI: 10.1161/STR.0000000000000158), the American Heart Association/American Stroke Association has reviewed the guideline and is preparing clarifications, modifications, and/or updates to several sections in it. Currently, those sections, listed here, have been deleted from the guideline while this clarifying work is in process:

Section 1.3 EMS Systems Recommendation 4
Section 1.4 Hospital Stroke Capabilities Recommendation 1
Section 1.6 Telemedicine Recommendation 3
Section 2.2 Brain Imaging Recommendation 11
Section 3.2 Blood Pressure Recommendation 3
Section 4.3 Blood Pressure Recommendation 2
Section 4.6 Dysphagia Recommendation 1
Section 6.0 All subsections (11)

We continue to support this corrected version of the guideline and its support for clinical decision-making. After review, a revised guideline, with consideration given to the clarifications, modifications, and/or updates of the sections noted above, will be posted over the coming weeks.

Ensuring our scientific guidelines reflect the best, most comprehensive scientific analysis has always been, and remains, the Association's top priority. We appreciate the continuing commitment and dedication of our volunteer writing group, peer reviewers, and the scientific community at large, who share our devotion to the integrity and quality of guideline development.

The revised, online version of the guideline is available at http://stroke.ahajournals.org/content/49/3/e46.

1. On page e49, in Table 2, the following changes have been made:
   - The fourth row beginning "2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol…" has been deleted.
   - The eighth row beginning "Guidelines for the Prevention of Stroke in Patients with Stroke…" has been deleted.

2. On page e50, in Table 3, the entry for "TJC," defined as "The Joint Commission," has been deleted.

3. On page e52, in section "1.3. EMS Systems," recommendation 4, the associated knowledge byte, and the associated references have been deleted.

4. On page e52, section "1.4. Hospital Stroke Capabilities," recommendation 1, the associated knowledge byte, and the associated references have been deleted.

5. On page e54, in section “1.6 Telemedicine,” recommendation 3 has been deleted.

6. On page e59, in section “2.2 Brain Imaging,” recommendation 11, the associated knowledge byte, and the associated references have been deleted.

7. On page e61 (previously page e62), in section “3.2 Blood Pressure,” recommendation 3, the associated knowledge byte, and the associated references have been deleted.

8. On page e78 (previously page e79), in section “4.3 Blood Pressure,” recommendation 2, the associated knowledge byte, and the associated references have been deleted.

9. On page e80 (previously page e81), in section “4.6 Dysphagia Screening,” recommendation 1, the associated knowledge byte, and the associated references have been deleted.

10. On pages e87 through e93 in the previous version, section “6. In-Hospital Institution of Secondary Prevention: Evaluation” (recommendations, associated knowledge bytes, and references) has been deleted.

11. On page e87 (previously page e93), the following sentence was updated to include references 202, 216, 217, 220, 221, 224, 226, 227, 229, 322, 323, 325, and 326: “Additional reference support for this guideline is provided in online Data Supplement 1.[200,202,216,217,220,221,224,226,227,229,322,323,325,326,336-402,404-421]”

12. On pages e88 through e99 (previously pages e96 through e110), the following references have been deleted: 7, 11, 24-31, 33, 34, 230-234, 258-321, 324, and 327-335.

13. In Data Supplement 1, the following changes have been made:
    - Table V, Table VI, Table LI, Table LII, Tables LXI-LXXVI, and Tables LXXVIII-LXXXII have been deleted.
    - In Table LXXXIII, the original wording of text for the following has been deleted:
        - 1.4 Rec 1
        - 6.4. Rec 1
        - 6.6. Recs 1, 2, 3, 4, and 5
        - 6.7. Recs 1, 4, and 5
        - 6.10. Recs 1 and 6
    - References 7, 11, 24-31, 33, 34, 230-234, 258-321, 324, and 327-335 have been deleted.

14. In Data Supplement 2, the following changes have been made:
    - All references to Data Supplement 1 Table V, Table LI, Tables LXI-LXXVI, and Tables LXXVIII-LXXXII have been deleted.
    - Because of these deletions, the following literature search sections have been removed:
        - ASA Failure
        - Statins
        - Smoking
        - Carotid Endarterectomy and Carotid Artery Stenting Timing
        - Complications After Acute Carotid Endarterectomy or Stenting
        - Guidelines for Treatment of Blood Cholesterol for Secondary Stroke Prevention
        - Cost-Effectiveness of Echocardiography in Acute Stroke
        - Prolonged Cardiac Monitoring for Secondary Stroke Prevention
        - Symptomatic Carotid Stenosis and Early Recurrent Stroke
        - Risk of Early Carotid Intervention
        - Routine Screening of Patients With Recent Ischemic Stroke for Obstructive Sleep Apnea

- MRA Intracranial, Non-Invasive Imaging Intracranial
- CTA Intracranial, Non-Invasive Imaging
- Association of AMIMCC With Stroke Etiologic Classification
- Infarct Topography and Detection of AF By Long Term Monitoring
- Evolocumab and Secondary Stroke Prevention
- Dysphagia Screening

The pagination of this article has changed from e46–e110 to e46–e99. This has been updated in the citations on pages e46 and e47 and in the issue's online table of contents.

Stroke **is available at http://stroke.ahajournals.org**

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2018 AIS GL Data Supplement 1

Table of Contents

Table I. Nonrandomized Studies of Stroke Awareness and Emergency Medical Services Use

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Ojike N, et al.[17] 2016 27478680	**Study type:** Survey **Size:** N=36,697	**Inclusion criteria:** National Health Interview Survey **Exclusion criteria:** N/A	**1° end point:** Assess stroke knowledge and likelihood of calling 911 **Results:** • Age-adjusted stroke awareness was 66% • Stroke awareness lowest for Hispanics, Blacks and those residing in the Western United States; least recognized stroke symptom was sudden severe headache	• Stroke awareness varied by race/ethnicity, sex and region/location but not by level of education or insurance coverage • Stroke awareness lowest for Hispanics, Blacks and those residing in the Western United States.
Schwartz J, et al.[336] 2016 26953776	**Study type:** Registry **Size:** N=184,179	**Inclusion criteria:** 911 calls for patients ≥18 y with an EMS provider impression of stroke **Exclusion criteria:** N/A	**1° end point:** EMS response time **Results:** • Median EMS response time (911 call to ED arrival) was 36 (IQR, 28.7–48.0) min • On-scene time (15 min) was the largest component of this time • Longer times were noted for patients aged 65–74 y, of white race, females, and non-urban areas	There are opportunities for improvement in EMS stroke recognition and response times
Mochari-Greenberger H, et al.[19] 2015 26268882	**Study type:** Observational study **Size:** N=398,798	**Inclusion criteria:** Get With the Guidelines Hospitalized Stroke Cases **Exclusion criteria:** N/A	**1° end point:** Association of race/ethnicity and EMS use among stroke patients **Results:** • 59% of all patients used EMS • White women were most likely to use EMS (62%), and Hispanic men least likely (52%)	EMS use differs by race ethnicity and gender
Berglund A, et al.[21] 2014 24576912	**Study type:** Observational study **Size:** N=900	**Inclusion criteria:** Dispatch EMS stroke activation **Exclusion criteria:** N/A	**1° end point:** PPV for discharge diagnosis of stroke/TIA **Results:** • PPV for a discharge diagnosis of stroke/TIA was 51% (95% CI, 47–54%) for dispatch and 58% (95% CI, 52-64%) in ambulance • Positive FAST increased PPV to 56% (95% CI: 52–61%) for dispatch and 73% (95% CI, 66–80%) for ambulance	Better stroke identification tools are needed in the prehospital setting

			• Positive FAST also found in 44% of non-stroke by dispatch and a negative FAST in up to 17% of true dispatch stroke cases	
De Luca A, et al.[22] 2013 24330761	**Study type:** Cross-sectional observational study **Size:** N=21,760	**Inclusion criteria:** Dispatch EMS stroke activation **Exclusion criteria:** N/A	**1° end point:** PPV of EMS dispatchers' ability to recognize stroke/TIA with CPSS **Results:** • 9791 of 21760 dispatch cases were confirmed as stroke on scene • PPV of the dispatch stroke/TIA symptoms identification was 34.3% (95% CI, 33.7–35.0), and sensitivity was 64.0% (95% CI, 63.0–64.9) • Centers using CPSS had higher PPV and sensitivity	Better stroke identification tools are needed in the prehospital setting
Ekundayo OJ, et al.[18] 2013 23633218	**Study type:** Observational study **Size:** N=204,591	**Inclusion criteria:** Get With the Guidelines Hospitalized Stroke Cases **Exclusion criteria:** N/A	**1° end point:** EMS use by stroke patients **Results:** EMS transport was independently associated with: • Earlier arrival (onset-to-door time, ≤3 h; adjusted OR, 2.00; 95% CI,1.93–2.08) • Prompt ER evaluation (more patients with door-to-imaging time, ≤25 min; OR, 1.89; 95% CI, 1.78–2.00) • More rapid treatment (more patients with door-to-needle time, ≤60 min; OR, 1.44; 95% CI, 1.28–1.63) • More patients eligible to be treated with tissue-type plasminogen activator if onset is ≤2 h (67% vs. 44%; OR, 1.47; 95% CI, 1.33–1.64).	Interventions aimed at increased EMS use should target at-risk populations, particularly young and minority race/ethnic populations
Lin CB, et al.[23] 2012 22787065	**Study type:** Observational study **Size:** N=371,988	**Inclusion criteria:** Get With the Guidelines Hospitalized Stroke Cases Transported by EMS **Exclusion criteria:** N/A	**1° end point:** Evaluation and treatment times **Results:** • Prenotification occurred in 67% of EMS transports • Patients with EMS prenotification were more likely to be treated with alteplase within 3 h (82.8% vs. 79.2%, *P*<0.0001) • Patients with EMS prenotification had shorter door-to-imaging times (26 min vs. 31 min, *P*<0.0001), shorter door-to-needle times (78 min vs. 80 min, *P*<0.0001), and shorter symptom onset-to-needle times (141 min vs. 145 min, *P*<0.0001)	EMS prenotification is associated with improved and timelier treatment, and initiatives to improve prenotification rates should be implemented

Abbreviations: CI indicates confidence interval; CPSS, Cincinnati Prehospital Stroke Scale; EMS, emergency medical services; FAST, Face, Arm, Speech, Time test; h, hour; min, minute; N/A, not available; OR, odds ratio; PPV, positive predictive value; and TIA, transient ischemic attack.
Literature search topic: Public education, EMS assessment and management: recognize stroke, call 911.

Table II. Randomized Clinical Trials for Improving Stroke Awareness

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
SWIFT Boden-Albala B, et al.[20] 2015 26069259	**Aim:** "Determine whether a culturally tailored, interactive educational program in a racially and ethnically diverse high risk population, aimed at stroke awareness and emergency treatment will lead to increased stroke knowledge, behavioral change and improved time to arrival to the ED upon onset of stroke symptoms." **Study type:** Single-center RCT **Size:** N=1193	**Inclusion criteria:** Ischemic stroke or TIA, patients >18 y and living in a household with a telephone **Exclusion criteria:** Unable to give informed consent; discharged to long term nursing home, or requiring 24-h care; mRS >4 at baseline; severe aphasia limiting comprehension; pre-stroke dementia history, or end stage disease resulting in probable mortality ≤1 y	**Intervention:** Two interactive multimedia educational group sessions (N=601) **Comparator:** Standard stroke care and treatment, as well as the distribution of stroke pamphlets in English and Spanish designed by the American Heart Association (N=592)	**1° end point:** Recurrent event rates, early arrival at recurrent event, and stroke knowledge: • At baseline, 28% arrived at the ED within 3 h • Over 5 y, 224 (19%) participants experienced a recurrent event • 40% of the interactive intervention group vs. 46% of the enhanced education group arrived within 3 h (*P*=0.33) • The interactive intervention group had greater stroke knowledge at 1 mo (OR, 1.63; 95% CI, 1.23–2.15) **Safety end point:** N/A	N/A	Underpowered to detect impact of intervention on earlier arrival times and education provided to both groups may have enhanced knowledge in the "non-intervention" group	A multi-media approach to stroke education and awareness is feasible. More work is needed to impact subsequent be-havior to improve early arrival after stroke onset.
KIDS Morgenstern LB, et al.[337] 2007 17885255	**Aim:** "Increase the correct identification of stroke signs and symptoms and encourage immediate contact with emergency medical	**Inclusion criteria:** CCISD 6th graders **Exclusion criteria:** Non-6th	**Intervention:** 12 h of classroom instruction in 6th, 7th, and 8th graders; parents were educated	**1° end point:** Pre- and post-test on stroke knowledge: • Knowledge of stroke pathophysiology improved	N/A	• High loss to follow-up • Parents not directly educated	An educational intervention may improve stroke knowledge in children. A multi-pronged

	services (calling 911) when these signs and symptoms were detected" **Study type:** RCT **Size:** N=573 kids, N=462 parents	grader, non CCISD student	through homework assignments (N=294 kids, N=256 parents) **Comparator:** Schools that did not receive the intervention (N=279 kids, N=206 parents)	in intervention students from 29% to 34% correct, whereas control students changed from 28% correct to 25% • Stroke symptom knowledge improved from 28% correct to 43% in intervention students, and 25% correct to 29% in control • For a witnessed stroke, intervention students improved their correct answers from 36% to 54% whereas control changed from 32% correct to 34% • Parental response rate was not testable due to poor response rate **Safety end point:** N/A			approach with education dedicated to parents/adults is warranted to improve overall societal stroke knowledge

Abbreviations: CCISD indicates Corpus Christi Independent School District; ED, emergency department; h, hour; mRS, modified Rankin Scale; N/A, not available; OR, odds ratio; RCT, randomized clinical trial; and RR, relative risk; TIA, transient ischemic attack, and y, years.
Literature search topic: Public education, EMS assessment and management: recognize stroke, call 911.

Table III. Nonrandomized Trials, Observational Studies, and/or Registries of Prediction Value of National Institutes of Health Stroke Scale

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Fonarow GC, et al.[65] 2012 23130117	**Study type:** Retrospective cohort (GWTG-Stroke Registry) **Size**: N=33102 AIS patients	**Inclusion criteria:** GWTG-Stroke Registry inclusion and Medicare Part A claim data with AIS at centers w ≥25 AIS between 2003–07	**1° end point:** All-cause mortality within 30 d **Results**: • There was a strong graded relation between increasing NIHSS score and higher 30-d mortality • The 30-d mortality rates for acute ischemic stroke by NIHSS categories were as follows: 0–7, 4.2%; 8–13, 13.9%; 14–21, 31.6%; 22–42, 53.5%	The NIHSS provides substantial prognostic information regarding mortality within the first 30 d among Medicare beneficiaries with AIS

		with NIHSS documented **Exclusion criteria:** N/A	• A model with NIHSS alone provided excellent discrimination whether included as a continuous variable (c-statistic 0.82; 0.81 to 0.83), 4 categories (c-statistic 0.80; 0.79–0.80), or 3 categories (c-statistic 0.79; 0.78–0.79)	
Lyden P, et al.[64] 2009 19520998	**Study type:** Observational **Size:** 8214 NIHSS score ratings	**Inclusion criteria:** Convenience sample **Exclusion criteria:** N/A	**End Points:** Rater agreement on NIHSS score assessed using unweighted kappa statistic for multiple raters and intra-class correlation coefficient **Results:** • Individual NIHSS test item scoring agreement ranged from 0.15 (ataxia) to 0.81 (LOC item 1c) with agreement being similar across all subgroups and venues of raters. • Overall total NIHSS score intra-class correlation coefficient across all subgroups and venues was 0.85 (95% CI, 0.72–0.90) with no clinically meaningful differences between rater specialty and setting	• NIHSS training and certification using DVD is valid and reliable among general users with remarkable consistency across different venues • Reliability assessments of novice users were similar to what was found using experienced stroke centers • No differences in the ICC of the total NIHSS were identified when used by neurologists, emergency physicians, or nurses • Agreement across various settings was similar and generally moderate to excellent
SITS-MOST Wahlgren N, et al.[61] 2008 18927461	**Study type:** Post hoc subgroup analysis of a prospective, open, monitored, observational study **Size:** N=6483	**Inclusion criteria:** See SITS-MOST **Exclusion criteria:** Same	**1° end point:** Symptomatic intracerebral hemorrhage, mortality and independency (mRS 0–2 at 3 mo post-stroke) **Results:** In the multivariable analysis, older age, high blood glucose, high NIHSS score and current infarction on imaging scans were related to poor outcome in all parameters	• Stroke severity at baseline as measured by NIHSS score and functional disability before current stroke appeared to be strongest predictors for mortality and rate of independence at 3 mo • The association between NIHSS scores and symptomatic ICH (SITS-MOST definition) was not linear
Josephson SA, et al.[63] 2006 16888381	**Study type**: Retrospective observational **Size:** N=7405 unique raters	**Inclusion criteria:** Convenience sample **Exclusion criteria:** N/A	**End Points:** Rater agreement on overall NIHSS score; determination of passing scores on examination; individual questions assessed using unweighted and modified kappa statistics **Results:** •Greater mean NIHSS scores were associated with greater scoring variance • Nurses (RNs) demonstrated less variance from the most common response compared to other professions (*P*<0.0001)	• Substantial variability was found in total NIHSS score for the videotape vignettes; the author suggests this was due to problems with the test itself, rather than poorly performing raters • High agreement was found on many items in the NIHSS

			• Observed agreement on individual NIHSS elements ranged from 0.697 (aphasia) to 0.995 (LOC item 1c) • Modified kappa ranged from 0.596 (aphasia) to 0.993 (LOC 1c)	
NINDS t-PA Stroke Study Frankel MR, et al.[60] 2000 11061250	**Study type:** Post hoc subgroup analysis of the placebo group of a randomized, double-blind, placebo controlled trial **Size:** N=312	**Inclusion criteria:** See NINDS t-PA Stroke Study **Exclusion criteria:** Same	**1° end point:** Outcome was measured with four stroke rating scales administered 3 mo after treatment **Results:** Baseline variables that predicted a poor outcome were NIHSS score >17 plus atrial fibrillation, yielding a PPV for poor outcome of 96% (95% CI, 88–100); at 24 h the best predictor was an NIHSS score >22 (PPV 98%; 95% CI, 93–100), and at 7–10 d the best predictor was NIHSS >16 (PPV 92%; 95% CI, 85–99)	• Baseline NIHSS strongly predicts long-term outcome in stroke patients
Adams HP Jr, et al.[59] 1999 10408548	**Study type:** Post hoc subgroup analysis of a randomized, double-blind, placebo controlled trial **Size:** N=1281	**Inclusion criteria:** See Trial of ORG 10172 in Acute Stroke **Exclusion criteria:** Same	**1° end point:** Outcomes assessed at 7 d and 3 mo using the Barthel Index and Glasgow Outcome Scale **Results:** Baseline NIHSS score strongly predicted outcome, with one additional point on the NIHSS decreasing the likelihood of excellent outcome at 3 mo by 17%	• Baseline NIHSS strongly predicts long-term outcome in stroke patients
NINDS t-PA Stroke Trial Subgroup Analysis NINDS t-PA Stroke Study Group[58] 1997 9368551	**Study type:** Post hoc subgroup analysis of a randomized, double-blind, placebo controlled trial **Size:** N=624 subjects	**Inclusion criteria:** See NINDS t-PA Stroke Study **Exclusion criteria:** Same	**1° end point:** Outcome was measured with four stroke rating scales administered 3 mo after treatment **Results:** • No pretreatment information significantly affected patients' response to alteplase (all *P*>0.05) • Outcome was related to age-by-deficit severity interaction, diabetes, age-by-blood pressure interaction, and early CT findings	• No patient subgroups with differential response to alteplase could be identified • Older patients with severe deficits (high NIHSS) were less likely to do well in the long term compared to those younger or with less severe deficits; however, these patients still benefited from t-PA treatment

Abbreviations: AIS indicates acute ischemic stroke; CI, confidence interval; GWTG, Get With The Guidelines; ICH, intracerebral hemorrhage; ICC, intraclass correlation coefficient; LOC, level of consciousness; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders; PPV, positive predictive value; OR, odds ratio; and RN, registered nurse.

Literature search topic: Emergency evaluation: benefit of stroke scale use

Table IV. Nonrandomized Studies of Emergency Medical Services Use of Prehospital Stroke Severity Scales

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Carrera D, et al.[338] 2017 27720525	**Study type:** Reanalysis of observational data **Size:** N=341	**Inclusion criteria:** Previously enrolled in original RACE derivation **Exclusion criteria:** No prehospital RACE score available	**1° end point:** Receiver operating characteristics of test performance **Results:** • Seven simpler versions of RACE scale derived • Original RACE scale had an AUC of 0.82 for detecting LVO • The 7 simpler RACE versions generated slightly lower AUC for detecting LVO	• The use of simplified versions of the original RACE scale reduced performance • No direct comparison to other scores was feasible, and biases of patient selection in the original cohort persist
Kim JT, et al.[339] 2017 28087807	**Study type:** Secondary analysis of prospective data from the FAST-MAG trial **Size:** N=1632	**Inclusion criteria:** Confirmed cerebrovascular disease, transported by EMS and enrolled in FAST-MAG **Exclusion criteria:** Non-FAST-MAG transports	**1° end point:** Correlation of prehospital LAMS with early ED NIHSS **Results:** • ED LAMS score correlated with concurrently performed NIHSS in all cerebrovascular cases (r=0.89) • Prehospital LAMS correlated moderately with ED NIHSS (r=0.49) • Although the ED LAMS correlated moderately with 3-month mRS, r=0.55, the association of prehospital LAMS with 3-month mRS was less strong (r=0.34)	• LAMS score correlates well with NIHSS and outcomes when performed in the ED but only moderately when performed by prehospital personnel • This paper did not address the utility of LAMS for LVO detection and triage
McMullan JT, et al.[340] 2017 28121225	**Study type:** Observational study **Size:** N=58	**Inclusion criteria:** Prehospital suspected stroke (FAST-positive), C-STAT scored, and transported to a comprehensive stroke center or having a stroke team consult note **Exclusion criteria:** FAST-negative	**1° end point:** C-STAT sensitivity and specificity **Results:** C-STAT sensitivity and specificity for each outcome were: • NIHSS≥ 15, 77% (95% CI, 46–95) and 84% (95% CI, 69–93) • NIHSS≥10, 64% (95% CI, 41–83) and 91% (95% CI, 76–98) • LVO, 71% (95% CI, 29–96) and 70% (95% CI, 55–83)	• Among FAST-positive prehospital suspected stroke patients, C-STAT could be readily performed and incorporated into the prehospital workflow • The small study sample size and regional restriction preclude meaningful conclusions on test characteristics for predicting LVO to inform prehospital triage

Abbreviations: AUC indicates area under the receiver operating characteristic curve; CI, confidence inter\val; C-STAT, Cincinnati Stroke Triage Assessment Tool; ED, emergency department; EMS, emergency medical services; FAST, Face Arm Speech Time algorithm; LAMS, Los Angeles Motor Scale; LVO, large vessel occlusion; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; and RACE, Rapid Arterial Occlusion Evaluation.
Literature search topic: Public Education, EMS assessment and management: recognize, call 911

Table V. Deleted
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Table VII. Nonrandomized Studies of Hospitals Achieving Rapid Door-to-Needle Times for IV Alteplase in Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; 95% CI)	Summary/Conclusion Comment(s)
Xian Y, et al.[36] 2017 28096207	**Study type**: Retrospective, observational study of 888 hospitals. **Size**: 16,901 patients with AIS treated with alteplase within 4.5h of onset.	**Inclusion criteria**: Patients receiving IV alteplase within 4.5 hours of symptom onset between June 2014 and April 2015. **Exclusion criteria**: N/A	**1° endpoint**: No primary endpoint declared. Door-to-needle times for alteplase administration determined along with survey assessing extent which hospitals were using the Target:Stroke interventions to reduce DTN times and quantify the association. **Results:** • Median DTN time for alteplase administration was 56 minutes (IQR 42-75). • 59.3% of patients received IV alteplase within 60 minutes. • 30.4% of patients were treated within 45 minutes. • 16 strategies were associated with significant reductions in DTN times.	• Median DTN times of less than 60 minutes were achievable in a majority of patients. • The achievement of DTN times within 45 minutes is feasible in a substantial proportion of patients.
Fonarow GC, et al.[35] 2014 24756513	**Study type**: Retrospective, observational study with pre-/post-Target:Stroke intervention design	**Inclusion criteria**: Patients receiving guideline concordant intravenous alteplase at GWTG-Stroke participating hospitals	**1° endpoint**: No primary endpoint declared. Door-to-needle times for alteplase administration; in-hospital all-cause mortality; discharge status determined. **Results:**	• Implementation of the Target:Stroke quality improvement initiative was associated with improved timeliness of tPA delivery.

	using GWTG hospital convenience sample **<u>Size</u>:** 71,169 patients with AIS treated with tPA (27,319 pre-intervention period, 43,850 post-intervention period) at 1,030 Get With The Guidelines-Stroke participating hospitals (52.8% of total)	from April 2003 to Sept 2013. **<u>Exclusion criteria</u>:** N/A	• Median DTN time for tPA administration declined from 77 minutes (IQR, 60-98 minutes) during the pre-intervention period to 67 minutes (IQR, 51-87 minutes) during the post-intervention period (*P* < .001). • The DTN times for tPA administration of 60 minutes or less increased from 26.5% (95% CI, 26.0%-27.1%) of patients during the pre-intervention period to 41.3% (95% CI, 40.8%-41.7%) during the post-intervention period (*P*<.001)	• Median hospital door-to-needle target times of less than 60 minutes were achievable in over 50% of cases.
Sauser K, et al.[341] 2014 25023407	**<u>Study type</u>:** Retrospective, observational study of 25 hospitals. **<u>Size</u>:** 1193 patients with AIS treated with alteplase within 4.5h of onset.	**<u>Inclusion criteria</u>:** Patients receiving IV alteplase within 4.5 hours of symptom onset between Jan 2009 and Dec 2012. **<u>Exclusion criteria</u>:** N/A	**<u>1° endpoint</u>:** Continuous measure of DTN time, in minutes, from emergency department arrival to thrombolytic delivery. **<u>Results:</u>** • Mean (SD) DTN time for alteplase administration was 82.9 minutes (35.4). Median time was 76 minutes. • 28.7% of patients received IV alteplase within 60 minutes.	• In this study, mean and median DTN times exceeded 60 minutes in a clear majority of patients. • Approximately one-quarter of patients were treated within 60 minutes.

Abbreviations: CI indicates confidence interval; DTN, Door-to-Needle; HR, hazard ratio; IQR, interquartile range; N/A, not available; OR, odds ratio; and RR, relative risk.
Literature search topic: Achieving rapid door-to-needle treatment time in stroke

Table VIII. Randomized Clinical Trials Comparing Efficacy of Multilevel Interventions to Increase Intravenous Alteplase Use

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
INSTINCT Scott PA, et al.[38] 2013 23260188	**Aim:** To test a multilevel intervention to increase community hospital alteplase use **Study type:** Multicenter cluster RCT using matched-pair design **Size:** N= 24 hospitals	**Inclusion criteria:** Adult, non-specialty, acute-care, community hospitals in Michigan with ≥ 100 stroke patients/y **Exclusion criteria:** Academic comprehensive stroke centers; hospitals with >100,000 ED visits per year	**Intervention:** Standardized, barrier-assessment, multicomponent intervention (n=12) **Comparator:** No intervention (n=12)	**1° end point:** From pre- to post-intervention periods, alteplase use increase in intervention group hospitals (59/5882 [1.00%] to 191/7288 [2.62%]) was significantly greater than control group (65/5957 [1.09%] to 120/6989 [1.72%]); RR, 1.68; 95% CI, 1.09–2.57; *P*=0.02. **Safety end point:** Total symptomatic intracranial hemorrhage within 36 h occurred in 24/404 [5.9%]; total mortality was 62/557 [11.1%]; between group differences were NS (*P*=0.84)	The difference was not significant in the comparison based on the mixed-effects Poisson model (RR 1.37, 95% CI 0·96–1.93; *P*=0·08;	One hospital pair was excluded from analysis due to conversion to academic comprehensive stroke center mid-trial	• The pragmatic INSTINCT multilevel intervention modestly increased alteplase use in target group community hospital EDs • Identified safety of alteplase use in community EDs with sufficient numbers to ensure precise safety metrics
PRACTISE Dirks M, et al.[39] 2011 21393587	**Aim:** To test a multidimensional implementation strategy to increase alteplase use **Study type:** Multicenter, cluster-randomized controlled trial using matched pair design **Size:** N=5515 patients admitted with stroke (12	**Inclusion criteria:** Convenience sample 12 hospitals **Exclusion criteria:** None listed	**Intervention:** Intervention meetings based on Breakthrough Series model (n=6 hospitals) **Comparator:** No intervention (n=6 hospitals)	**1° end point:** Intervention hospitals treated 393 (13.1% of all patients with acute stroke) vs. 308 (12.2%) at control hospitals, adjusted OR, 1.25 (95% CI, 0.93–1.68) **Safety end point:** Symptomatic intracranial hemorrhage rate was 5.6% (intervention) vs.	Among the 1657 patients with ischemic stroke admitted within 4 hours from onset, 391 (44.5%) of 880 in the intervention centers were treated with thrombolysis	The intensive intervention may not be generalizable to all hospital settings as it included forming local teams consisting of a stroke neurologist and stroke nurse	The PRACTISE intervention increased the proportion of stroke patients treated with alteplase

	hospitals); 2990 in 6 intervention hospitals, 2525 in 6 control hosptials			4.6% (control); RR, 1.08; 95% CI, 0.83–1.43	and 305 (39.3%) of 777 in the control centers (adjusted OR, 1.58 (95% CI, 1.11-2.27).		

Abbreviations: CI indicates confidence interval; ED, emergency department; HR, hazard ratio; NS, not significant; OR, odds ratio; RCT, randomized clinical trial; and RR, relative risk.
Literature search topic: Increasing alteplase treatment in stroke

Table IX. Nonrandomized Studies Comparing Efficacy of Multilevel Interventions to Increase Intravenous Alteplase Use

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Ganesh A, et al.[33] 2016 26850979	**Study type**: Retrospective cohort analysis **Size**: N=319,972	**Inclusion criteria:** Patients with stroke (ischemic or hemorrhagic) or TIA admitted to acute care hospitals in Canada in fiscal years 2003/2004 to 2013/2014 **Exclusion criteria:** Patients hospitalized in Quebec province because complete data were not available	**1° end point:** Crude 30-day mortality **Results**: • Crude 30-day mortality rate decreased from 15.8% in 2003/2004 to 12.7% in 2012/2013 in provinces with stroke systems, while remaining 14.5% in provinces without such systems • Starting with the fiscal year 2009/2010, there was a clear reduction in relative mortality in provinces with stroke systems vs. those without, sustained at aIRR of 0.85 (95% CI, 0.79–0.92) in the 2011/ 2012, 2012/2013, and 2013/2014 fiscal years • The surveys indicated that facilities in provinces with such systems were more likely to care for patients on a stroke unit, and have timely access to a stroke prevention clinic and telestroke services	• First demonstration of population-wide reduction in mortality from stroke systems of care Could not account for the potential effects of concurrent interventions, such as stroke specialist training programs and variability in adherence to national best practices recommendations • The outcome of 30-day mortality in the study may not reflect other clinical outcomes of interest, like 90-d or longer-term mortality
Fonarow GC, et al.[35] 2014 24756513	**Study type:** Target: Stroke intervention (multi-modal), pre-post design, convenience sample **Size**: N=71,169	**Inclusion criteria**: • Patients with AIS treated with alteplase • GWTG hospital **Exclusion criteria**: • Not treated with alteplase	**1° end point:** DTN times for alteplase administration of ≤60 min **Results:** • Median DTN time for alteplase administration declined from 77 min (IQR: 60–98 min) during the preintervention period to 67 min (IQR: 51–87 min) during the postintervention period (*P*<0.001)	• Implementation of a national quality improvement initiative was associated with improved timeliness of alteplase administration following AIS on a national scale, and this improvement was associated with lower in-hospital mortality and intracranial hemorrhage, along with

		• Transferred from another facility • Had stroke while in hospital	• DTN times for alteplase administration ≤60 min increased from 26.5% (95% CI, 26.0%–27.1%) of patients during the preintervention period to 41.3% (95% CI, 40.8%-41.7%) during the postintervention period (*P*<0.001)	an increase in the percentage of patients discharged home • Study limitations included convenience sample; lack of concurrent control; potential unmeasured confounders; retrospectively collected data
van Wijngaarden JD, et al.[342] 2011 21613273	**Study type**: Prospective observational cohort **Size**: N=5515	**Inclusion criteria:** • Patients age>18 y admitted with acute stroke • Symptom onset ≤24 h before admission **Exclusion criteria:** N/A	**1° end point:** Treatment with thrombolysis or not as measured by proportion of stroke patients admitted within 24 h of symptom onset treated with thrombolysis **Results**: • The unadjusted multilevel logistic regression shows a significant association between thrombolysis rates and availability of intramural protocols (OR, 1.46; 95% CI, 1.12–1.91) • After adjusting for hospital size and teaching vs. non-teaching hospitals, the strength of the association increased (adjusted OR, 1.77; CI, 1.30–2.39)	• Intramural protocols are important tools to increase thrombolysis rates for acute ischemic stroke in hospitals • The study was carried out at 12 sites
Jeng JS, et al.[343] 2009 19362319	**Study type**: Multicenter national Taiwan stroke center survey **Size**: Survey sent to 17 medical centers/69 regional teaching hospitals in 2004, and 19 medical centers/97 regional teaching hospitals in 2006	**Inclusion criteria:** Qualified medical centers and regional teaching hospitals in Taiwan **Exclusion criteria:** N/A	**1° end point:** Factors influencing administration of thrombolytic therapy were analyzed **Results**: • The frequency of thrombolytic therapy administration significantly correlated with stroke center criteria (Spearman's rho=0.731, *P*<0.001) • Multivariate analysis showed routine IV alteplase protocol in the ED (OR, 4.6; *P*=0.042) and supervision by the stroke center director OR, 3.7; *P*=0.031) significantly influenced the administration of thrombolytic therapy	Well-organized stroke centers, routine use of thrombolytic therapy protocols in the emergency room, and guidance by a stroke center director are important for enhancing thrombolytic therapy in patients with acute ischemic stroke
Douglas VC, et al.[344] 2005 15699369	**Study type**: Retrospective multicenter study **Size**: N=16,853 patients (34 academic medical centers)	**Inclusion criteria:** Patients admitted with ischemic stroke **Exclusion criteria:** Patients <18 y were excluded from analysis of alteplase	**1° end point:** In-hospital mortality rate **Results**: • None of the 11 major stroke center elements was associated with decreased in-hospital mortality or increased frequency of discharge home • In-hospital mortality rate was 6.3% (n=1062), and 2.4% (n=399) of patients received alteplase	• Four elements predicted increased alteplase use, including written care protocols, integrated EMS, organized EDs, and continuing medical/public education in stroke (each OR>2.0, *P*<0.05) • Use of alteplase also tended to be greater at centers with an

				acute stroke team, a stroke unit, or rapid neuroimaging (each OR>2.0, *P*<0.10)
Asimos AW, et al.[345] 2004 15064210	**Study type**: Retrospective registry review of single community teaching hospital **Size**: N=255	**Inclusion criteria:** • History and physical exam consistent with acute stroke **Exclusion criteria:** • Age≤18 y • Stroke onset >2 h prior to triage And many others	**1° end point:** Descriptive **Results**: • Over a 56-month period, CSP activation occurred 255 times, with 24% (n=60) of patients treated with IV alteplase • Within 36 h of IV alteplase treatment, 10% (NINDS=6%) of patients (n=6) sustained a sICH • Treatment protocol violations occurred in 32% of IV alteplase-treated patients but were not significantly associated with sICH (Fisher's exact test, *P*>0.05) • Three mo after IV alteplase treatment, 60% of patients had achieved an excellent neurologic outcome based on Barthel Index ≥95 (NINDS=52%), while mortality measured 12% (NINDS=17%)	• ED-directed CSPs are a feasible and effective means to screen AIS patients for treatment with thrombolysis • There were multiple study limitations

Abbreviations: aIRR indicates adjusted incidence rate ratio; AIS, acute ischemic stroke; CI, confidence interval; CSP, code stroke protocol; DTN, door-to-needle; ED, emergency department; EMS, emergency medical services; GWTG, American Heart Association's Get with the Guideline; h, hour; IQR, interquartile range; IV, intravenous; min, minutes; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; and sICH, symptomatic intracerebral hemorrhage.
Literature search topic: Increasing alteplast treatment in stroke AND Achieving rapid door-to-needle treatment time in stroke AND Benefit of participation in QI registry

Table X. Randomized Clinical Trials of Level of Agreement Between Central Read and Spoke Radiologists and Hub Neurologists in Interpreting Head Computed Tomography Scans of Stroke Patients Presenting to Telestroke Hospitals

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
Spokoyny I, et al.[44] 2014 23697761	**Aim:** To determine the agreement levels between central read and each of two groups, spoke radiologists and hub vascular neurologists, on head CT scans of stroke patients	**Inclusion criteria:** Acute stroke syndrome **Exclusion criteria:**	**Intervention:** Telemedicine arm: CT interpretation by hub vascular neurologist and central read (n=130)	**1° end point:** Level of agreement between central read and spoke radiologists and hub neurologists in interpreting	Vascular neurologist and spoke radiologist percent agreement with central read in the presence of normal scan (74.6%,77.1%), acute stroke (74.6%,77.9%), ICH (99.2%, 98.5%), SAH	• Low incidence of secondary end points that resulted in less opportunity to assess differences between groups	• Reports from neurologists and spoke radiologists had excellent reliability in identifying radiologic

	Study type: Pooled RCTs **Size:** N=261	Time >12 h, incarceration	**Comparator:** Telephone arm CT interpretation by spoke radiologist and central read (n=131)	head CT scans of stroke patients presenting to telestroke hospitals: overall agreement (95.4%; κ=0.74; 95% CI, 0.59–0.88) **Safety end point:** N/A	(98.5%, 96.9%), subdural hematoma (100%, 100%), tumor (100%, 97.7%), and hyperdense artery (93.8%, 88.5%)	• Bias in favor of the interpreting vascular neurologist	contra-indications to IV alteplase • These pooled findings demonstrated that telestroke evaluation of head CT scans for acute stroke assessments were reliable
Puetz V, et al.[45] 2013 23255831	**Aim:** To determine the reliability and therapeutic impact of standardized cerebral CT evaluation by telestroke neurologists **Study type:** retrospective cohort study of prospectively collected data **Size:** N=536	**Inclusion:** Acute stroke syndrome patients **Exclusion:** NA	NA	NA	The neuroradiologists detected discrepant CT findings in 43 patients (8.0%) that were rated as clinically relevant in 9 patients (1.7%).	Retrospective study design and interpretation bias	Clinically relevant mis-interpretations of the CT scans were rare in an acute telestroke service
Demaerschalk BM, et al.[43] 2012 22984007	**Aim:** To determine the agreement levels between neuroradiologists and each of 2 groups, spoke radiologists and telestrokologists, on baseline brain CT scan of acute stroke patients **Study type:** RCT **Size:** N=54	**Inclusion criteria:** Acute stroke syndrome **Exclusion criteria:** Time >12 h, incarceration	**Intervention:** Telemedicine Arm: CT interpretation by spoke radiologist and hub neuroradiologist (n=27) **Comparator:** Telephone-only Arm: CT interpretation by telestrokologist and	**1° end point:** Level of agreement between central read and spoke radiologists and hub neurologists in interpreting head CT scans of stroke patients presenting to telestroke hospitals: overall	Spoke radiologist and telestrokologist percent agreement with hub neuroradiologist in the presence of normal scan (85%, 89%), acute stroke (81%, 73%), chronic stroke (63%, 85%), edema (78%, 77%), tumor (96%, 100%), hyperdense artery (93%, 92%)	• Small number of subjects • Concern about applicability of the findings to real world of acute head CT interpretation in patients • Bias in favor of the interpreting telestrokologist	In the context of a telestroke network designed to assess patients with acute stroke syndromes, agreement over the presence or absence of radiological contraindication s to IV alteplase was excellent whether the

			neuroradiologist (n=26)	agreement 91.0% **Safety end point:**			comparisons were between a telestrokologist and neuroradiologist or between spoke radiologist and neuroradiologist

Abbreviations: CI indicates confidence Interval; CT, computed tomography; h, hours; ICH, intracerebral hemorrhage; IV, intravenous; N/A, not available; RCT, randomized clinical trial; and SAH, subarachnoid hemorrhage.
Literature search topic: Telestroke and Teleradiology

Table XI. Randomized Clinical Trials Comparing Synchronous Audio Video Telemedicine to Telephone-Only for Acute Ischemic Stroke

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
STRokEDOC Pooled Analysis Demaerschalk BM, et al.[46] 2012 22400970	**Aim:** To assess whether telemedicine or telephone consultation was superior for acute stroke decision making **Study type:** Meta-analysis of RCTs **Size:** N=276	**Inclusion criteria:** Acute stroke syndrome **Exclusion criteria:** Time >12 h, incarceration	**Intervention:** Telemedicine (n=138) **Comparator:** Telephone (n=138)	**1° end point:** Correct thrombolysis decision making**:** 96% vs. 83%, OR, 4.2 (95% CI, 1.7–10.5; *P*=0.002) **Safety end point**: N/A	Alteplase use rate 29% vs. 24% (OR, 1.27; 95% CI, 0.71–2.25; *P*=0.41), 90 d BI 46% vs. 45% (OR, 0.69; 95% CI, 0.41–1.16; *P*=0.167), 90 d mRS 36% vs. 38% (OR, 0.70; 95% CI, 0.41-1.19; *P*=0.201), ICH rate 8% vs. 6% (*P*>0.999)	Underpowered to detect differences in 90 d functional outcome	Pooled analysis supported the hypothesis that telemedicine consultations, compared with telephone only, resulted in more accurate decision making

STRokEDOC AZ TIME Demaerschalk BM, et al.[346] 2010 20431081	**Aim:** To assess the efficacy of telemedicine and telephone consultations for acute stroke decision making **Study type:** RCT **Size:** N=54	**Inclusion criteria:** Acute stroke syndrome **Exclusion criteria:** Time >12 h, incarceration	**Intervention:** Telemedicine (n=27) **Comparator:** Telephone (n=27)	**1° end point:** Correct thrombolysis decision making: 85% vs. 89% (*P*>0.99) **Safety end point**: N/A	• Thrombolytic use rate 30% vs. 30% (*P*>0.99), 90 d BI 59% vs. 58% (*P*=0.77), 90 d mRS 46% vs. 38% (*P*=0.61), ICH rate 4% vs. 0% (*P*>0.99)	Trial was not designed to detect a difference between telemedicine and telephone only modes of consultation	• Not designed to have sufficient power to detect a difference • Feasibility RCT • Technical problems were frequent
STRokEDOC Meyer BC, et al.[347] 2008 18676180	**Aim:** To compare telemedicine to telephone consultations for assessing decision making in acute stroke **Study type:** RCT **Size:** N=222	**Inclusion criteria:** Acute stroke syndrome **Exclusion criteria:** Time >12 h, incarceration	**Intervention:** Telemedicine (n=111) **Comparator:** Telephone (n=111)	**1° end point:** Correct thrombolysis decision making: 98% v 82%, OR: 10.9 (95% CI, 2.7–44.69; *P*=0.0009) **Safety end point:** N/A	• Alteplase use-rate 28% vs. 23% (OR,1.3; 95% CI, 0.7–2.5; *P*=0.4248), 90 d BI (OR, 0.6; 95% CI, 0.4–1.1; *P*=0.1268), 90 d mRS (OR, 0.6; 95% CI, 0.3–1.1; *P*=0.0898), ICH rate 7% vs. 8% (OR, 0.8; 95% CI, 0.1–6.3; *P*=1.0)	• Increase in alteplase use not measured • Absence of placebo comparator, resulting in underestimating the true benefit of telemedicine • Lack of complete reproducibility between telephone practice in "real world" and the trial	• First trial to establish the benefit of telemedicine over telephone specifically for acute medical decision-making • Stopped early for superiority

Abbreviations: BI indicates Barthel Index; CI, confidence interval*;* h, hours; ICH, intracerebral hemorrhage; mRS, modified Rankin Scale; N/A, not available; OR, odds ratio; RCT, randomized clinical trial.
Literature search topic: Telestroke and Teleradiology

Table XII. Nonrandomized Trials, Observational Studies, and/or Registries of Telestroke for Triaging Patients for Endovascular Therapy

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Barlinn J, et al.[49] 2017 27899742	**Study type:** Retrospective review of consecutively collected cases **Size:** N=151 48 (31.8%) patients were transferred after teleconsultation and 103 (68.2%) were primarily admitted to our emergency department.	**Inclusion criteria:** Patients with intracranial large vessel occlusion who underwent endovascular treatment presenting either via telestroke network or directly **Exclusion criteria:** NA	**1° end point:** Baseline characteristics, onset-to-treatment times, symptomatic intracranial hemorrhage, in-hospital mortality, reperfusion (modified Treatment in Cerebral Infarction 2b/3), and favorable functional outcome **Results:** Transferred patients were younger (*P*=0.020), received more frequently intravenous tissue plasminogen activator (*P*=0.008), had prolonged time from stroke onset to endovascular treatment initiation (*P*<0.0001) and tended to have lower rates of symptomatic intracranial hemorrhage (4.2% vs. 11.7%; *P*=0.227) and mortality (8.3% vs. 22.6%; *P*=0.041) than directly admitted patients. Similar rates of reperfusion (56.2% vs. 61.2%; *P*=0.567) and favorable functional outcome (18.8% vs. 13.7%; *P*=0.470) were observed in telestroke patients and those who were directly admitted.	• Telestroke networks may enable delivery of endovascular treatment to selected ischemic stroke patients transferred from remote hospitals that is equitable to patients admitted directly to tertiary hospitals.
Kepplinger J, et al.[47] 2016 27566746	**Study type:** Systematic review and meta-analysis **Size:** 7 studies totaling 1,863 patients	**Inclusion criteria:** studies which evaluate the safety and efficacy of IV thrombolysis (IVT) with tissue plasminogen activator (tPA) delivered through telestroke networks in patients with acute ischemic stroke. **Exclusion criteria:** NA	**1° end point:** functional independence, SICH, mortality **Results:** Symptomatic intracerebral hemorrhage rates were similar between patients subjected to telemedicine-guided IVT and those receiving tPA at stroke centers (risk ratio [RR],1.01; 95% CI, 0.37-2.80; *P*=0.978) with low evidence of heterogeneity (I(2), 37%; *P*=0.189). There was no difference in mortality (RR, 1.04, 95% CI, 0.74-1.48; *P*=0.806) or in functional independence (RR, 1.11; 95% CI, 0.78-1.57; *P*=0.565) at 3 mo between telemedicine-guided and stroke center thrombolysis. No heterogeneity was identified (I(2), 0%; *P*=0.964 and I(2), 52%; *P*=0.123, respectively).	• IV tPA delivery through telestroke networks is safe and effective in the 3-h time window.

Abbreviations: CI indicates confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; and RR, relative risk.
Literature Search: Telestroke and Teleradiology

Table XIII. Nonrandomized Trials, Observational Studies, and/or Registries of Alteplase Decision-Making via Telephone Consultation

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Fong, WC, et al.[48] 2015 25906936	**Study type:** Retrospective Comparative Cohort Study **Size:** N=152	**Inclusion criteria:** Patients with stroke treated with IV alteplase by telephone with teleradiology compared with patients treated by in-person assessment **Exclusion criteria:** N/A	**1° end point:** clinical outcomes, sICH, mortality **Results:** • Excellent clinical outcome achieved by 52% of telephone group vs 43% of the neurologist on-site group (*P*=0.30) • Symptomatic intracranial hemorrhage 4.0% vs 4.9% (*P*=1.0) • Mortality 8.3 vs 11.9% (*P*=0.49)	• Telephone consultation and teleradiology-guided IV alteplase administration appeared safe and effective • Limitations: small sample size, non-randomized design

Table XIV. Nonrandomized Studies Assessing the Impact of Stroke System Quality Improvement Processes

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; 95% CI)	Summary/Conclusion Comment(s)
Ganesh A, et al.[33] 2016 26850979	**Study type:** Retrospective, cohort analysis using Canadian Institute of Health Information's Discharge Abstract Database	**Inclusion criteria:** All patients with stroke (ischemic or hemorrhagic) or TIA admitted to Canadian acute care hospital	**1° endpoint:** Summary statistics used to describe all patient and stroke resource information. Multivariable generalized linear Poisson regression model constructed for 30-day in-hospital mortality included the following predictors: presence or absence of a stroke system, fiscal years of discharge, common prognostic variables (age, sex, stroke type and comorbid conditions). Comparison of adjusted incidence rate ratio (aIRR) for each single fiscal year, estimated from the model, compared provinces with stroke systems of care vs. those without.	• A sustained decrease in 30-day in-hospital mortality over time was identified in Canadian provinces with integrated stroke systems of care compared to provinces without such systems. • These data demonstrate an association between

	(excludes Province of Quebec) from 2003/04 to 2012/13 combined with surveys of stroke care resources in Canadian hospitals in 2009 (n = 309) and 2013 (n = 601). **Size**: Cohort of 319,972 hospitalized stroke/TIA patients.	(excluding Quebec) **Exclusion criteria**: N/A	**Results:** • Overall crude 30-day mortality rate decreased from 15.8% in 2003/04 to 12.7% in 2013/14 in the provinces with stroke care systems, while remaining constant at 14.5% in provinces without such systems. • Relative mortality rate (aIRR) was 0.85 (95% CI, 0.79-0.92) in 2013/14 in provinces with stroke care systems vs those without. • Prior to 2010/11, there was no clear difference in stroke mortality between provinces with or without stroke care systems.	integrated stroke systems of care and population-wide reduction in acute stroke mortality.
Song S, et al.[57] 2016 27079809	**Study type**: Retrospective, observational matched cohort study using difference-in-differences design. Changes in outcomes at hospitals joining GWTG-Stroke program were compared with non-joining matched hospitals.	**Inclusion criteria**: Hospitals implementing GWTG-Stroke between 2003 and 2008 and matched hospitals that did not during the same period. **Exclusion criteria**: N/A	**1° endpoint**: Primary clinical outcomes analyzed functional status; mortality measures; Secondary outcomes included length of stay and readmission measures. **Results:** • Adjusted Comparison of Change (Difference-in-Differences) on Discharge Home/Mortality Outcomes From Run-Up, Early, or Sustained vs Pre Period Between at Get With The Guidelines-Stroke Hospitals vs at Matched Non–Get With The Guidelines-Stroke Hospitals (HR = Hazard Ratio)	• Hospital adoption of the GWTG-Stroke program was associated with improved functional outcomes at discharge and reduced post-discharge mortality.

Discharge home/Mortality Outcomes	RUN-UP			EARLY			SUSTAINED		
	HR	95% CI	*P* value	HR	95% CI	*P* value	HR	95% CI	*P* value

<table>
<tr>
<td></td>
<td><u>Size</u>: Matching algorithm identified 366 GWTG-Stroke adopting hospitals that cared for 88,584 AIS admissions and 366 non-GWTG-Stroke hospitals that cared for 85,401 AIS admissions</td>
<td></td>
<td>
<table>
<tr><td>Discharge Home</td><td>1.07</td><td>1.00-1.14</td><td>.06</td><td>1.08</td><td>1.01-1.16</td><td>0.02</td><td>1.06</td><td>1.00-1.12</td><td>0.06</td></tr>
<tr><td>30d Mortality</td><td>0.97</td><td>0.90-1.05</td><td>0.48</td><td>0.92</td><td>0.86-0.99</td><td>0.04</td><td>0.96</td><td>0.90-1.02</td><td>0.16</td></tr>
<tr><td>1-year Mortality</td><td>1.00</td><td>0.94-1.05</td><td>0.92</td><td>0.89</td><td>0.85-0.95</td><td>0.0001</td><td>0.92</td><td>0.88-0.97</td><td>0.0005</td></tr>
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<tr>
<td>Fonarow GC, et al.[35]
2014
24756513</td>
<td><u>Study type</u>:
Retrospective, observational study with pre-/post-Target:Stroke intervention design using GWTG hospital convenience sample

<u>Size</u>: 71,169 patients with AIS treated with tPA (27,319 pre-intervention period, 43,850 post-intervention period) at 1,030 Get With The Guidelines-</td>
<td><u>Inclusion criteria</u>:
Patients receiving guideline concordant intravenous alteplase at GWTG-Stroke participating hospitals from April 2003 to Sept 2013.

<u>Exclusion criteria</u>: N/A</td>
<td><u>1° endpoint</u>:
No primary endpoint declared. Door-to-needle times for alteplase administration; in-hospital all-cause mortality; discharge status determined.

<u>Results:</u>
• Median DTN time for tPA administration declined from 77 minutes (interquartile range [IQR], 60-98 minutes) during the pre-intervention period to 67 minutes (IQR, 51-87 minutes) during the post-intervention period (P<.001). The DTN times for tPA administration of 60 minutes or less increased from 26.5% (95% CI, 26.0%-27.1%) of patients during the pre-intervention period to 41.3% (95% CI, 40.8%-41.7%) during the post-intervention period (P<.001)

• In-hospital all-cause mortality improved significantly from the pre-intervention to the post-intervention period (9.93% vs 8.25%, respectively; adjusted odds ratio [OR], 0.89; 95% CI, 0.83-0.94; P<.001). Symptomatic intracranial hemorrhage within 36 hours was less likely to occur post-intervention (5.68% vs 4.68%; adjusted OR, 0.83; 95% CI, 0.76-0.91; P<.001) and discharge to home was more frequent (37.6% vs 42.7%; adjusted OR, 1.14; 95% CI, 1.09-1.19; P<.001).</td>
<td>• Implementation of the Target:Stroke quality improvement initiative was associated with improved timeliness of tPA.

• This improvement was associated with lower in-hospital mortality and intracranial hemorrhage, along with an increase in the percentage of patients discharged home.</td>
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	Stroke participating hospitals (52.8% of total)			

Abbreviations: CI indicates confidence interval; HR, hazard ratio; N/A, not available; OR, odds ratio; and RR, relative risk.
Literature search topic: Benefit of participation in QI registry

Table XV. Nonrandomized Trials, Observational Studies, and/or Registries of Computed Tomography and Magnetic Resonance Imaging for Routine Stroke Care

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Wardlaw J, et al.[69] 2014 24791949	**Study type:** Cost-effectiveness of MRI, including DWI, in patients with transient ischemic attack and minor stroke; a systematic review, meta-analysis and economic evaluation; decision-analytic model of stroke prevention including on a 20-y time horizon including nine representative imaging scenarios **Size:** Nine key scanning strategies were assessed in the modelling exercise	**Inclusion criteria:** Patients with a TIA or minor ischemic stroke/stroke mimics presenting within a few hours who are not being treated with statins and antiplatelet drugs **Exclusion criteria:** None provided	**1° end point:** The primary outcome was the incremental cost-effectiveness of MR scanning compared with CT for the whole population **Results:** • Compared with "CT scan all patients" MRI was more expensive and no more cost-effective, except for patients presenting at >1 wk after symptoms to diagnose hemorrhage • "One-stop" CT/MRI angiographic-plus-brain imaging was not cost-effective	• Magnetic resonance with DW-MRI is not cost-effective for secondary stroke prevention for TIA and minor stroke • MRI was most helpful in patients presenting at >1 wk after symptoms if blood-sensitive sequences were used • Rapid specialist assessment, CT brain scanning, and identification of serious underlying stroke causes is the most cost-effective stroke prevention strategy
Brazzelli M, et al.[68] 2009	**Study type:** Review	**Inclusion criteria:** Studies that either compared DW-MRI	**1° end point:** Sensitivity and specificity for detection of acute ischemic stroke	Further well-designed studies without methodological biases, in more representative patient

19821415	**Size:** N=308 patients (8 studies)	and CT in the same patients for detection of ischemic stroke or examined the utility of MRI for detection of hemorrhagic stroke, had imaging performed within 12 h of stroke onset, and presented sufficient data to allow construction of contingency tables **Exclusion criteria:** Studies that focused on patients presenting exclusively with a clinical syndrome suggesting either subarachnoid hemorrhage or isolated intraventricular hemorrhage; studies that: addressed specific anatomical, metabolic, microvascular, or volumetric aspects of stroke; focused on specific technical aspects of CT and MRI; analyzed perfusion versus diffusion imaging differences in patients with acute cerebral ischemia	**Results:** DW-MRI appears to be more sensitive than CT for the early detection of ischemic stroke in highly selected patients; however, the variability in the quality of included studies and the presence of spectrum and incorporation biases render the reliability and generalizability of observed results questionable	samples, with practicality and cost estimates are now needed to determine which patients should undergo MRI and which CT in suspected acute stroke

Wardlaw JM, et al.[70] 2004 15459431	**Study type:** Decision tree representing acute stroke care pathways populated with data from multiple sources; determined the effect of diagnostic information from CT scanning on functional outcome, length of stay, costs, and quality of life during 5 y for 13 alternative CT strategies (varying proportions and types of patients and rapidity of scanning) **Size:** The primary analysis was conducted for a cohort of 1000 patients aged 70–74 y and repeated for 1000 patients aged 60–64 y and 80–84 y in teaching urban and rural general hospitals	**Inclusion criteria:** Data were obtained from many sources including systematic reviews of: (1) the accuracy of clinical diagnosis of stroke; (2) CT scan diagnosis (stroke vs. not stroke and infarct from hemorrhage); (3) antithrombotic drugs for primary treatment and secondary prevention of ischemic stroke and after intracranial hemorrhage; and (4) thrombolysis **Exclusion criteria:** Subarachnoid hemorrhage	**1° end point:** Cost and QALYs **Results:** • The most cost-effective strategy was "scan all immediately" (£9 993 676 and 1982.4 QALYs) • The least cost-effective was "scan patients on anticoagulants and those in a life-threatening condition immediately and the rest within 14 d" (£12 592 666 and 1931.8 QALYs) • "Scan no patients" reduced QALYs (1904.2) and increased cost (£10 544 000)	• Immediate CT scanning is the most cost-effective strategy • For the majority of acute stroke patients, increasing independent survival by correct early diagnosis, ensuring appropriate subsequent treatment and management decisions, reduced costs of stroke and increased QALYs

Abbreviations: CT indicates computed tomography; DWI, diffusion-weighted imaging; h, hour; MRI, magnetic resonance imaging; N/A, not available; QALY, quality-adjusted life year; TIA, transient ischemic attack; and y, year.

Literature search topics: Cost-effectiveness of CT/MRI in acute stroke

Table XVI. Observational Studies of 2016 Door-to-Computed Tomography Times

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Aghaebrahim A, et al.[74] 2017 27048957	**Study type:** Prospective, single-center, observational pre- and post-workflow optimization **Size:** N=286	**Inclusion criteria:** Patients with anterior circulation LVO with baseline CT showing an ASPECTS of ≥6 or mismatch between infarct and threatened but viable brain who were treated with endovascular therapy April 2012 to July 2014 **Exclusion criteria:** No time of onset exclusion	**1° end point:** Door-to-CT **Results:** • Pre-optimization, median 14 min (IQR, 6–28) • Post-optimization, median 11 min (IQR, 5–22)	Median 11-min door-to-CT achieved
Lees KR, et al.[73] 2016 27507856	**Study type:** Pooled analysis of 9 RCTs of IV alteplase **Size:** N=6756	**Inclusion criteria:** Various by trial **Exclusion criteria:** Various by trial	**2° end point:** Time to treatment interaction with benefit **Results:** Treatment initiation within 4.5 h was associated with statistically significant net benefit, 55 patients (95% CI, 13–91) per 1000 treated were better with alteplase (*P*=0.004), with earlier treatment resulting in bigger proportional benefits	The earlier the treatment with IV alteplase, the greater the benefit
Messe SR, et al.[75] 2016 27629092	**Study type:** Multicenter, retrospective analysis of Get With the Guidelines database (2003–2011) **Size:** N=61,698	**Inclusion criteria:** Within 2 h of onset of ischemic stroke **Exclusion criteria:** Documented contraindication to thrombolysis	**1° end point:** Door-to-image time **Results:** • Received alteplase, median 20 min (IQR, 13–30) • Did not receive alteplase, median 40 min (IQR, 23–65)	Median 20-min door-to-image achieved
Rai AT, et al.[348] 2016 26863106	**Study type:** Prospective, single-center, observational	**Inclusion criteria:** Endovascular	**1° end point:** ER to CT **Results:**	Mean 26-min door-to-CT achieved

	pre- and post-workflow optimization **Size:** N=94	patients presenting to ER **Exclusion criteria:** In-house patients undergoing an intervention for stroke, patients undergoing another procedure in the hospital with a stroke and patients treated with unknown symptom onset	Pre-optimization, mean 42±8 min; post-optimization, mean 26±13 min (mean±SD)	
Saver JL, et al.[32] 2016 [27673305](27673305)	**Study type:** Pooled analysis of 5 RCTs of endovascular treatment with second-generation devices **Size:** N=1287	**Inclusion criteria:** Various by trial **Exclusion criteria:** Various by trial	**1° end point:** Degree of disability at 3 mo **Results:** The degree of treatment benefit declined with longer times from symptom onset to expected arterial puncture	The earlier the treatment with mechanical thrombectomy, the greater the benefit
Zaidi SF, et al.[76] 2016 [27342763](27342763)	**Study type:** Prospective, observational before and after EMS training and ED protocols in two hospitals **Size:** N=251	**Inclusion criteria:** All Stroke Alert and RACE alert patients January 1–December 31, 2015 **Exclusion criteria:** >12 h since onset	**1° end point:** Arrival-to-CT **Results:** • Pre-intervention, median 15 min (IQR, 7–17) • Post-intervention, median 8.5 min (IQR, 6–15)	Mean 8.5 min door-to-CT achieved

Abbreviations: ASPECTS indicates Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; ED, emergency department; EMS, emergency medical services; ER, emergency room; h, hours; min, minutes; IQR, interquartile range; IV, intravenous; LVO, large vessel occlusion; N/A, not available; OR, odds ratio; RCT, randomized clinical trial; and SD, standard deviation.

Literature search topic: Door-to-imaging times achievable

Table XVII. Randomized Clinical Trials of Interaction of Baseline Imaging Computed Tomography Hypodensity with Treatment Effect for Intravenous Alteplase

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Charidimou A, et al.[82] 2016 27491738	**Study type**: Meta-analysis of baseline CT in NINDS rt-PA, ECASS I & II, IST-3 **Size:** N=2234	**Inclusion criteria:** For individual trials **Exclusion criteria:** For individual trials	**1° end point:** mRS>2 at 90 d or Oxford Handicap Score at 6 mo **Results:** Statistically significantly lower risk of poor outcome with IV alteplase for patients with leukoaraiosis (OR, 0.75; 95% CI, 0.60–0.95)	Statistically significantly lower risk of poor outcome with IV alteplase for patients with leukoaraiosis (OR: 0.75, 95% CI: 0.60–0.95) in pooled analysis of NINDS rt-PA, ECASS I & II, and IST-3
IST-3 IST-3 Collaborative Group[77] 2015 25819484	**Study type:** Pooled analysis of baseline imaging in NINDS rt-PA, ECASS II, PROACT II, IST-3 **Size:** N=4567	**Inclusion criteria:** For individual trials **Exclusion criteria:** For individual trials	**1° end point:** Good functional outcome **Results:** No statistically significant subgroup difference (*P*=0.94) for IV alteplase effect on functional outcome for ASPECTS subgroups (0–7 vs. 8–10)	No statistically significant subgroup difference (*P*=0.94) for IV alteplase effect on functional outcome for ASPECTS subgroups (0–7 vs. 8–10) in pooled analysis of NINDS rt-PA, ECASS II, PROACT II, IST-3
IST-3 IST-3 Collaborative Group[77] 2015 25819484	**Study type:** Analysis of baseline CT or MRI in IST-3 **Size:** N=3017	**Inclusion criteria:** IST-3 **Exclusion criteria:** ISt-3	**1° end point:** Oxford Handicap Score at 6 mo **Results:** No statistically significant interactions (all *P*>0.20) for IV alteplase with function outcome for: • Acute ischemic change • Swelling • Tissue attenuation change • Lesion size • Old lesions • Leukoaraiosis	No statistically significant interactions (all *P*>0.20) between baseline imaging × effect of IV alteplase in IST-3
NINDS rt-PA Demchuk AM, et al.[78] 2008 18560214	**Study type:** Analysis of baseline CT in NINDS rt-PA Trial **Size:** N=788	**Inclusion criteria:** NINDS rt-PA **Exclusion criteria:** NINDS rt-PA	**1° end point:** mRS 0–1 at 90 d **Results:** Van Swieten Score for leukoaraiosis × IV alteplase interaction: *P*=0.528	No statistically significant interaction (*P*=0.528) between baseline Van Swieten Score for leukoaraiosis × effect of IV alteplase in NINDS rt-PA Trial
ECASS II Dzialowski I, et al.[79]	**Study type:** Analysis of baseline CT in ECASS II	**Inclusion criteria:** ECASS II	**1° end point:** mRS 0–2 at 90 d **Results:** ASPECTS × IV alteplase interaction: *P*=0.29	No statistically significant interaction (*P*=0.29) between baseline

2006 16497977	**Size:** N=603	**Exclusion criteria:** ECASS II		ASPECTS × effect of IV alteplase in ECASS II
NINDS rt-PA Demchuk AM, et al.[80] 2005 16166579	**Study type:** Analysis of baseline CT in NINDS rt-PA Trial **Size:** N=616	**Inclusion criteria:** NINDS rt-PA **Exclusion criteria:** NINDS rt-PA	**1° end point:** Favorable outcome at 3 mo **Results:** ASPECTS × IV alteplase interaction: "no evidence"	No evidence of treatment effect modification by the baseline ASPECTS value in the NINDS rt-PA Stroke Study
NINDS rt-PA Patel SC, et al.[81] 2001 11735758	**Study type:** Analysis of baseline CT in NINDS rt-PA Trial **Size:** N=616	**Inclusion criteria:** NINDS rt-PA **Exclusion criteria:** NINDS rt-PA	**1° end point:** Favorable outcome at 3 mo **Results:** Adjusted early ischemic change × IV alteplase interaction, *P*=0.52	No statistically significant interaction (*P*=0.52) between baseline CT early ischemic change × effect of IV alteplase in NINDS rt-PA Trial

Abbreviations: ASPECTS indicates Alberta Stroke Program Early CT Score; CI, confidence interval; CT, computed tomography; IV, intravenous; MRI, magnetic resonance imaging; N/A, not available; NINDS, National Institute of Neurological Disorders; and OR, odds ratio.
Literature search topic: CT attenuation IV alteplase interaction; CT attenuation IAT interaction

Table XVIII. Randomized Clinical Trials of Interaction of Baseline Computed Tomography Hyperdense Middle Cerebral Artery Sign with Treatment Effect for Intravenous Alteplase

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (P value; OR or RR; & 95% CI)	Summary Conclusions Comments
IST-3 Mair G, et al.[84] 2016 26658907	**Study type:** Analysis of baseline CT in IST3 **Size:** N=2961	**Inclusion criteria:** IST-3 **Exclusion criteria:** IST-3	**1° end point:** Oxford Handicap Score at 6 mo **Results:** No significant interaction with benefit of alteplase, *P*=0.167	No statistically significant interaction *P*=0.167) between baseline HMCAS × effect of IV alteplase in IST-3 Trial
IST-3 IST Collaborative Group[77] 2015 25819484	**Study type:** Analysis of baseline imaging in IST3 **Size:** N=3017	**Inclusion criteria:** IST-3 **Exclusion criteria:** IST-3	**1° end point:** Oxford Handicap Score at 6 mo **Results:** No interaction between hyperattenuated arteries and IV alteplase for function outcome (*P*=0.517)	No statistically significant interaction (*P*=0.517) between baseline hyperattenuated artery × effect of IV alteplase in IST-3 Trial
NINDS rt-PA Qureshi AI, et al.[83] 2006 16636232	**Study type:** Analysis of baseline CT in NINDS rt-PA **Size:** N=616	**Inclusion criteria:** NINDS rt-PA **Exclusion criteria:** NINDS rt-PA	**1° end point:** mRS 0–1, NIHSS 0–1, Barthel Index ≥95, GOS 0–1, death at 90 days	No statistically significant interaction between baseline HMCAS × effect of IV alteplase in NINDS rt-PA Trial (*P*>0.30)

			Results: No statistically significant HMCAS × treatment interaction for any of the four clinical scales or death (all *P*>0.30)	

Abbreviations: CT indicates computed tomography; GOS, Glasgow Outcome Scale; HMCAS, hyperdense middle cerebral artery sign; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and NINDS, National Institute of Neurological Disorders.

Literature search: CT attenuation IV alteplase interaction; Hyperdense MCA IV alteplase interaction

Table XIX. Observational Studies of Interaction of Baseline Magnetic Resonance Imaging of Cerebral Microbleeds with Symptomatic Intracerebral Hemorrhage After Intravenous Alteplase

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
META-MICROBLEEDS Charidimou A, et al.[85] 2016 27629086	**Study type:** Systematic review and analysis of 8 studies **Size:** N=2601	**Inclusion criteria:** 1) Defined and assessed sICH risk or 3- to 6-month functional outcome in patients with acute ischemic stroke treated with IV alteplase thrombolysis and (2) quantified this risk in relation to the presence of CMBs detected on pretreatment MRI scans **Exclusion criteria** Studies of patients treated with endovascular therapies were only included in the post hoc subanalysis; in cases of multiple publications from the same or overlapping cohorts, only the report with the largest sample size was used in the analysis	**1° end point:** sICH **Results:** • sICH with CMBs: 6.1% (38/624) vs. sICH w/o CMBs: 4.4% (87/1977), OR, 2.18; 95% CI, 1.12–4.22	sICH statistically significantly more common in those with CMBs (OR, 2.18; 95% CI, 1.12–4.22) but no more common than in NINDS rt-PA Trial
Tsivgoulis G, et al.[86]	**Study type:** Systematic review	**Inclusion criteria:** Studies of incidence	**1° end point:** sICH	• sICH statistically significantly more common in those with CMBs (OR:

2016 27088650	and analysis of 9 studies **Size:** N=2479	of sICH after IV alteplase in patients with and without cerebral microbleeds on pre-Rx MRI **Exclusion criteria:** IST-3	**Results:** • sICH with CMBs: 6.5% (38/581) vs. sICH w/o CMBs: 4.4% (87/1898), OR, 2.36; 95% CI, 1.21–4.61) • sICH with 1–10 CMBs, 6.1% (21/343) vs. sICH with >10 CMBs, 40% (6/15), OR, 7.01; 95% CI, 3.20–15.38	2.36, 95% CI: 1.21–4.61), but no more common than in NINDS rt-PA Trial • sICH with >10 CMB 40% but occurred only in 15/1808 (0.8%)
NINDS rt-PA Study NINDS rt-PA Study Group[87] 1995 7477192	**Study type:** Randomized, double-blinded controlled trial **Size:** N=624	**Inclusion criteria:** Acute ischemic stroke with treatment possible within 3 h of onset **Exclusion criteria:** NINDS rt-PA	**2° end point:** sICH withni 36 h **Results:** • sICH with alteplase 6.4% • sICH w/o alteplase 0.6%	• sICH 6.4% vs. 0.6%, but still overall clinical benefit at 3 mo

Abbreviations: CI indicates confidence interval; CMB, cerebral microbleed; h, hours; IV, intravenous; MRI, magnetic resonance imaging; NINDS, National Institute of Neurological Disorders; OR, odds ratio; and Rx, treatment; sICH, symptomatic intracerebral hemorrhage; and w/o, without.
Literature search topic: Hyperdense MCA IV alteplase interaction II; Interaction of baseline MRI microbleeds with IV alteplase

Table XX. Randomized Clinical Trials of Intravenous Thrombolytics Employing Multimodal Imaging

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
DIAS 3 Albers GW, et al.[168] 2015 25937443	**Aim:** Assess the safety and efficacy of desmoteplase between 3 h and 9 h after symptom onset in patients with occlusion or high-grade stenosis in major cerebral arteries **Study type:** Phase III RCT **Size:** N=492	**Inclusion criteria:** AIS 3–9 h, 18-85, NIHSS 4–24, occlusion or stenosis of M1, M2, ACA, PCA; mRS 0–1 **Exclusion criteria:** Pre-stroke mRS >1, standard criteria	**Intervention:** IV desmoteplase 90 mcg/kg (n=247) **Comparator:** Placebo (n=245)	**1° end point:** mRS 0–2 at day 90: desmoteplase 51%, placebo 50%; (adjusted OR, 1.20; 95% CI, 0.79–1.81; *P*=0.40) **Safety end point:** SAEs, sICH	• SAEs: desmoteplase 27%, placebo 29% • sICH 3% vs. 2%	N/A	No benefit, no safety concerns

ATTEST Huang X, et al.[89] 2015 25726502	**Aim:** Assess the efficacy and safety of tenecteplase vs. alteplase within 4.5 h of stroke onset in a population not selected on the basis of advanced neuroimaging **Study type:** Phase II RCT **Size:** N=104	**Inclusion criteria:** AIS <4.5 h; baseline CT, CTP, CTA **Exclusion criteria:** Standard criteria	**Intervention:** IV tenecteplase 0.25 mg/kg (n=52) **Comparator:** IV alteplase 0.9 mg/kg (n=52)	**1° end point:** Penumbral salvage: alteplase 68% (23%), tenecteplase 68% (28%), *P*=0.81 **Safety end point:** sICH: tenecteplase 6%, alteplase 8%, *P*=0.59	Recanalization: alteplase 74%, tenecteplase 66%, *P*=0.38	N/A	Not designed to prove imaging selection hypothesis; no difference in neurologic or radiologic outcomes
IST III Wardlaw JM, et al.[349] 2014 25642519	**Aim:** To determine if CT or MR perfusion or angiography (CTP/CTA; MRP/MRA) imaging provide important information to guide the use of rt-PA up to 6 h after a stroke **Study type:** Observational study of IST-3 **Size:** N=151 with perfusion imaging, N=423 with vessel imaging	**Inclusion criteria:** AIS, age≥18 y, <6 h to treatment **Exclusion criteria:** Standard alteplase exclusions	**Intervention:** IV alteplase 0.9 mg/kg (n=NR) **Comparator:** Standard care (NR)	**1° end point:** Oxford Handicap Score 0–2 at 6 mo **Safety end point:** • Hemorrhage • Neither perfusion lesion size nor mismatch modified rt-PA effect on hemorrhage or 6-month outcome. • rt-PA effects did not differ between patients with angiographic occlusion compared with those without	N/A	N/A	No evidence that imaging biomarkers of mismatch or vessel occlusion modified alteplase treatment effects
Parsons M, et al.[91] 2012 22435369	**Aim:** To compare IV tenecteplase vs. IV alteplase enhanced by imaging selection **Study type:** Phase IIB RCT **Size:** N=75	**Inclusion criteria:** AIS <6 h, CTA vessel occlusion **Exclusion criteria:** Standard alteplase exclusions	**Intervention:** IV tenecteplase 0.1 mg/kg (n=25); IV tenecteplase 0.25 mg/kg (n=25) **Comparator:** IV alteplase 0.9 mg/kg (n=25)	**1° end point:** Percent of perfusion lesion reperfused at 24 h: alteplase 55.4±38.7, tenecteplase 79.3±28.8, *P*=0.004; extent of clinical improvement (NIHSS) at 24 h: alteplase 3.0±6.3, tenecteplase 8.0±5.5, *P*<0.001	N/A	N/A	Imaging selection used to identify patients most likely to benefit; not designed to prove selection hypothesis

				Safety end point: Parenchymal hematoma: 4% tenecteplase, 16% alteplase (*P*=0.09)			
DIAS 2 Hacke W, et al.[92] 2009 19097942	**Aim:** Investigate further the clinical efficacy and safety of desmoteplase in patients with AIS who have tissue at risk, as assessed by MR PI–DWI or perfusion CT **Study type:** Phase III RCT **Size:** N=193	**Inclusion criteria:** AIS 3–9 h, 18-85, NIHSS 4-24, 20% diffusion-perfusion mismatch (CT or MRI) **Exclusion criteria:** Pre-stroke mRS>1, standard criteria, ICA occlusion	**Intervention:** Desmoteplase 90 mcg/kg (n=57); desmoteplase 125 mcg/kg (n=66) **Comparator:** Placebo (n=63)	**1° end point:** Day 90 good outcome (composite): 46% placebo, 47% 90 mcg/kg, 36% 125 mcg/kg **Safety end point:** ICH: 3.5% 90 mcg/kg desmoteplase, 4.5% 125 mcg/kg desmoteplase, 0% placebo	N/A	N/A	No benefit vs. placebo; not designed to prove imaging selection hypothesis
EPITHET Davis SM, et al.[93] 2008 18296121	**Aim:** Compare reperfusion and infarct growth measures in patients treated with alteplase vs. placebo 3-6 h from onset **Study type:** Phase II RCT **Size:** N=101	**Inclusion criteria:** AIS 3–6 h, baseline MRI, age≥18 y, NIHSS>4, MRS≤2 **Exclusion criteria:** Inability to undergo MRI, standard alteplase criteria	**Intervention:** IV alteplase 0.9 mg/kg (n=52) **Comparator:** Placebo (n=49)	**1° end point:** Infarct growth in mismatch patients (geometric mean): alteplase 1.24; placebo 1.78; ratio 0.69; 95% CI, 0.38–1.28; *P*=0.239 **Safety end point:** Not reported	• Reperfusion greater in alteplase vs. placebo (*P*=0.001) and associated with better functional outcome (*P*=0.01) • Infarct growth in mismatch patients (geometric mean: reperfusion 0.79; no reperfusion 2.25; ratio 0.35; 95% CI, 0.20–0.63; *P*=0.001	Underpowered for no mismatch group	Failed to demonstrate significantly better outcomes in mismatch treated group vs. other groups

					• Good neurologic outcome in mismatch patients: reperfusion 73%, no reperfusion 27%, *P*<0.0001		
DEDAS Furlan AJ, et al.[94] 2006 16574922	**Aim:** Evaluate safety and efficacy of IV desmoteplase in patients with perfusion/diffusion mismatch on MRI 3 to 9 h after onset of acute ischemic stroke **Study type:** Dose escalation Phase II RCT **Size:** N=37	**Inclusion criteria:** AIS 3–9 h, 18–85 y, NIHSS 4–20, 20% diffusion-perfusion mismatch **Exclusion criteria:** Standard criteria; ICA occlusion	**Intervention:** Desmoteplase 90 mcg/kg (N=14); desmoteplase 125 mcg/kg (N=15) **Comparator:** Placebo (N=8)	**1° end point:** • Reperfusion 4–8 h: 37.5% placebo, 18.2% 90 mcg/kg, 53.3% 125 mcg/kg • Good outcome (composite) at day 90: 25%, 28.6%, 60%; desmoteplase overall vs. placebo (*P*=0.022) **Safety end point:** sICH: none	N/A	N/A	Phase II study not powered for clinical end points; not designed to prove penumbral selection hypothesis
DIAS Hacke W, et al.[95] 2005 15569863	**Aim:** Evaluate safety and efficacy of IV desmoteplase in patients with perfusion/diffusion mismatch on MRI 3 to 9 h after onset of acute ischemic stroke **Study type:** Dose escalation Phase II RCT **Size:** N=104	**Inclusion criteria:** AIS 3–9 h, 18–85 y, NIHSS 4–20, 20% diffusion-perfusion mismatch **Exclusion criteria:** Prestroke mRS of >1, standard criteria	**Intervention:** Part 1: desmoteplase 25 mg (n=17), 37.5 mg (n=13), 50 mg (n=13); Part 2: 62.5 mcg/kg (n=15), 90 mcg/kg (n=15), 125 mcg/kg (n=15) **Comparator:** Placebo Part 1: (n=16); Part 2 (n=11)	**1° end point:** • Reperfusion 4–8 h: up to 71.4% (*P*=0.0012) in desmoteplase vs. 19.2% placebo • Good outcome (composite) at day 90: Part 2: 22.2% placebo, 13.3%–60% desmoteplase **Safety end point:** sICH; Part I: halted due to sICH; part 2: 0% placebo, 2.2% desmoteplase	N/A	Part I: halted due to sICH	Phase II study not powered for clinical end points; not designed to prove penumbral selection hypothesis

Abbreviations: ACA indicates anterior cerebral artery; AIS, acute ischemic stroke; CI, confidence interval; CT, computed tomography; CTA, computed tomography angiography; CTP, computed tomography perfusion; h, hours; ICA, internal carotid artery; IV, intravenous; M1, middle cerebral artery segment 1; M2, middle cerebral artery segment 2; MRI, magnetic resonance imaging; MR PI-DWI, magnetic resonance perfusion imaging–diffusion-weighted imaging; MRP/MRA, magnetic resonance perfusion/magnetic resonance angiography; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NR, not reported; OR, odds ratio; PCA, posterior cerebral artery; RCT, randomized clinical trial; SAEs, serious adverse events; sICH, symptomatic intracerebral hemorrhage; and y, years.

Literature search topic: Multimodal imaging

Table XXI. Nonrandomized Trials, Observational Studies, and/or Registries of Intravenous Thrombolytics Employing Multimodal Imaging

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
DEFUSE Albers GW, et al.[88] 2006 17066483	**Study type:** Single-arm study **Size:** N=74	**Inclusion criteria:** AIS 3–6 h, age ≥18 y, NIHSS>5, MRS≤2, baseline MRI **Exclusion criteria:** Prestroke mRS>2	**1° end point:** FCR **Results:** • FCR in Mismatch with Reperfusion (n=18): 56% (34–75) • FCR in Mismatch without Reperfusion: (n=16): 19% (7–43) • FCR in TM with Reperfusion (n=15): 67% (42-84) • TM without Reperfusion (n=16): 19% (7-43)	• Single-arm study not designed to determine if MRI profiles can identify clinical responders treated with IV alteplase 3–6 h from onset • Single-arm study not designed to prove penumbral selection hypothesis

Abbreviations: AIS indicates acute ischemic stroke; CI, confidence interval; FCR, favorable clinical response; IV, intravenous; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; TM, target mismatch; and y, years

Literature search topic: Multimodal imaging

Table XXII. Nonrandomized Trials, Observational Studies, and/or Registries of Creatinine Testing Prior to Contrast Computed Tomography

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Ehrlich ME, et al.[96] 2016 27364528	**Study type:** Retrospective observational study **Size:** N=289	**Inclusion criteria:** Acute ischemic stroke patients comparing CTA vs. no CTA **Exclusion criteria:** Inpatient acute stroke alerts; missing 24–48 h creatinine value	**1° end point:** Acute kidney injury and time to IV alteplase, mean creatinine **Results:** Mean creatinine at 24–48 h: CTA, 1.06; no CTA, 1.40 (*P*=0.059); acute kidney injury in 5/157 with CTA, 7/132 without CTA (*P*=0.422)	CTA was safe, did not delay IV alteplase, and had added clinical value
Aulicky P, et al.[97] 2010	**Study type:** Retrospective	**Inclusion criteria:** Acute ischemic stroke patients	**1° end point:** Creatinine increase ≥ 44 micromol/l **Results:** 3% in CTA group vs. 4% in control (*P*=0.50)	Contrast agents given for CTA, performed in patients with normal and abnormal creatinine levels,

19965846	observational study with historical control **Size:** N=241	treated with IV alteplase undergoing CTA vs. control group treated with IV alteplase without CTA **Exclusion criteria:** Missing creatinine levels, or no CTA performed		neither caused renal injury nor interfered with the safety of alteplase treatment
Lima FO, et al.[98] 2010 20044502	**Study type:** Prospective observational study with retrospective controls. **Size:** N=918	**Inclusion criteria:** Acute ischemic stroke patients, non-contrast vs. contrast CT exposure **Exclusion criteria:** Dialysis-dependent patients	**1° end point:** 25% increase in creatinine **Results:** 5% in exposed vs. 10% in non-exposed (*P*=0.003); no difference in patients with conventional angiography following CTA/CTP vs. CTA/CTP alone (5% vs. 5%, *P*=0.7)	Administration of a contrast-enhanced CT protocol involving CTA/CTP and conventional angiography in selected patients does not appear to increase the incidence of contrast-induced nephropathy
Hopyan JJ, et al.[99] 2008 18719035	**Study type:** Retrospective observational study **Size:** N=198	**Inclusion criteria:** Acute stroke patients undergoing contrast CT **Exclusion criteria:** GFR<30 ml/min	**1° end point:** Contrast-induced nephropathy within 72 h, chronic kidney disease **Results:** 2.9% developed contrast-induced nephropathy, 0% chronic kidney disease	Prompt CTA/CTP imaging of acute stroke, if indicated, need not be delayed in those with no history of renal impairment.
Krol AL, et al.[100] 2007 17600231	**Study type:** Retrospective observational study **Size:** N=224	**Inclusion criteria:** Acute ischemic stroke patients undergoing CTA within 24 h of onset **Exclusion criteria:** Short-term follow-up creatinine not available	**1° end point:** Radiocontrast nephropathy **Results:** 3% developed radiocontrast nephropathy	Low incidence of radiocontrast nephropathy in acute stroke patients undergoing emergency CTA
Josephson SA, et al.[101] 2005	**Study type:** Retrospective observational study	**Inclusion criteria:** Patients undergoing	**1° end point:** Rise in creatinine ≥0.5	Contrast nephropathy incidence is low in neurovascular patients

[15911820](#)	**Size:** N=1075	stroke protocol CTA and CTP imaging **Exclusion criteria:** No pre- or post-study creatinine	**Results:** 3.7% without hemodialysis dependency had creatinine increase; 0.37% had contrast nephropathy	

Abbreviations: CTA indicates computed tomography angiography; CT, computed tomography; CTP, computed tomography perfusion; GFR, glomerular filtration rate; h, hours; IV, intravenous; and min, minutes.

Literature search topics: Vessel and collateral status imaging

Table XXIII. Randomized Clinical Trials Comparing Endovascular Therapy

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
DEFUSE 3 Albers GW et al.[109] 2018	**Aim:** to test the hypothesis that patients who were likely to have salvageable ischemic brain tissue identified on perfusion imaging and who undergo endovascular therapy 6-16 hours after last known to have been well will have better functional outcomes compared to subjects treated with standard medical therapy. **Study type:** multi-center, prospective, open-label, blinded end-point RCT **Size:** N=182 [Stopped early for efficacy at first interim analysis]	**Inclusion criteria:** Age 18-90 years; NIHSSS ≥ 6; femoral puncture within 6 -16 hours of stroke onset/last known well; pre-morbid mRS2≤2; ICA or M1 occlusion by MRA or CTA AND Target Mismatch Profile on CT perfusion or MRI (ischemic core volume is <70 ml, mismatch ratio is >1.8 and mismatch	**Intervention:** Mechanical thrombectomy with FDA-approved device (n=92) **Comparator:** Medical management according to 2013 AHA/ASA guidelines (n=90)	**1° end point:** mRS shift analysis at 90 d unadjusted OR 2.77; 95% CI, 1.63-4.70; *P*=0.0002 **Safety end point:** Mortality at 90 d: 14% vs 26%; *P*=0.053 sICH: 6.5% vs 4.4%; *P*=0.75	**2° End Point** mRS 0-2 at 90 d: 44.6% % vs 16.7%, Relative risk 2.67; 95% CI 1.60-4.48; *P*< 0.0001 **Subgroup analysis by DAWN eligibility** DAWN eligible (n=112) OR 2.66; 95% CI, 1.36-5.23 Dawn ineligible (n=70)	•Stopped early at first interim analysis, may overestimate treatment effect	•Expands criteria to identify patients who benefit from mechanical thrombectomy after 6 hours

		volume is >15 ml) **Exclusion criteria:** Many, similar to IV alteplase exclusions, including BP > 185/110; treated with tPA >4.5 hours after time last known well; treated with tPA 3-4.5 hours after last known well AND any of the following: age >80, current anticoagulant use, history of diabetes AND prior stroke, NIHSS >25; ASPECT score <6 on non-contrast CT; Significant mass effect with midline shift; acute symptomatic arterial occlusions in more than one vascular territory			OR 2.96; 95% CI, 1.26-6.97			

DAWN Nogueira RG, et al.[108] 2017 29129157	**Aim:** To demonstrate superior functional outcomes at 90 days with stent retriever plus medical management compared to medical management alone in selected patients treated six to 24 hours after last seen well **Study type:** multi-center, prospective, open-label, blinded end-point RCT **Size: N=206** [Stopped early for efficacy at first planned interim analysis]	**Inclusion criteria:** Age ≥18; failed or contraindicated for IV t-PA; NIHSS ≥10; Pre-stroke -mRS 0-1; Time last seen well to Randomization: 6-24h; <1/3 MCA territory by CT or MRI**;** ICA-T and/or MCA-M1 occlusion;-Clinical Imaging Mismatch: A. ≥80 y/o, NIHSS ≥10 + core <21 mL B. <80 y/o, NIHSS ≥10 + core <31 mL C. < 80 y/o, NIHSS ≥20 + core <51 mL **Exclusion criteria:** Many, similar to IV alteplase exclusions, including BP > 185/110	**Intervention:** Mechanical thrombectomy with specified stent retriever (n=107) **Comparator:** Medical management according to respective national guidelines (n=99)	**Co-1° end points:** 90-day disability assessed by utility weighted mRS: 5.5 +/- 3.8 vs 3.4 +/- 3.1, Adjusted Difference 2.0; 95% CI, 1.1-3.0, posterior probability of superiority >0.999 mRS 0-2 at 90 d: 49% vs 13%, Adjusted Difference 33%, 95% CI, 21%-44%, posterior probability of superiority >0.999 **Safety end point:** Mortality at 90 d: 19% vs 18%, *P*=1.00 sICH: 6% vs 3%, *P*=0.50	**Subgroups by time:** 90-day mRS 0-2 • 6-12 hrs 55.1% vs 20.0%, posterior probability of superiority >0.99 • 12-24 hrs 43.1% vs 7.4%, posterior probability of superiority >0.99	•Stopped early at first interim analysis, may overestimate treatment effect •Mostly M1 occlusions: M1 78%/78% ICA 21%/19% M2 2%/3% •Few strokes with witnessed onset: Wake up 63%/47% Unwitnesed 27%/38% Witnessed 10%/14%	•The first RCT evidence of a group identifiable by clinical and imaging criteria who derive benefit from mechanical thrombectomy after 6 hours

ASTER Lapergue B et al.[178] 28763550	**Aim:** To compare efficacy and adverse events using the contact aspiration technique vs the standard stent retriever technique as a first-line endovascular treatment among patients with acute ischemic stroke and large vessel occlusion. **Study Type:** multi-center, open-label, blinded end-point RCT **Size:** N=381	**Major Inclusion Criteria:** Age > 18 years with no upper age limit; Cerebral infarction in the anterior circulation; Occlusion of the anterior circulation proven by CT angiography or MR angiography; With or without previous Intravenous thrombolysis Start of thrombectomy procedure within 6 hours of symptoms onset. **Major Exclusion Criteria:** Occlusion of the cervical carotid artery; mRS > 3 prior to stroke	**Intervention:** first-line contact aspiration (n = 192) **Comparator:** first-line stent retriever (n = 189)	**1° end point:** proportion of patients with mTICI 2b-3 at the end of all endovascular procedures: Contact aspiration 85.4% (n=164) vs stent retriever 83.1% (n=157) (odds ratio, 1.20; 95% CI, 0.68-2.10; *P*=.53; difference, 2.4%; 95% CI, −5.4%-9.7%). **Safety end point:** Symptomatic intracranial hemorrhage at 24 h: Contact aspiration 10/188 vs (5.3%) vs stent retriever 12/188 (6.5%)	•mRS 0-2 at 90 days, •Contact aspiration 82/181 (45.3%) vs stent retriever 91/182 (50.0%); OR 0.83 (95% CI 0.54-1.26) *P*= 0.38 •Difference −4.6% (95% CI, −14.7% to 6.1%)	•Primary end point was technical (successful revasculari-zation after all interventions);trial was not powered to detect a smaller yet potentially clinically important difference between groups. •Given its superiority design to detect a 15% difference in the primary end point, this trial was not designed to establish noninferiority.	•Among patients with ischemic stroke in the anterior circulation undergoing thrombectomy, first-line thrombectomy with contact aspiration compared with stent retriever did not result in an increased successful revasculari-zation rate at the end of the procedure.
THRACE Bracard S, et al.[106] 2016 27567239	**Aim:** To determine whether mechanical thrombectomy in addition to IV thrombolysis improves clinical outcome	**Inclusion criteria:** Age 18–80 y; IV alteplase <4 h; ET <5 h; NIHSS 10–25; ICA, M1,	**Intervention:** ET (n=204) **Comparator:** Standard care -	**1° end point:** mRS 0–2 at 90 d: 53% vs. 42%, *P*=0.028 **Safety end point:**	• TICI 2b/3: 69% • Median time to reperfusion: 250 mins (IQR 210–290)	Study halted early after MR CLEAN results reported; 3 mo mRS non-blinded; long	For patients with acute ischemic stroke due to anterior circulation, proximal large

	in patients with acute ischemic stroke. **Study type:** RCT **Size:** N=414 (halted prematurely)	superior 1/3 basilar **Exclusion criteria:** Cervical ICA occlusion, subocclusive stenosis, BP > 185/110 and many more	IV alteplase (n=208)	• Death: 12% vs. 13%, *P*=0.7 • sICH: 2% vs. 2%, *P*=0.71		duration of trial (5 y) with subsequent protocol evolution	vessel occlusion not selected on the basis of additional imaging criteria endovascular therapy with medical management showed benefit over medical therapy alone
THERAPY Mocco J, et al.[350] 2016 27486173	**Aim:** To determine if benefit from thrombectomy is exclusive to stent retrievers or also includes primary aspiration **Study type:** RCT **Size:** N=108 (halted prematurely)	**Inclusion criteria:** Age ≥18 y, ICA or MCA LVO; NIHSS ≥8, mRS 0–1, CTA thrombus ≥8 mm on thin section CT **Exclusion criteria:** Cervical ICA stenosis, 1/3 of MCA territory hypodensity, and mRS >1 pre-stroke, and many more	**Intervention:** Aspiration thrombectomy + IV alteplase (n=55) **Comparator:** Standard care - IV alteplase (n=53)	**1° end point:** mRS 0–2 at 90 d: 38% vs. 30%, *P*=0.52 **Safety end point:** • Death: 12% vs. 23.9%, *P*=0.18 • sICH: 9.3% vs. 9.7%, *P*=1.0	• TICI 2b/3: 70% • Trend of benefit towards endovascular therapy in pre-specified secondary outcomes	• Study halted early after MR CLEAN results reported • Not powered to meet primary end point • Stent retriever rescue utilized in 13% of patients	First trial evaluating primary aspiration thrombectomy vs. medical management in the treatment of anterior circulation acute ischemic stroke from large vessel occlusion
MR CLEAN Berkhemer OA, et al.[107] 2015 25517348	**Aim:** To determine whether IAT plus usual care would be more effective than usual care alone in patients with a proximal arterial occlusion in the anterior cerebral circulation that could be treated intraarterially	**Inclusion criteria:** Age>18 y, 6 h to IAT, anterior circulation LVO, NIHSS>2 **Exclusion criteria:**	**Intervention:** ET (n=233) **Comparator:** Standard care - IV alteplase (n=267)	**1° end point:** mRS shift analysis at 90 d, adjusted OR, 1.67; 95% CI, 1.21–2.3; mRS of 0–2 in 32.6% vs. 19.1% **Safety end point:** • Death: 21% vs. 22% (*P*=0.75)	• TICI 2b/3: 59% • Median time to reperfusion: 332 min (IQR, 279–394)	• Relatively low reperfusion rates • Low percentage of patients with functional neurological outcome	• First randomized trial to demonstrate benefit of current ET with medical management over medical management

	within 6 h after symptom onset **Study type:** RCT **Size:** N=500	Exclusion of ICA dissection or occlusion at discretion of treating physician, BP > 185/110, and many more		• sICH: 7.7% vs. 6.4% (*P*=0.24)			alone for anterior circulation acute ischemic stroke • Broad inclusion criteria
EXTEND-IA Campbell BC, et al.[105] 2015 [25671797](25671797)	**Aim:** To test whether more advanced imaging selection, recently developed devices, and earlier intervention improve outcomes **Study type:** RCT **Size:** N=70 (halted prematurely)	**Inclusion criteria:** Age ≥18 y, 6 h to groin, complete in 8 h, LVO anterior circulation, mRS 0–1, mismatch on automated perfusion imaging (Tmax threshold 6 s, CBF threshold 30%) **Exclusion criteria:** Carotid dissection, >1/3 MCA hypodensity, BP > 185/110, and many more	**Intervention:** ET (n=35) **Comparator:** Standard care - IV alteplase (n=35)	**1° end point:** • Median reperfusion at 24 h: 100% vs. 37%, adjusted OR, 4.7 (95% CI, 2.5–9) • Decrease in NIHSS of 8 points or NIHSS 0–1 at 3 d: 80% vs. 37%, adjusted OR, 6 (95% CI, 2–18) **Safety end point:** • Death: 9% vs. 20%, adjusted OR, 0.45 (95% CI, 0.1–2.1) • sICH: 0 vs. 6%	• TICI 2b/3: 86% • Median time to reperfusion: 248 min (IQR, 204–277)	• Limited ability to generalize results given homogenous study population with narrow selection parameters, provision of care at tertiary care facilities only and early timeframe presentation and treatment • Study halted early after MR CLEAN results reported • Small patient numbers	Substantial benefit to endovascular therapy in patients with anterior circulation large vessel occlusion ischemic stroke, small ischemic cores randomized after IV alteplase and treated <6 h from onset of symptoms
ESCAPE Goyal M, et al.[104] 2015 [25671798](25671798)	**Aim:** To test whether patients with acute ischemic stroke, who were selected on the basis of results of CT and CTA, would benefit from rapid endovascular treatment involving contemporary endovascular techniques	**Inclusion criteria:** Age>18 y, 12 h to randomization, ICA/MCA LVO, NIHSS>5, Barthel score≥90, ASPECTS>6, CT collateral	**Intervention:** ET (n=150) **Comparator:** Standard care ± IV alteplase (n=165)	**1° end point:** mRS shift analysis at 90 d; adjusted OR, 3.1 (95% CI, 2–4.7) **Safety end point:** • Death: 10.4% vs. 19%; adjusted rate ratio, 0.5 (95% CI, 0.3–0.8)	• TICI 2b/3: 72% • Median time to reperfusion: 241 min (IQR, 176–359) • Median time CT to groin puncture: 51 min (IQR, 39–68)	• Screening logs not required • Small numbers of patients in 6- to 12-h treatment window • Study halted early after MR	• Emphasized process improvement to maximize treatment effect in patients selected based on collateral assessment of core and

	Study type: RCT **Size:** N=316 (halted prematurely)	score good or intermediate on multiphase CTA **Exclusion criteria:** ASPECTS≤6, and many more		• sICH: 3.6% vs. 2.7%; adjusted rate ratio, 1.2 (95% CI, 0.3–4.6)	• Mortality: 10.4% endovascular vs. 19% medical (*P*=0.04)	CLEAN published	penumbral tissue • Only recent trial to show mortality benefit from endovascular therapy
REVASCAT Jovin TG, et al.[102] 2015 25882510	**Aim:** To assess the safety and efficacy of thrombectomy for the treatment of acute ischemic stroke in a trial embedded within a population-based acute ischemic stroke reperfusion registry **Study type:** RCT **Size:** N=206 (halted prematurely)	**Inclusion criteria:** Age 18–80 (85) y, 8 h to groin, LVO ICA/M1, NIHSS ≥6, mRS 0–1 **Exclusion criteria:** ASPECTS<7 on CT or <6 on MRI, BP > 185/110, and many many more	**Intervention:** ET (n=103) **Comparator:** Standard care - IV alteplase (n=103)	**1° end point:** mRS shift analysis at 90 d (mRS 5 and 6 combined), adjusted OR, 1.7 (95% CI, 1.05–2.8) **Safety end point:** • Death: 18% vs. 16%; adjusted risk ratio, 1.2 (95% CI, 0.6–2.2) • sICH: 2% vs. 2%; adjusted risk ratio, 1.0 (95% CI, 0.1–7)	• TICI 2b/3: 66% • Median time to reperfusion: 355 min (IQR, 269–430)	• Study halted early after MR CLEAN results reported • Small numbers of patients in 6- to 8-h treatment window • Screening logs not available	For patients with acute ischemic stroke due to anterior circulation, proximal large vessel occlusion without large core on CT imaging and treated within 8 h of onset, endovascular therapy with medical management showed benefit over medical therapy alone
SWIFT-PRIME Saver JL, et al.[103] 2015 25882376	**Aim:** To establish the efficacy and safety of rapid neurovascular thrombectomy with the stent retriever in conjunction with IV alteplase vs. IV alteplase alone in patients with acute ischemic stroke **Study type:** RCT	**Inclusion criteria:** Age 18–80 y, 6 h to groin puncture, ICA/M1 LVO, target mismatch profile on imaging with RAPID or local perfusion software, NIHSS 8–29, mRS 0–1	**Intervention:** ET (n=98) **Comparator:** Standard care - IV alteplase (n=98)	**1° end point:** mRS shift analysis at 90 d (mRS 5 and 6 combined), *P*<0.001 **Safety end point:** • Death: 9% vs. 12%, adjusted rate ratio: 0.74 (95% CI, 0.33–1.68) • sICH: 0 vs. 3%	• Functional independence at 90 d: 60% endovascular vs. 35% medical (*P*<0.001) • TICI 2b/3: 88% • Median time to reperfusion: 332 min (IQR, 279–394)	• Limited ability to generalize results given homogenous study population with narrow selection parameters, provision of care at tertiary care facilities only and workflow and process	Substantial benefit to endovascular therapy in patients with anterior circulation LVO ischemic stroke; small ischemic cores randomized after IV alteplase and

	Size: N=196 (halted prematurely)	**Exclusion criteria:** Inability to receive IV alteplase, cervical dissection or complete occlusion requiring stenting, CT ASPECTS<6, BP > 185/110 and many more			• Reperfusion at 24 h: 83% endovascular vs. 40% medical management (*P*<0.001)	development as part of protocol • Study halted early after MR CLEAN results reported • CT or MRI mismatch for selection of first 71 patients, then only ASPECTS≥6 for the next 125	treated <6 h from onset of symptoms
IMS-III Broderick JP, et al.[351] 2013 23390923	**Aim:** To test the approach of IV alteplase followed by protocol-approved endovascular treatment, as compared with standard IV alteplase **Study type:** RCT **Size:** N=656	**Inclusion criteria:** Age18–82 y; 3 h to IV alteplase; 5 h to ET; NIHSS≥10 or 8–9 with occlusion; mRS 0–2 **Exclusion criteria:** Inability to receive alteplase, hypodensity >1/3 of MCA territory, and many more	**Intervention:** IAT (n=434) **Comparator:** Standard care - IV alteplase (n=222)	**1° end point:** mRS 0–2 at 90 d: 40.8% vs. 38.7%; adjusted difference: 1.5% (95% CI, -6 to 9) **Safety end point:** • Death: 19.1% vs. 21.6% (*P*=0.52) • sICH: 6.2% vs. 5.9% (*P*=0.83)	• TICI 2b/3: 41% • Mean time to reperfusion: 325±52 min	• Limited use of newer-generation, more efficient thrombectomy devices • Evolving protocol during the duration of the study (addition of CTA, newer thrombectomy devices) • Reduced dose of IV alteplase (two-thirds) for endovascular patients	Trial halted due to futility; no outcome benefit to endovascular therapy with medical therapy over medical therapy alone
SYNTHESIS Expansion Ciccone A, et al.[352] 2013 23387822	**Aim:** To investigate whether endovascular treatment, including the options of a mechanical device and intraarterial alteplase, is more effective than the currently	**Inclusion criteria:** Age 18–80 y; 6 h to ET, NIHSS≤25, mRS 0–1	**Intervention:** ET with IA drug, device, both (n=181)	**1° end point:** mRS 0–1 at 3 mo: 39% vs. 34.8%, adjusted OR, 0.71; 95% CI, 0.44–1.14 **Safety end point:**	• No secondary outcome differences between groups	• Limited use of newer-generation, more efficient thrombectomy devices	No benefit to endovascular therapy with medical management over medical therapy alone in

	available treatment with IV alteplase **Study type:** RCT **Size:** N=362	**Exclusion criteria:** Hemorrhage on initial imaging	**Comparator:** IV alteplase (n=181)	• Death: 14.4% vs. 9.9% (*P*=0.22) • sICH: 6% vs. 6% (*P*=0.53)		• No reperfusion rates reported • Vessel occlusion not a prerequisite for treatment selection (3/181 endovascular pts not treated because of no occlusion)	a broadly selected patient group with anterior circulation acute ischemic stroke
MR RESCUE Kidwell CS, et al.[353] 2013 23394476	**Aim:** To determine whether brain imaging can identify patients who are most likely to benefit from therapies for acute ischemic stroke and whether endovascular thrombectomy improves clinical outcomes **Study type:** RCT **Size:** N=118	**Inclusion criteria:** Anterior circulation LVO <8 h; favorable penumbral multimodal imaging for stratification (favorable defined as core <90 cc, or <70% of volume of tissue at risk) **Exclusion criteria:** Cervical artery occlusion, severe stenosis or dissection, inability to process imaging by study software, and many more	**Intervention:** ET (n=64) **Comparator:** Standard care ± IV alteplase) (n=54)	**1° end point:** Mean mRS at 90 d: 3.9 vs. 3.9, *P*=0.99 **Safety end point:** • Death: 19% vs. 24% (*P*=0.75) • sICH: 5% vs. 4% (*P*=0.24)	• TICI 2b/3: 27% • No difference in infarct growth or final infarct volume between groups • No benefit in favorable penumbra group	• No use of newer-generation, more efficient thrombectomy devices • Long trial duration (8 y) • Relative delays to groin puncture from imaging acquisition	Trial showed no benefit from endovascular therapy with medical management compared to medical management alone after treatment selection based on penumbral imaging

TREVO 2 Nogueira RG, et al.[354] 2012 22932714	**Aim:** To compare efficacy and safety of the Trevo Retriever with its US FDA-cleared predecessor, the Merci Retriever **Study type:** RCT **Size:** N=178	**Inclusion criteria:** Age 18–85 y, anterior circulation LVO <8 h, NIHSS 8–29 **Exclusion criteria:** Exclusions for IV alteplase, excessive tortuosity, proximal cervical stenosis, >1/3 MCA hypodensity, and many more	**Intervention:** Trevo thrombectomy (n=88) **Comparator:** Merci thrombectomy (n=90)	**1° end point:** TICI scale 2/3: 86% vs. 60%; OR, 4.22; 95% CI, 1.92–9.69 **Safety end point:** • Death 33% vs. 24% (*P*=0.18) • sICH 7% vs. 9% (*P*=0.78)	mRS 0–2 at 90 d: 40% vs. 22%, OR, 2.39; 95% CI, 1.16–4.95	• Did not compare to aspiration systems or other stent retrievers • No tandem carotid occlusions included	Demonstrated the superiority of Trevo stent retrievers over early-generation devices for thrombectomy
SWIFT Saver JL, et al.[355] 2012 22932715	**Aim:** To compare the efficacy and safety of Solitaire with the standard, predicate mechanical thrombectomy device, the Merci Retrieval System **Study type:** RCT **Size:** N=113	**Inclusion criteria:** Age 22–85 y, anterior circulation LVO <8 h, NIHSS 8–30, ineligible for/failure to respond to IV alteplase **Exclusion criteria:** Infarct >1/3 of MCA territory, and many more	**Intervention:** Solitaire thrombectomy (n=58) **Comparator:** Merci thrombectomy (n=55)	**1° end point:** TIMI scale 2/3 without sICH: 61% vs. 24%; OR, 4.87; 95% CI, 2.14–11.1 **Safety end point:** • Death: 17% vs. 38% (*P*=0.02) • sICH: 2% vs. 11% (*P*=0.057)	mRS 0–2 at 90 d: 58% vs. 33%; OR, 2.78; 95% CI, 1.25–6.22	• Did not compare to aspiration systems or other stent retrievers • Halted early, which limited precision of treatment effect estimates • No tandem carotid occlusions included	First acute ischemic stroke trial to randomize one endovascular technique for reperfusion against another; demonstrated the superiority of Solitaire stent retriever over early generation devices for thrombectomy
MELT Ogawa A, et al.[356] 2007 17702958	**Aim:** To determine the safety and clinical efficacy of intraarterial infusion of urokinase in patients with	**Inclusion criteria:** 20–75, NIHSS ≥5 <23, mRS 0–2,	**Intervention:** IAT urokinase (n=57)	**1° end point:** mRS 0–2 at 90 d: 49.1% vs. 39%; OR, 1.54; 95% CI, 0.73–3.23; *P*=0.345	TIMI 2/3: 73% (extrapolated mTICI 2b/3: 53%)	• Comparator group not contemporary medical acute	Multicenter randomized trial assessing endovascular thrombolysis

	acute ischemic stroke within 6 h of onset **Study type:** RCT **Size:** N=114	initiation of IAT within 6 h **Exclusion criteria:** High intracranial hemorrhage risk, NIHSS>22, and many more	**Comparator:** Control (n=57)	**Safety end point:** • Death: 5.3% vs. 3.5% (*P*=1.0) • ICH <24 h: 9% vs. 2% (*P*=0.21)		ischemic stroke therapy • Study halted early after IV alteplase approved in Japan • Not powered to meet primary end point	terminated early and therefore unable to meet primary end point
PROACT II Furlan A, et al.[357] 1999 10591382	**Aim:** To determine efficacy and safety of IA pro-urokinase in acute ischemic stroke <6 h in MCA occlusion **Study type:** RCT **Size:** N=180	**Inclusion criteria:** 18–85 y; NIHSS≥4–30 (except isolated aphasia, hemianopia) **Exclusion criteria:** High intracranial hemorrhage risk, NIHSS>30, and many more	**Intervention:** 9 mg IA pro-urokinase + heparin (n=121) **Comparator:** Heparin (n=59)	**1° end point:** mRS 0–2 at 90 d: 40% vs. 25%, *P*=0.04 **Safety end point:** • Death: 25% vs. 27% (*P*=0.8) • sICH: 10% vs. 2% (*P*=0.06)	TIMI 2/3: 66% in pro-urokinase group vs. 18% in controls on 2 h angiogram (*P*<0.001)	Comparator group not contemporary medical acute ischemic stroke therapy	Original multicenter randomized trial showing clinical efficacy of IA intervention (thrombolysis) in patients with acute MCA ischemic stroke <6 h duration

Abbreviations: ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CBF, cerebral blood flow; CI, confidence interval; CT, computed tomography; CTA, computed tomographic angiography; ET, endovascular therapy; h, hours; IA, intra-arterial; IAT, intra-arterial therapy; ICA, internal carotid artery; ICH, intracerebral hemorrhage; IQR, interquartile range; IV, intravenous; LVO, large vessel occlusion; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin Score; mTICI, modified thrombolysis in cerebral infarction; N/A, not available; NIHSS, National Institute of Health Stroke Scale; OR, odds ratio; RCT, randomized clinical trial; sICH, symptomatic intracerebral hemorrhage; TICI, thrombolysis in cerebral infarction; TIMI, thrombolysis in myocardial infarction; Tmax, time-to-maximum; US FDA, United States Food and Drug Administration; y, years.

Literature search topic: Hypotension AND Endovascular interventions

Table XXIV. Nonrandomized Trials, Observational Studies, and/or Registries of Collateral Status

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
MR CLEAN Berkhemer OA, et al.[110] 2016	**Study type:** Secondary analysis of CTA collateral	**Inclusion criteria:** MR CLEAN patients with CTA and ICA, M1, or M2 occlusion	**1° end point:** CTA collateral status (4-point scale ranging from 0 for absent collaterals and 3 for good collaterals with 100% filling of the occluded territory) and adjusted common OR for shift in mRS	The benefit of intra-arterial therapy was greatest in patients with good collaterals; treatment benefit appeared less and may be absent in

[26903582]	status from MR CLEAN RCT **Size:** N=493	**Exclusion criteria:** N/A	**Results:** Collateral status (CTA) modified treatment effect (*P*=0.038); common OR: grade 3, 3.2 (1.7–6.2); grade 2, 1.6 (1.0–2.7); grade 1, 1.2 (0.7-2.3); grade 0, 1.0 (0.1–8.7)	patients with absent or poor collaterals
IMS III Menon BK, et al.[111] 2015 [25791716]	**Study type:** Secondary analysis of CTA collateral status from IMS III RCT **Size:** N=185	**Inclusion criteria:** IMS III patients with CTA and M1/ICA occlusion **Exclusion criteria:** Incomplete CTA coverage, unavailable scans, or poor image quality	**1° end point:** CTA collateral status **Results:** Collateral status was a significant predictor of all clinical outcomes (*P*<0.05); maximal benefit with intermediate collaterals, some benefit with good collaterals; modification of treatment effect was not observed (limited power due to small number of patients noted)	Baseline CTA collaterals appear to be a robust determinant of final clinical outcome

Abbreviations: CTA indicates computed tomography angiography; ICA internal carotid artery; M1/ICA, middle cerebral artery segment; OR, odds ratio; and RCT, randomized clinical trial.
Literature search topic: Vessel and collateral status imaging

Table XXV. Nonrandomized Trials, Observational Studies, and/or Registries of Chest Radiography in Patients with Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Saber H, et al.[112] 2016 [27412145]	**Study type:** Secondary analysis of data from IMS-III **Size:** N=615	**Inclusion criteria:** IMS-III who had data recorded on pefromance of CXR on the initial evaluation **Exclusion criteria:** IMS-III, did not originally present to facility providing IV alteplase	**1° end point:** Door-to-needle time **Results:** Patients with CXR done before treatment (n=243) had longer mean door-to-needle times than those who did not (n=372); 75.8 vs 58.3 minutes, *P*=0.0001. **2° end point:** 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.	The benefit of intra-arterial therapy was greatest in patients with good collaterals; treatment benefit appeared less and may be absent in patients with absent or poor collaterals

Abbreviations: CXR indicates chest X-ray

Table XXVI. Randomized Clinical Trials Comparing Supplemental Oxygen

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
SO_2S Roffe, et al.[113] 2017 28973619	**Aim:** to determine whether low-dose oxygen therapy during the first 3 days after an acute stroke improves outcome compared with usual care (oxygen only when needed) **Study type:** RCT with blinded **1° end point assessment** **Size:** N=8003	**Inclusion criteria:** clinical diagnosis of acute stroke within 24 hours of hospital admission **Exclusion criteria:** Indications or contraindiactions for O_2	**Intervention:** O_2 at 3 L/min if baseline saturation was 93% or below or at of 2 L/min if baseline saturation was greater than 93%. (1) continuous oxygen for 72 h (n=2668); (2) nocturnal oxygen only for 3 nights (n=2667) **Comparator:** No O_2 (n=2668)	**1° end point:** Ordinal mRS at 90 d was similar among groups: unadjusted OR for a better outcome was 0.97; 95% CI, 0.89-1.05; *P* = .47; for oxygen vs control, and 1.03; 95% CI, 0.93-1.13; *P* = .61; for continuous vs nocturnal oxygen. **Safety end point:** No oxygen related adverse events	No subgroup could be identified that benefited from oxygen	• Includes some participants with ICH (7.3%), stroke mimics (3.6%) or transient ischemic attacks (2.1%) •**1° end point** assessed by postal questionnaire and supported by telephone interviews with nonresponders	Among nonhypoxic patients with acute stroke, the prophylactic use of low-dose oxygen supplementation did not reduce death or disability at 3 months. These findings do not support low-dose oxygen in this setting.
SOS Ali K, et al.[358] 2014 23755093	**Aim:** Supplemental O_2 to prevent hypoxia **Study type:** Randomized single-blind pilot study **Size:** N=289	**Inclusion criteria:** Acute stroke **Exclusion criteria:** Indications for O_2	**Intervention:** 2 L O_2 by NC if baseline O_2 >93% or 3 L NC if baseline O_2 <93% for 72 h (n=148)	**1° end point:** Ordinal mRS at 6 mo was similar among groups (1.04 [0.67–1.60]; *P*=0.86)	Barthel Index at 6 mo trended worse in patients who received O_2 (1.50 [0.94–2.37]; *P*=0.09)	• Includes some participantswith ICH • SaO_2 was not continuously monitored	No clear benefit to supplemental O_2, and maybe some harm

			Comparator: No O_2 (n=141)	**Safety end point:** N/A		• Larger study is underway	
SPOTRIAS Singhal AB, et al.[359] 2013 Link to article	**Aim:** Benefit of O_2 **Study type:** RCT **Size:** N=85	**Inclusion criteria:** AIS <9 h and NIHSS >4 **Exclusion criteria:** Use of alteplase; need for >3 L/min oxygen to maintain SaO_2 >92%; NYHA Class III heart failure	**Intervention:** Supplemental O_2 (n=43) **Comparator:** Room air (n=42)	**1° end point:** Change in NIHSS at 0–4 h: no difference **Safety end point:** 0–24 h change in NIHSS: no difference between groups	• Percent lesion growth at 3 mo • Tissue reperfusion and % mismatch lost were all similar •SAEs, brain hemorrhage and brain edema were all similar	Imbalance in stroke severity in treated groups; no difference if controlled for comorbidities	Study stopped early by DSMB and published only as an abstract
SOS pilot study Roffe C, et al.[360] 2011 21625533	**Aim:** Effect of oxygen within 24 h on 7-day outcomes **Study type:** Single-blind RCT **Size:** N=148 vs. N=141	**Inclusion criteria:** Acute stroke admitted within the preceding 24 h **Exclusion criteria:** Recognized need for oxygen or contraindication for oxygen	**Intervention:** Oxygen supplementation via NC for 72 h (n=148) **Comparator:** Room air (n=141)	**1° end point:** Similar NIHSS at 1 wk; oxygen-treated patients had more improvement in NIHSS at 7 d; more oxygen-treated patients had at least a 4-point improvement in NIHSS (OR, 2.9; 95% CI, 1.59–5.4) **Safety end point:** N/A	There were no differences in physiologic parameters (BP and HR) between groups	Supplemental oxygen did not prevent desaturations	Patients with supplemental oxygen appeared to have greater improvement in NIHSS over the first wk, but the absolute NIHSS did not differ between groups
Roffe C, et al.[361] 2010 20123224	**Aim:** Study the effects of supplemental oxygen at night on oxygen saturation	**Inclusion criteria:** RX within 72 h	**Intervention:** 2 L/min oxygen at night (n=30)	**1° end point:** Nocturnal oxygen supplementation increased the	There were no differences in physiologic	Supplemental oxygen did not prevent desaturations	Supplemental oxygen prevents desaturations, but there is no

	Study type: RCT **Size:** N=63 (59 with actual stroke)	**Exclusion criteria:** Definite need for oxygen	**Comparator:** Room air (n=33)	mean nocturnal oxygen by 2.5% and decreased desaturations by 1.3% **Safety end point:** N/A	parameters (BP and HR) between groups		clinical correlate in this study
Singhal AB, et al.[362] 2005 15761201	**Aim:** Evaluate high flow O_2 in those with acute stroke with diffusion perfusion mismatch **Study type:** RCT **Size:** N=16	**Inclusion criteria:** RX within 12 h; diffusion perfusion mismatch **Exclusion criteria:** COPD, need for >3 L/min to maintain SaO_2 >95%, medical instability, inability to obtain MRI	**Intervention:** High-flow O_2 by face mask (n=9) **Comparator:** Room air (n=7)	**1° end point:** No difference in stroke scale scores at 3 mo; transient improvements in MRI in hyperoxia-treated patients **Safety end point:** N/A	24-h MRIs showed petechial hemorrhages in 50% of hyperoxia-treated patients vs. 17% of controls (NS)	Very small pilot study	Study too small to say anything
Ronning OM, et al.[363] 1999 10512903	**Aim:** Supplemental oxygen (100%) vs. no supplemental oxygen **Study type:** Quasi-randomized RCT **Size:** N=550	**Inclusion criteria:** RX within 24 h of stroke onset **Exclusion criteria:** Age<60 y	**Intervention:** 3 L oxygen via NC for 24 h (n=292) **Comparator:** No supplemental oxygen (or NC) (n=258)	**1° end point:** 1-y survival: no differences between groups Scandinavian stroke scale and BI at 7 mo: no difference between groups **Safety end point:** N/A	• For those with minor strokes, oxygen use was associated with decreased 1-y survival (0.45 [0.23–0.90]; *P*=0.02) • Trend towards worse BI at 7 mo (*P*=0.07)	Not all patients (11%) allocated to treatment received oxygen for the full 24 h, implying that oxygen therapy may be even worse than the data suggest	No clear benefit to supplemental oxygen, and maybe some harm

Abbreviations: AIS, indicates acute ischemic stroke; BP, blood pressure; BI, Barthel Index; COPD, chronic obstructive pulmonary disease; DSMB, data safety and monitoring board; h, hours; HR, heart rate; ICH, intracerebral hemorrhage; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; N/A, not available; NC, nasal cannula; NIHSS, National Institutes of Health Stroke Scale; NS, not significant; NYHA, New York Heart Association; OR, odds ratio; RCT, randomized clinical trial; RX, treatment; SAE, serious adverse event; SaO_2, oxygen saturation; and y, year.
Literature search topic: Oxygen supplementation

Table XXVII. Nonrandomized Trials, Observational Studies, and/or Registries of Hyperbaric Oxygen

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary Endpoint and Results (P values; OR or RR; & 95% CI)	Summary/Conclusion Comment(s)
Heyboer M, et al.[115] 2017 28616361	**Study type:** Review of side effects of HBO **Size:** NA	**Inclusion criteria:** Review of HBO studies **Exclusion criteria:** N/A	**1° endpoint:** Side-effects **Results:** • Middle ear barotrauma is the most common complication – reported rates vary drastically but a recent review suggests it may be as common as 43%. • Other side effects include sinus/paranasal barotrauma, dental barotrauma, pulmonary barotrauma, increased BP, claustrophobia and seizures.	• HBO therapy is associated with a number of potential side effects • Review; no primary data
Heyboer M, et al.[116] 2014 25558546	**Study type:** retrospective chart review **Size:** 931 patients undergoing 23,328 treatments	**Inclusion criteria:** any patient undergoing HBO treatment at a university hospital and an outpatient center for any indication **Exclusion criteria:** N/A	**1° endpoint:** frequency of seizures **Results:** Seizures occurred at a rate of 1/2121 treatments (5/10,000) and were more common at higher pressures – 0/16,430 at 2.0 atm, 1/669 at 2.4/2.5 atm and 1/197 at 2.8 atm ($P<0.001$)	• HBO therapy is associated with an increased risk of seizures, with the risk being greater at higher pressures • Retrospective chart review in a cohort of patients undergoing HBO therapy, but not for stroke
Bennett MH, et al.[114] 2014 25387992	**Study type:** Cochrane review of RCTs	**Inclusion criteria:** Pooled analysis of HBO RTCs for AIS	**1° endpoint:** death at 3-6 months **Results:**	• There is no evidence that HBO therapy improves outcome in AIS, although the possibility of clinical benefit has not been excluded.

	Size: 11 RCTs with 705 patients	**Exclusion criteria:** N/A	• No difference in case fatalities at 6 mo for those receiving HBO compared with controls (RR, 0.97; 95% CI, 0.34-2.75; *P*=0.96) • 4/14 measures of disability/functional outcome showed some benefit to HBO therapy	• Methodologies of trials differed making pooled analysis of outcomes other than fatality difficult.

Abbreviations: CI indicates confidence interval; HBO, hyperbaric oxygen; HR, hazard ratio; N/A, not available; OR, odds ratio; RCT, randomized clinical trial; and RR, relative risk.
Literature search topic: HBO

Table XXVIII. Nonrandomized Trials, Observational Studies, and/or Registries of Hypotension and Hypovolemia

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Visvanathan A, et al.[125] 2015 26329401	**Study type:** Cochrane systematic review **Size:** N=2351 participants (12 studies)	**Inclusion criteria:** Randomized trials of parenteral fluid regimens in adults with ischemic or hemorrhagic stroke within 7 d of onset that reported death or dependence **Exclusion criteria:** Quasi-randomized, non-randomized, and cross-over trials	**1° end point:** Death or dependence at follow-up **Results:** • Odds of death or dependence were similar (OR, 0.97; 95% CI, 0.79–1.21) • Pulmonary edema was more common in participants allocated to colloids (OR, 2.34; 95% CI, 1.28–4.29) and a higher risk of cerebral edema (OR, 0.20; 95% CI, 0.02–1.74) and pneumonia (OR, 0.58; 95% CI, 0.17–2.01) was observed with crystalloids • Clinically important benefits or harms could not be excluded • There was no evidence to guide volume, duration, or mode of parenteral fluid delivery	• No evidence that colloids were associated with lower odds of death or dependence in the medium term after stroke compared with crystalloids • No evidence to guide the best volume, duration, or mode of parenteral fluid delivery for people with acute stroke
Wohlfahrt P, et al.[117] 2015 25380168	**Study type:** Consecutive patients, Observational **Size:** N=532	**Inclusion criteria:** • Consecutive hospitalized patients <81 y with symptoms more than 24 h (unless thrombolytic therapy was applied) • Only patients with CT or MRI excluding hemorrhagic stroke	**1° end point:** Total mortality, median follow-up was 66 wk **Results:** • Admission MBP<100 mmHg had a higher risk of death than those with MBP between 100–110 and 110–121 mmHg, whereas the risk of mortality did not differ from the group with admission MBP>122 mmHg • Similarly, patients with discharge SBP<120 mmHg had an increased risk of death as compared to groups with SBP between 120–130 and 130–141 mmHg, whereas the risk of death was similar to that with discharge SBP>141 mmHg	Among patients hospitalized for their first-ever ischemic stroke, the risk of all-cause death is significantly increased in those with admission MB*P*<100 mmHg and discharge SBP<120 mmHg, even after adjustments for other confounders

		Exclusion criteria: Admission and discharge BP value unavailable		
Muscari A, et al.[124] 2013 [23561704](23561704)	**Study type:** Observational **Size:** N=252	**Inclusion criteria:** Patients with ischemic stroke admitted to the stroke unit within 24 h from onset of symptoms **Exclusion criteria:** Undergoing systemic thrombolysis	**1° end point:** Improvement defined as a difference between initial and final assessment (ΔNIHSS) ≥2 points **Results:** Among 27 patients with average SBP≤118 mmHg, 21 improved (77.8%) vs. 100 of 225 patients with average SBP>118 mmHg (44.4%; Chi-square ,10.7; *P*=0·001) • With respect to the patients with average SBP>118 mmHg, those with average SBP≤118 mmHg had an OR of improving of 4.29 (95% CI, 1.60–1.50; *P*=0.004), after adjustment for the three other variables independently associated with improvement	Lower blood pressure associated with early neurological improvement
Manning LS, et al.[123] 2015 [25908462](25908462)	**Study type:** Subsequent analysis of 2 RCTs of blood pressure management in acute ischemic stroke **Size:** N=706 (COSSACS) + N=171 (CHHIPS)	**Inclusion criteria:** • CHHIPS: symptom onset <36 h and SBP>160 mmHg • COSSACS: patients with acute stroke, recruited <48 h of symptom onset **Exclusion criteria:** • CHHIPS: SBP>200 mmHg or DBP>120 mmHg in association with ICH, impaired conscious level, and premorbid dependency (mRS>3) • COSSACS: same as those in CHHIPS (listed above), with the addition of: dysphagia; definite indication or contraindication to	**1° end point:** Death or major disability (defined as mRS>3 at 2 wk) **Results:** Neither maximum or minimum SBP or DBP associated with death or major disability (defined as mRS>3 at 2 wk)	Minimum BP not associated with 2-week outcome

		continue/discontinue antihypertensive therapy		
Okamura K, et al.[119] 2005 15894898	**Study type:** Registry **Size:** N=1004	**Inclusion criteria:** Brain infarction admitted on the first day and who had undergone CT **Exclusion criteria:** No available data on SBP, DBP, and level of consciousness on admission	**1° end point:** Death within 30 d **Results:** • A U-shaped relationship was observed between admission BP levels (both SBP and DBP) and mortality rate within 30 d • Patients at the lowest BP level (SBP<130 mmHg or DBP<70 mmHg) had the poorest outcomes	Lower and higher BP after brain infarction were predictors for poor early prognosis
Stead LG, et al.[120] 2005 16247043	**Study type:** Consecutive patients, observational **Size:** N=357	**Inclusion criteria**: Presented to the ED with acute ischemic stroke (ICD-CM codes 433 through 437) between mid-December 2001 and March 2004 within 24 h of symptom onset, for whom the initial BP was available **Exclusion criteria:** Limited to the 381 patients who resided in the local county or the surrounding nine-county area	**1° end point:** 90 d mortality **Results:** • Patients with DBP<70 mmHg were significantly more likely to die than those with DBP in the 70–105 mmHg range even after adjusting for age, gender, and NIHSS (RR, 1.8; 95% CI, 1.1–3.1; *P*=0.024) • Patients with SBP <155 mmHg were significantly more likely to die within 90 d when compared to those with SBP in the range of 156–220 mmHg, even after adjusting for age, gender, and NIHSS score (RR, 1.8; 95% CI, 1.1–3.0; *P*=0.022) • Patients with MA*P*<100 mmHg were more likely to die than patients with a MAP in the range of 101–140 mmHg, even after adjusting for age, sex, and NIHSS score (RR, 1.8; 95% CI, 1.1–2.9; *P*=0.027)	Early hypotension (as measured by DBP, SBP, and MAP) is associated with increased early mortality risk
Castillo J, et al.[121] 2004 14726553	**Study type:** Consecutive patients, observational **Size:** N=300/258/258 (numbers evaluated for each of the primary end points)	**Inclusion criteria:** Patients admitted consecutively for a first episode of hemispheric ischemic stroke within 24 h	**1° end point:** • Early neurological deterioration • Neurological deficit at 3 mo • Mortality at 90 d **Results:** A U-shaped effect was observed: for every 10 mmHg ≤180 mmHg of SBP, the risk of early neurological deterioration, poor outcome, and mortality increased by 6%,	• Both high and low SBP or DBP values within the first 24 h after stroke onset are associated with a poor prognosis in terms of early neurological deterioration, neurological deficit at 90 d, and infarct volume

		Exclusion criteria: Patients without a confirmed diagnosis of cerebral infarct (n=13), treated in an acute clinical trial (n=32), or with vasoactive amines (n=3) were excluded	25%, and 7%, respectively, whereas for every 10 mmHg >180 mmHg, the risk of early neurological deterioration increased by 40% and the risk of poor outcome increased by 23%, with no effect on mortality	• This effect is independent of prognostic factors such as stroke severity, body temperature, serum glucose, and stroke subtype
Vemmos KN, et al.[118] 2004 14746563	**Study type:** Consecutive patients, observational **Size:** N=930	**Inclusion criteria:** First-ever stroke patients admitted to hospital between July 1992 and November 2000 **Exclusion criteria:** Patients with transient ischemic attack, age <18 y, recurrent stroke and subarachnoid hemorrhage	**1° end point:** Mortality at 1 mo and 12 mo **Results:** Early (16.6%) and late (29.0%) mortality rate in patients with acute ischemic stroke showed the characteristic U-shaped distribution relative to the registered admission BP value; inflection at SBP 121–140, DBP 81–90	Acute ischemic stroke patients with high and low admission BP values have a higher early and late mortality
Leonardi-Bee J, et al.[122] 2002 11988609	**Study type:** Subsequent analysis of RCT of heparin and aspirin in acute ischemic stroke **Size:** N=17,398	**Inclusion criteria:** Patients with CT-confirmed ischemic stroke from the International Stroke Trial (IST) **Exclusion criteria:** Nonstroke, hemorrhagic stroke, or stroke of unknown type (i.e., no CT scan or postmortem was performed)	**1° end points:** Death within 14 d and death or dependency at 6 mo **Results:** • A U-shaped relationship was found between baseline SBP and both primary outcomes of death within 14 d and death or dependency at 6 mo • The lowest frequency of poor outcome occurred in patients with a baseline SBP of 140–179 mmHg, with the nadir around 150 mmHg • Patients with an SBP<150 mmHg had, for every 10-mmHg fall in blood pressure, an increased risk of early death of 17.9% (*P*<0.0001) and an increased risk of death or dependency at 6 mo of 3.6% (*P*=0.044) • Deaths resulting from coronary heart disease within 14 d were independently associated with low SBP (*P*=0.002)	Both high blood pressure and low blood pressure were independent prognostic factors for poor outcome, relationships that appear to be mediated in part by increased rates of early recurrence and death resulting from presumed cerebral edema in patients with high blood pressure and increased coronary heart disease events in those with low blood pressure

Abbreviations: BP indicates blood pressure; CHHIPS, Controlling Hypertension and Hypotension Immediately Post-stroke; CI, confidence interval; COSSACS, Continue or Stop Post-stroke Antihypertensives Collaborative Study; CT, computed tomography; DBP, diastolic blood pressure; ED, emergency department; h, hours; HR, hazard ratio; ICD-CM, International Classification of Diseases-Clinical Modification; ICH, intracerebral hemorrhage; MAP, mean arterial pressure; MBP, mean blood pressure; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RCT, randomizerd clinical trial; RR, relative risk; and SBP, systolic blood pressure.
Literature search topics: Treatment of hypotension AND Intravenous fluids and stroke

Table XXIX. Nonrandomized Trials, Observational Studies, and/or Registries of Blood Pressure and Thrombolysis

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Adelman EE, et al.[364] 2016 26419527	**Study type:** Review of data from an RCT to increase alteplase use in Michigan **Size:** N=557 (233 patients with protocol deviations)	**Inclusion criteria:** AIS and thrombolysis **Exclusion criteria:** N/A	**1° end point:** sICH and other bad outcomes **Results:** No increase in sICH among patients with protocol violations, including BP	Data from community hospitals
Kodankandath TV, et al.[365] 2016 27160383	**Study type:** Retrospective review of drip and ship patients to single CSC **Size:** N=130	**Inclusion criteria:** IV alteplase at OSH and transfer to CSC **Exclusion criteria:** Stroke mimics	**1° end point:** Poor outcomes – discharge to SNF, death, and discharge mRS>2, sICH **Results:** • Increased risk of death and d/c to hospice among patients with inadequate BP control (SBP>180) upon arrival to CSC • sICH not associated with inadequate BP control at arrival to CSC	Elevated BP at arrival to a CSC after thrombolysis at an outside hospital is associated with worse outcomes, but not necessarily sICH
Liu K, et al.[133] 2016 26892891	**Study type:** Observational **Size:** N=461	**Inclusion criteria:** AIS s/p thrombolysis **Exclusion criteria:** N/A	**1° end point:** Severe hemorrhagic transformation **Results:** Early (within the first 6 h) high SBP variability is associated with severe hemorrhagic transformation	• Chinese cohort • Severe hemorrhagic transformation was defined as sICH with worsening of the NIHSS by at least 4 points for parenchymal hematoma
Waltimo T, et al.[132] 2016 27529662	**Study type:** Cohort **Size:** N=1868	**Inclusion criteria:** AIS treated with IV alteplase	**1° end point:** sICH **Results:** The OR for development of ICH per 10 mmHg increase in SBP at 2 h was 1.14 (1.03–1.25), at 4 h was 1.14	Higher BP after alteplase associated with sICH

		Exclusion criteria: N/A	(1.03–1.25), at 12 h was 1.12 (1.01–1.23), and at 48 h was 1.12 (1.01–1.23)	
TIMS-China Wu W, et al.[130] 2016 26828609	**Study type:** Review of data from alteplase registry **Size:** N=1128	**Inclusion criteria:** AIS and thrombolysis within 4.5 h **Exclusion criteria:** N/A	**1° end point:** sICH **Results:** • Lower BP at baseline, at 2 h and 24 h after alteplase was associated with better outcomes (mRS<2 at 90 d) • SBP>160 2 h after alteplase was associated with sICH (compared to SBP<140) • An increase or no change in SBP after thrombolysis was associated with sICH compared to a decrease in SBP	• Lower SBP is associated with decreased risk of sICH • Lower SBP is associated with better outcomes
Lyerly MJ, et al.[366] 2014 23954609	**Study type:** Retrospective review of stroke registry **Size:** 76 violations out of 212	**Inclusion criteria:** AIS and thrombolysis **Exclusion criteria:** N/A	**1° end point:** sICH and other bad outcomes **Results:** No increase in sICH among patients with protocol violations	• Very few patients with BP violations
SAMURAI rt-PA registry Endo K, et al.[131] 2013 23329210	**Study type:** Analysis of sICH in SAMURAI registry (0.6 mg/kg) **Size:** N=527	**Inclusion criteria:** AIS s/p alteplase **Exclusion criteria:** N/A	**1° end point:** Outcomes **Results:** Initial BPs before thrombolysis were not associated with sICH, but SBP variability within the first 25 h was associated with sICH and death	Increased SBP variability, as opposed to absolute SBPs, was associated with worse outcomes
SITS Mazya M, et al.[129] 2012 22442178	**Study type:** Analysis of sICH in SITS registry **Size:** N=31,627	**Inclusion criteria:** AIS, thrombolysis **Exclusion criteria:** N/A	**1° end point:** sICH **Results:** SBP≥146 before treatment associated with sICH (1.6; [1.3–2.0]; *P*<0.001)	• Higher BP before treatment with alteplase is associated with an increased risk of sICH • The inflection point for risk occurs within the target BP range for administering alteplase
SITS-ISTR Toni D, et al.[128] 2012 22402853	**Study type:** Subgroup analysis of SITS registry for outcomes in the young **Size:** N=3246	**Inclusion criteria:** Age 18–50 y, AIS s/p thrombolysis **Exclusion criteria:** N/A	**1° end point:** Outcome, sICH **Results:** Baseline SBP predicted sICH	No direct mention of BPs>185/110 or 180/105
Kellert L, et al.[367] 2011 21527769	**Study type:** Observational/retrospective	**Inclusion criteria:** AIS with thrombolysis	**1° end point:** Hemorrhagic transformation **Results:** BP protocol violations did not predict ICH or sICH	BP violations were frequent but not associated with ICH or sICH

	Size: N=427	**Exclusion criteria:** N/A		
Butcher K, et al.[126] 2010 19926841	**Study type:** Observation of blood pressures within the EPITHET RCT **Size:** N=97	**Inclusion criteria:** AIS with thrombolysis **Exclusion criteria:** N/A	**1° end point:** Hemorrhagic conversion **Results:** Increased hemorrhagic conversion in patients with large DWI lesion volumes and atrial fibrillation and higher 24-h weighted BP	• No direct mention of BPs >185/110 or 180/105
Perini F, et al.[127] 2010 20674932	**Study type:** Observational **Size:** N=86	**Inclusion criteria:** AIS with thrombolysis **Exclusion criteria:** N/A	**1° end point:** Hemorrhagic conversion – HI or PH **Results:** There was an association between higher SBP and ICH, but not MBP and ICH	No direct mention of BPs>185/110 or 180/105

Abbreviations: AIS indicates acute ischemic stroke; BP, blood pressure; CI, confidence interval; CSC, comprehensive stroke center; HI, hemorrhagic infarction; ICH, intracerebral hemorrhage; IV, intravenous; MBP, myelin basic protein; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OSH, outside hospital; PH, parenchymal hemorrhage; RCT, randomizerd clinical trial; SBP, systolic blood pressure; sICH, symptomatic intracerebral hemorrhage; SNF, skilled nursing facility; and s/p, status post.

Literature search topic: Blood pressure AND Blood pressure and Endovascular Therapy AND Blood Pressure and Thrombolysis

Table XXX. Nonrandomized Studies of Hyperthermia After Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Saxena M, et al.[134] 2015 25643903	**Study type:** Retrospective observational (2 countries) **Size:** N=53,942 in Australia and New Zealand (5176 with acute ischemic stroke) and N=56.696 in the UK (4190 with acute ischemic stroke)	**Inclusion criteria:** Adult patients admitted to one of 148 ICUs in New Zealand or the UK with a primary neurological diagnosis **Exclusion criteria:** CPR in the last 24 h	**1° end point:** Relationship between peak temperature and stroke outcome **Results:** Both low (<37.0) and high (>39.0) temperatures are associated with worse stroke outcome	Both hypothermia and hyperthermia are associated with worse stroke outcomes

Karaszewski B, et al.[368] 2012 23075282	**Study type:** Prospective, observational **Size:** N=44	**Inclusion criteria:** AIS **Exclusion criteria:** ICH, stroke mimics	**1° end point:** Relationship between body temperature changes and stroke severity **Results:** Delayed fever is associated with severe stroke and worse outcome	Delayed fever after stroke is associated with severe stroke and more closely associated with poor outcome than admission body temperature; very small patient cohort
PAIS den Hertog HM, et al.[369] 2011 20878419	**Study type:** Observation within an RCT **Size:** N=1332	**Inclusion criteria:** Admission within 12 h of AIS **Exclusion criteria:** Temp <36˚C or >39˚C, imminent death, liver disease, ETOH abuse	**1° end point:** Relationship between admission temperature and stroke outcome **Results:** Admission temperature does not predict outcome, but elevation within the first 24 h does; the odds for poor outcome increase by 1.3 (95% CI, 1.05–1.63) for each degree C increase in temperature, and the odds for death increase by 1.51 (95% CI, 1.15–1.98) for each degree C increase in temperature	• An increase in body temperature over the first 24 h after admission is associated with worse stroke outcome • Patients were treated with antipyretics

Abbreviations: AIS indicates acute ischemic stroke; CI, confidence interval; CPR, cardiopulmonary resuscitation; ETOH, ethanol; h, hours; ICH, intracerebral hemorrhage; ICU, intensive care unit; RCT, randomizerd clinical trial; and UK, United Kingdom.
Literature search topic: Temperature

Table XXXI. Randomized Clinical Trials of Normothermia

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
Broessner G, et al.[370] 2009 19762706	**Aim:** To assess the feasibility of endovascular cooling to achieve prophylactic normothermia in an ICU cohort. **Study type:** Prospective RCT **Size:** N=102	**Inclusion criteria:** AIS, SAH, ICH in ICU **Exclusion criteria:** Active sepsis, h/o HIT, contraindication to placement of a central line, thrombolysis in the last 12 h	**Intervention:** Endovascular maintenance of normothermia (n=51) **Comparator:** Standard of care (n=51)	**1° end point:** Feasibility and fever burden, which was lower in the endovascularly cooled patients **Safety end point:** Infections were more common in patients with endovascular cooling (96% vs. 80%; *P*=0.03)	Mortality and neurological outcome (GOS) were similar among groups at discharge, day 30, and month 6	Very few patients with ischemic stroke were included	No clear clinical benefit of achieving normothermia

PAIS den Hertog HM, et al.[371] 2009 19297248	**Aim:** To determine if early treatment with paracetamol (acetaminophen) improves outcome by reducing body temperature. **Study type:** Prospective double-blind RCT **Size:** N=1400	**Inclusion criteria:** AIS or ICH with treatment within 12 h of onset **Exclusion criteria:** Temp <36˚C or >39˚C, imminent death, liver disease, ETOH abuse	**Intervention:** Paracetamol (acetaminophen) at a dose of 6 g/d for 3 d (n=697) **Comparator:** Matched placebo (n=703)	**1° end point:** Improvement on the mRS using the sliding dichotomy approach at 3 mo: there was no overall benefit. OR, 1.20 (95% CI, 0.96–1.50) **Safety end point:** No difference in SAEs between groups.	The study was terminated early (planned enrollment was 2500) due to poor enrollment and funding issues	In post hoc analysis, patients with baseline body temperature of 37–39˚C did improve (1.43, 1.02–1.97)	There is no benefit to routine use of acetaminophen in acute stroke

Abbreviations: AIS indicates acute ischemic stroke; ETOH, ethanol; GOS, Glasgow Outcome Scale; HIT, heparin-induced thrombocytopenia; h/o, history of; ICU, intensive care unit; OR, odds ratio; RCT, randomized clinical trial; SAE, serious adverse event; and SAH, subarachnoid hemorrhage.
Literature search topic: Temperature

Table XXXII. Nonrandomized Trials, Observational Studies, and/or Registries of Hypothermia

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
ReCCLAIM I Horn CM, et al.[372] 2014 23468538	**Study type:** Single-arm study, open-label, single site of hypothermia in patients treated with thrombectomy; endovascular cooling **Size:** N=20	**Inclusion criteria:** AIS, age 18–85 y, ASPECTS 5–7 on pretreatment imaging, M1/M2 occlusion or ICA T occlusion, presentation within 8 h of symptom onset **Exclusion criteria:** Mild cognitive impairment, IVC filter, end-stage renal failure on HD, anaphylaxis to iodinated contrast, h/o ventricular arrhythmia leading to	**1° end point:** Feasibility and safety of intravascular hypothermia after reperfusion **Results:** • Three patients developed new hemorrhages on the 24 h CT scan, one of which was symptomatic • Six patients died due to malignant cerebral edema • Pneumonia occurred in 25% of patients, UTI occurred in 20% of patients, and DVT in 1 patient	Endovascular cooling is possible after intervention for stroke, but there are no data to suggest it improves outcome

		cardiac arrest, bleeding diathesis		

Abbreviations: ASPECTS indicates Alberta Stroke Program Early Computed Tomography Score; CT, computed tomography; ICA T, internal carotid artery terminus; HD, hemodialysis; IVC, inferior venal cava.; DVT, deep vein thrombosis; UTI, urinary tract infection; HD, hemodialysis; AIS, acute ischemic stroke; and y, years
Literature search topic: Temperature

Table XXXIII. Randomized Clinical Trials of Hypothermia

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
COOLIST Geurts M, et al.[136] 2017 27856954	**Aim:** Safety and feasibility of surface cooling **Study type:** Open-label multicenter RCT **Size:** N=22 (stopped early due to poor recruitment)	**Inclusion criteria:** AIS, RX within 4.5 h of stroke onset; NIHSS≥6 **Exclusion criteria:** ICH, any conditions that might be exacerbated by hypothermia (i.e., bleeding diatheses), bradycardia, hypoxia	**Intervention:** Cooled IV fluids following by surface cooling within 4.5 h of symptom onset, 3 different temperature goals (34.0˚C, n=5; 34.5˚C, n=6; 35.0˚C, n=5) **Comparator:** Standard care (n=6)	**1° end point:** Safety and feasibility – could only cool to 35.0, not 34.5, with surface cooling **Safety end point:** Increased risk of PNA – absolute increase 53% (28%–79%; *P*=0.002)	Time to target temperature: no patients randomized to 34.0˚C achieved that goal, only 1 patient achieved the goal of 34.5	Shivering occurred in all patients	• Hypothermia is difficult to achieve with surface cooling • There is an increased risk of PNA with hypothermia
ICTUS2 Lyden P, et al.[135] 2016 27834742	**Aim:** Safety and feasibility of endovascular cooling **Study type:** Multicenter single-blind RCT **Size:** N=120	**Inclusion criteria:** AIS treated with alteplase; NIHSS ≥7 and ≤20 for left brain stroke and ≤24 for right brain stroke	**Intervention:** Cooled IV fluids followed by insertion of endovascular cooling device (n=63) **Comparator:** Standard care (n=57)	**1° end point:** mRS 0–1 at 90 d and the proportion of patients with mRS 0–1 at 90 d was similar (33% vs. 38%; 0.81; 0.36–1.85) **Safety end point:** Trends to increased mortality (15.9% vs. 8.8%; OR, 1.95; 95% CI, 0.56–7.79) and PNA (19.0% vs.	None	• Relatively small study and underpowered for the primary outcome • Patients received meperidine, buspirone and surface warming	Increased risk of PNA

		Exclusion criteria: Prestroke mRS >1, contraindica-tions to hypothermia, item 1a on NIHSS >1		10.5%; OR, 1.99; 95% CI 0.63–6.98) in hypothermic patients		to prevent shivering		
Su Y, et al.[373] 2016 26696645	**Aim:** Evaluate hypothermia in malignant MCA infarction **Study type:** Single-center RCT, not blinded **Size:** N=33	**Inclusion criteria:** • Age 18–80 y • RX within 48 h of onset • Infarct at least 2/3 MCA territory on MRI or CT • NIHSS ≥15 for non-dominant hemisphere or NIHSS ≥20 for dominant hemisphere • Reduced LOC (NIHSS≥1 on item 1a) • Unable to undergo DC **Exclusion criteria:** • Premorbid mRS >2 • Hemorrhagic conversion >1/3 MCA territory with space occupying effect • GCS<6; rapidly	**Intervention:** Hypothermia to 33˚C–34˚C for 24–72 h using endovascular catheter (n=16) **Comparator:** Standard medical care with goal temperature 36.5˚C–37.5˚C (n=17)	**1° end point:** • Feasibility and all-cause mortality and mRS at 6; mortality was similar in both groups (8/16 vs. 7/17) • Survivors treated with hypothermia achieved better neurological outcomes at 6 mo (OR, 10.5; 95% CI, 0.9–121.4; adjusted OR, 4.794; 95% CI, 0.323–71.103) **Safety end point:** More complications with hypothermia group (*P*<0.001)	N/A	• Very small study • No difference in PNA with hypothermia • Patients were not treated with decompressive hemicraniectomy • Patients were not treated with decompressive hemicraniectomy • Hypothermia was initiated rather late in the course of stroke (an average of 42 h)	Hypothermia was associated with a trend toward better outcomes in survivors, but there were many more complications

		improving symptoms • Both pupils fixed and dilated • Other brain lesions • Platelets <75K • Severe coagulopathy					
HARIS Hong JM, et al.[374] 2014 24203846	**Aim:** Hypothermia after recanalization **Study type:** RCT with randomization by center **Size:** N=75	**Inclusion criteria:** IA RX; NIHSS ≥10; DWI confirmation of infarct; recanalization (TICI ≥2b) within 6 h of symptom onset **Exclusion criteria:** Not specified	**Intervention:** Surface cooling to 34.5˚C–35.0˚C for 48 h (n=39) **Comparator:** Normothermia (n=36)	**1° end point:** More patients treated with hypothermia had a good outcome (mRS 0–2) at 3 mo; 45% vs. 23% (*P*=0.017); OR, 3.0 (95% CI, 1.02–8.90; *P*=0.047) **Safety end point:** Similar mortality in both groups (15% vs. 14%)	• Less HT, with no HT in 39% of hypothermia-treated patients and no HT in 14% standard care group (*P*=0.016) • Less cerebral edema with hypothermia (no cerebral edema in 54% with hypothermia and no cerebral edema in 17% with standard of care, *P*=0.001)	• Relatively small study done in 2 centers • Trends toward more favorable characteristics at baseline in the hypothermia group	• Therapeutic hypothermia after recanalization is associated with less HT, less cerebral edema and better outcomes at 3 mo • Further studies will need to be done to confirm these results
Piironen K, et al.[137] 2014 24436240	**Aim:** Safety and feasibility of mild hypothermia **Study type:** RCT **Size:** N=36	**Inclusion criteria:** AIS treated with alteplase; NIHSS 7–20 **Exclusion criteria:** mRS>2; CHF; angina, sepsis, ICH	**Intervention:** Hypothermia to 35˚C with surface cooling and IV cold saline (n=18) **Comparator:** Standard of care/normothermia (n=18)	**1° end point:** Feasibility: number of patients with temperature <36˚C for >80% of the cooling period was 15/18 (83%) **Safety end point:** AEs were more common in hypothermia group (19 vs. 12), with pneumonia occurring in 39% vs. 11%; *P*=0.054	No difference in good outcome (mRS 0–2) at 3 mo (7/18 [39%] in each group)	Trend towards more PNA with hypothermia (39% vs. 11%, *P*=0.054)	Increased risk of PNA with hypothermia

COOLAID Ovesen C, et al.[375] 2013 23278712	**Aim:** Feasibility study **Study type:** RCT (2 centers) **Size:** N=31	**Inclusion criteria:** Age≥18; NIHSS≥5 and ≤18; RX within 24 h of symptoms onset; stroke by CT or MRI **Exclusion criteria:** mRS≥3; >50% MCA territory; severe concomitant disease	**Intervention:** Endovascular cooling (n=7) or surface cooling (n=10) targeting temperature of 33˚C **Comparator:** Normothermia (n=14)	**1° end point:** Safety; feasibility: endovascular cooling achieves goal temperature more quickly than surface cooling **Safety end point:** More bradycardia in cooled patients (65% vs. 0%; *P*=0.0001); Trend towards more PNA in cooled patients (35% vs. 9%, *P*=0.09)	mRS at 90 d was 3.0 (1–6) in cooled patients and 1.5 (1–6) in controls	Small study	Hypothermia was not associated with clinical benefit but was associated with more AEs
ICTUS-L Hemmen TM, et al.[138] 2010 20724711	**Aim:** Feasibility and safety of hypothermia **Study type:** RCT **Size:** N=58	**Inclusion criteria:** AIS and RX with alteplase within 6 h **Exclusion criteria:** Contraindications to hypothermia	**Intervention:** 24 h of endovascular cooling (n=28) **Comparator:** No active cooling (n=30)	**1° end point:** Safety **Safety end point:** Increased PNA in hypothermia group (50% vs. 10%; *P*=0.001) and more patients with at least 1 SAE (75% vs. 43.3%; *P*=0.018)	90-d mortality was similar in both groups (21.4% vs. 16.7%) as was good outcome (mRS 0–1), which occurred in 5/28 in the hypothermia group and 7/30 in the normothermia group	• Small study • Patients received meperidine, buspirone and surface warming to prevent shivering	There is no signal of clinic benefit in this study, and hypothermia was associated with a significant risk of PNA

Abbreviations: AE indicates adverse event; AIS, acute ischemic stroke; CHF, congestive heart failure; CT, computed tomography; DC, decompressive craniectomy; DHC, decompressive hemicraniectomy; DWI, diffusion-weighted imaging; GCS, Glasgow Coma Scale; h, hour; HT, hemorrhagic transformation; IA, intra-arterial; ICH, intracerebral hemorrhage; IV, intravenous; LOC, level of consciousness; MCA, middle cerebral artery; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PNA, pneumonia; RCT, randomized clinical trial; RX, treatment; SAE, serious adverse event; and TICI, thrombolysis in cerebral infarction.
Literature search topic: Temperature

Table XXXIV. Randomized Clinical Trials Evaluating Intravenous Alteplase for Treatment of Acute Ischemic Stroke*

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
ENCHANTED Anderson CS, et al.[143] 2016 27161018	**Aim:** Determine if reduced-dose alteplase would be non-inferior to standard-dose alteplase **Study type:** RCT (open label) **Size:** N=3310	**Inclusion criteria:** Patients with disabling stroke symptoms within 4.5 h of onset who were candidates for IV alteplase as per approved indications **Exclusion criteria:** Pre-existent disability; hemorrhage on CT scan; high risk of bleeding	**Intervention:** Alteplase 0.6 mg/kg up to 60 mg (n=1653) **Comparator:** Alteplase 0.9 mg/kg up to 90 mg (n=1654)	**1° end point:** mRS 2–6 at 90 d: 53.2% vs. 51.1%; OR, 1.09; 95% CI, 0.95–1.25; *P*=0.51 **Safety end point:** sICH: 1% vs. 2.1%	• Ordinal shift analysis of mRS scores: OR, 1.0; 95% CI, 0.89–1.13; *P*=0.04 for non-inferiority • Mortality at 90 d: 8.9% vs. 10.3%, *P*=0.07	• Open label design • Large proportion of Asian patients	Low-dose IV alteplase did not meet the non-inferiority end point for the reduction of death and disability at 90 d in comparison to standard-dose IV alteplase
IST-3 IST-3 Collaborative Group[142] 2012 22632908	**Aim:** Determine whether alteplase would benefit patients who did not meet license criteria for alteplase (mainly older than 80 y and up to 6 h from onset) **Study type:** RCT (open control) **Size:** N=3035	**Inclusion criteria:** Disabling stroke symptoms within 6 h of onset **Exclusion criteria:** Hemorrhage on CT scan; prohibitive risk of bleeding	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=1515) **Comparator:** Open control (n=1520)	**1° end point:** OHS 0–2 at 6 mo: 37% vs. 35%; OR, 1.13; 95% CI, 0.95–1.35; *P*=0.18 **Safety end point:** sICH: 7% vs. 1%	Ordinal shift in OHS scores at 180 d: OR, 1.27; 95% CI, 1.10–1.47; *P*=0.001)	This trial enrolled patients without established indication for IV alteplase (e.g., age>80 y, time beyond 4.5 h) in Europe	IV alteplase did not meet the primary efficacy end point but improved outcomes based on an ordinal shift in the distribution of the OHS scores

EPITHET Davis SM, et al.[93] 2008 18296121	**Aim:** Establish the effect of IV alteplase on lesion growth, reperfusion, and clinical outcome in patients with radiological penumbra 3–6 h after stroke onset **Study type:** RCT **Size:** N=101	**Inclusion criteria:** Disabling stroke symptoms 3–6 h from onset **Exclusion criteria:** Age>80 y; hemorrhage on CT scan; infarction >1/3 of MCA territory on CT scan; high risk of bleeding	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=52) **Comparator:** Placebo (n=49)	**1° end point:** Infarct growth at 90 d by MRI: NS **Safety end point:** sICH: N/A	• mRS 0–1: 36% vs. 21% (*P*=0.15) • Reperfusion was more common with alteplase than with placebo and was associated with less infarct growth (*P*=0·001), better neurological outcome (*P*<0·0001), and better functional outcome (*P*=0·010) than was no reperfusion	• Small size • Primary analysis was per protocol	• The trial focused primarily on the value of MRI for patient selection • Alteplase was associated with increased reperfusion in patients who had mismatch and a trend to less infarct growth
ECASS 3 Hacke W, et al.[144] 2008 18815396	**Aim:** Determine the efficacy of alteplase between 3 and 4.5 h of stroke onset **Study type:** RCT **Size:** N=821	**Inclusion criteria:** Disabling stroke symptoms 3–4.5 h from onset **Exclusion criteria:** Age>80 y; hemorrhage on CT scan; infarction >1/3 of MCA territory on CT scan; high risk of bleeding, including: NIHSS >25, history of previous stroke	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=418) **Comparator:** Placebo (n=403)	**1° end point:** mRS 0–1 at 90 d: 52.4% vs. 45.2%; OR, 1.34; 95% CI, 1.02–1.76; *P*=0.04 **Safety end point:** sICH: 2.4% vs. 0.2%	• Global outcome analysis (algorithm for chances of favorable outcome): 1.28; 95% CI, 1.00–1.65; *P*=0.05 • Mortality at 90 d: 7.7% vs. 8.4% (*P*=0.68)	No difference in the rate of other serious adverse events	IV alteplase was superior to placebo in improving functional outcomes when administered between 3 and 4.5 h from stroke onset

		and diabetes; use of warfarin regardless of INR					
ATLANTIS A Clark WM, et al.[376] 2000 10753980	**Aim:** Determine the safety and efficacy of alteplase up to 6 h after stroke onset **Study type:** RCT **Size:** N=142	**Inclusion criteria:** Disabling stroke symptoms within 6 h of onset **Exclusion criteria:** Age>80 y; hemorrhage on CT scan; high risk of bleeding	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=71) **Comparator:** Placebo (n=71)	**1° end point:** • NIHSS score improvement by 4 points at 24 h: 40% vs. 21%; *P*=0.02 • NIHSS score improvement by 4 points at 30 d: 60% vs. 75%; *P*=0.05 **Safety end point:** sICH: 11% vs. 0%	Mortality at 90 d: 23% vs. 7% (*P*=0.01)	The trial was stopped by the DMSB because of safety concerns in the 5- to 6-h group	• IV alteplase administered within 6 h had early but not sustained benefit • Only a small minority were treated within 3 h • The small sample size limited power and reliability
ATLANTIS B Clark WM, et al.[377] 1999 10591384	**Aim:** Determine the safety and efficacy of alteplase 3-5 h after stroke onset **Study type:** RCT **Size:** N=613 (547 treated within 3–5 h)	**Inclusion criteria:** Disabling stroke symptoms 3–5 h from onset **Exclusion criteria:** Age>80 y; hemorrhage on CT scan; infarction >1/3 of MCA territory on CT scan; high risk of bleeding	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=307; n=272 within 3–5 h) **Comparator:** Placebo (n=306, n=275 within 3–5 h)	**1° end point:** NIHSS score ≤1 at 90 d: 34.5% vs. 34%; *P*=0.89 (34% vs. 32%; *P*=0.65 per protocol within 3–5 h) Secondary end point: mRS 0–1 at 90 d: 41.7% vs. 40.5%; *P*=0.77 (42.3% vs. 38.9%; *P*=0.42 per protocol within 3–5 h) **Safety end point:** sICH: 6.7% vs. 1.3% (7% vs. 1.1% per protocol within 3–5 h)	Mortality at 90 d: 11% vs. 6.9% (*P*=0.09)	More than 80% of the patients were enrolled after 3 h	• IV alteplase was not beneficial within the 3- to 5-h window • IV alteplase was beneficial in the small subgroup of patients treated within 3 h
ECASS II Hacke W, et al.[378] 1998 9788453	**Aim:** Determine the safety and efficacy of alteplase up to 6 h after stroke onset	**Inclusion criteria:** Disabling stroke symptoms within 6 h of onset	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=409)	**1° end point:** mRS 0–1 at 90 d: 40.3% vs. 36.6%; OR, 1.2; 95% CI, 0.9–1.6; *P*=0.28	• mRS scores dichotomized for death or dependency (post hoc	Small minority of patients treated within the first 3 h	IV alteplase was not significantly beneficial when therapeutic

	Study type: RCT **Size:** N=800	 **Exclusion criteria:** Age>80 y; hemorrhage on CT scan; infarction >1/3 of MCA territory on CT scan; high risk of bleeding	**Comparator:** Placebo (n=391)	**Safety end point:** sICH: 8.8% vs. 3.4%	analysis): 54.3% in the alteplase group and 46.0% in the placebo group had favorable outcomes (score 0–2; absolute difference 8.3%, *P*=0.024) • Mortality: no difference at 90		window was extended to 6 h
ECASS Hacke W, et al.[379] 1995 7563451	**Aim:** Determine the safety and efficacy of alteplase up to 6 h after stroke onset **Study type:** RCT **Size:** N=620	**Inclusion criteria:** Disabling stroke symptoms within 6 h of onset **Exclusion criteria:** Age>80 y; hemorrhage on CT scan; infarction >1/3 of MCA territory on CT scan; high risk of bleeding	**Intervention:** Alteplase 1.1 mg/kg up to 100 mg (n=313) **Comparator:** Placebo (n=307)	**1° end point:** •Median BI at 90 d: 75 vs. 85; *P*=0.99 •Median mRS at 90 d: 3 vs. 3; *P*=0.41 **Safety end point:** Parenchymal hematoma: 19.8% vs. 6.9%	N/A	Many patients with protocol violations (N=109) were included in the ITT analysis	Alteplase was not beneficial on the ITT analysis when patients with protocol violations were excluded from the target population analysis; there was a significant difference in favor of alteplase in the median mRS and mRS 0–1 (although not significant on the median BI score)
NINDS NINDS Stroke Study rt-PA Group[87] 1995 7477192	**Aim:** Determine the safety and efficacy of alteplase within 3 h after stroke onset **Study type:** RCT	**Inclusion criteria:** Disabling stroke symptoms within 3 h of onset	**Intervention:** Alteplase 0.9 mg/kg up to 90 mg (n=312) **Comparator:** Placebo (n=312)	**1° end point:** Global test of neurological function at 90 d (BI, mRS, GOS, NIHSS) • OR, 1.9; 95% CI, 1.3–2.9; *P*=0.002	Mortality at 90 d: alteplase 17% vs. placebo 21% (*P*=0.30)	The trial was composed of two parts, and parts 1 and 2 had different primary end points	IV alteplase was superior to placebo in improving functional outcomes when administered

	Size: N=624	**Exclusion criteria:** Hemorrhage on CT scan; high risk of bleeding		• mRS 0–1 at 90 d: 39% vs. 26%; OR, 2.4; 95% CI,1.5–3.7; *P*<0.001 **Safety end point:** sICH: 6.4% vs. 0.6%			within 3 h of stroke onset

*Trials with ≤100 subjects are not included

Abbreviations: BI, Barthel index; CI, confidence interval; CT, computed tomography DMSB, Data Monitoring and Safety Board; GOS, Glasgow Outcome Score; h, hour; ITT, intention-to-treat; IV, intravenous; MCA, middle cerebral artery; MRI, magnetic resonance imaging; mRS, modified Rankin scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NS: not significant; OHS: Oxford handicap scale; OR, odds ratio; RCT, randomized clinical trial; sICH, symptomatic intracerebral hemorrhage; and y, years.

Literature search topic: Alteplase, IV, stroke

Table XXXV. Randomized Clinical Trials of Intravenous Alteplase for Mild Stroke 3–4.5 Hours

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
ECASS III: additional subgroups Bluhmki E, et al.[145] 2009 [19850525]	**Aim:** To seek evidence of confounding factors or subgroups that might differentially affect treatment outcome **Study type:** RCT **Size:** N=821 (total); according to NIHSS: 0–5, 66(I)/62(C); 6–10, 169(I)/148(C); 11–15, 85(I)/77(C); 16–20, 77(I)/76(C); >20, 21(I)/40(C)	**Inclusion criteria:** • Clinical diagnosis of ischemic stroke causing a measurable neurological deficit defined as impairment of language, motor function, cognition and/or gaze, vision or neglect • Onset of symptoms between 3 and 4 h prior to initiation of	**Intervention:** Intravenous alteplase (0.9 mg/kg, maximum dose 90 mg over 60 min with initial 10% of dose given as bolus over 1 min) (n=418) **Comparator:** Standard care – no intravenous heparin, oral anticoagulants, aspirin, or volume expanders during the first	**1° end point:** mRS 0–1 at 90 d (OR, 95% CI) • Overall: 1.34 (1.02–1.76) [144] • According to NIHSS: 0–9, 1.28 (0.84–1.96); 10–19, 1.16 (0.73–1.84); ≥20, 2.32 (0.61–8.90); interaction *P*=0.63 **Safety end point:** Symptomatic intracranial hemorrhage (NINDS definition) • Overall: 2.38 (1.25–4.52) [144] • According to NIHSS: 0–9, 3.04 (0.82–11.22); 10–19, 2.18 (096–4.98); ≥20,	• NIHSS 0–1 at 90 d Overall: 1.33 (1.01–1.75) [144] According to NIHSS: 0–9, 1.17 (0.77–1.78); 10–19, 1.32 (0.82–2.12); ≥20, 1.88 (047–7.52) • Global outcome statistic at 90 d Overall: 1.28 (1.00–1.65) [144] According to NIHSS 0–9: 1.12 (0.77–1.64); 10–19:	Only 128 patients NIHSS 0–5, not analyzed separately	No interaction of benefit or safety with stroke severity

		administration of study drug, and others **Exclusion criteria:** Minor neurological deficit or symptoms rapidly improving before start of infusion, and others	24 h; subcutaneous heparin (≤10,000 IU), or of equivalent doses of low-molecular-weight heparin, was permitted for DVT prophylaxis (n=403)	3.03 (0.52–17.50); interaction *P*=0.89	1.15 (0.77–1.71); ≥ 20: 1.76 (0.44–7.15) • Mortality at 90 d Overall: 0.90 (0.54–1.49) [144] According to NIHSS: 0–9, 2.70 (0.54–13.53); 10–19, 0.81 (0.41–1.59); ≥20, 1.03 (0.37–2.87); interaction *P*=0.40		

Abbreviations: C indicates control; CI, confidence interval; d, days; DVT, deep vein thrombosis; h, hours; HR, hazard ratio; I, intervention; IV, intravenous; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NINDS, National Institute of Neurological Disorders and Stroke; OR, odds ratio; RCT, randomized clinical trial; and RR, relative risk.
Literature search topic: Intravenous alteplase for mild stroke 3-4.5 hours

Table XXXVI. Nonrandomized Trials, Observational Studies, and/or Registries of Intravenous Alteplase 3–4.5 Hours for Mild Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
GWTG Romano JG, et al.[147] 2015 25642650	**Study type:** Registry of hospitalized patients with stroke **Size:** N=7621 patients with NIHSS ≤5 treated with IV alteplase within 4.5 h	**Inclusion criteria:** Final diagnosis of acute ischemic stroke **Exclusion criteria:** • Less than 75% completion on medical history variables, arrived beyond 4.5 h from symptom onset, not treated with alteplase, NIHSS>5, missing an NIHSS score	**End Points:** Discharge home, independent ambulation, death, sICH **Results:** Discharge home: • 0–3 h: 70.3%% • 3–4.5 h: 71.6% Independent ambulation • 0–3 h: 69.6% • 3–4.5 h: 70.2% Death • 0–3 h: 1.3%	Good functional outcomes, mortality, and risk of sICH are the same in mild stroke treated 0–3 h and 3–4.5 h

		• Did not arrive through the emergency department, not discharged from the same hospital, time to treatment longer than 4.5 h or missing	• 3–4.5 h: 1.3% sICH • 0–3 h: 2.0% • 3–4.5 h: 1.4%	
SITS-ISTR Ahmed N, et al.[146] 2010 20667790	**Study type:** Registry of patients treated with IV alteplase for acute ischemic stroke **Size:** N=23,942 between 12/2002 and 2/2010; N=2376 treated 3–4.5 h after symptom onset	**Inclusion criteria:** Ischemic stroke and were treated with IV alteplase within 4.5 h after symptom onset **Exclusion criteria:** European Summary of Product Characteristics criteria	**1° end point:** mRS at 3 mo **Results:** Baseline NIHSS ≤5 • 0–3 h: mRS 0–1, 71% • 3–4.5 h: mRS 0–1, 72% **Safety:** Mortality at 3 mo Baseline NIHSS ≤5 • 0–3 h: mRS 0–1, 3% • 3–4.5 h: mRS 0–1, 4%	Good functional outcomes (mRS 0–1) and risk of sICH are the same in mild stroke treated 0–3 h and 3–4.5 h

Abbreviations: CI indicates confidence interval; h, hours; HR, hazard ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; and sICH, symptomatic intracerebral hemorrhage.
Literature search topic: Intravenous alteplase for mild stroke 3-4.5 hours

Table XXXVII. Nonrandomized trials, Observational Studies, and/or Registries of Sickle Cell Disease and IV Alteplase

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Adams RJ, et al.[148] 2017 28183857	**Study type:** Observational case-control study **Size:** 832 Sickle cell disease cases and 3328 non-sickle cell disease controls (matched for age, sex and race)	**Inclusion criteria:** Get With the Guidelines Hospitalized Stroke Cases **Exclusion criteria:** N/A	**1° end point:** Outcomes after IV alteplase **Results:** • No difference in IV alteplase use (8.2% in cases vs 10.1% in controls, *P*=0.9818) • No difference in rates of symptomatic ICH (4.9% in cases vs 3.2% in controls, *P*=0.4502) • No difference in rates of in-hospital death (3.5% in cases vs 5.0% in controls, *P*=0.5654)	• IV alteplase is safe and effective in adult patients with sickle cell disease

Table XXXVIII. Nonrandomized Trials, Observational Studies of Antithrombotic Agents given within 24 hours after Intravenous Alteplase for the Treatment of Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Jeong HG, et al.[166] 2016 27521435	**Study type:** Single-center, retrospective analysis of early antithrombotics (<24 h) in AIS + alteplase/EVT **Size:** N=712	**Inclusion criteria:** AIS and IV alteplase or EVT **Exclusion criteria:** Early sICH or systemic bleeding, grave prognosis, planned surgical treatment	**1° end point:** Hemorrhagic transformation at 4-7 d post-treatment, mRS 0-1 at 3 mo **Results:** No increased odds of sICH (0.85; 0.35–2.10) or difference in mRS at 3 mo (1.09; 0.75–1.59) in patients with early initiation of antithrombotics	• No increased risk of hemorrhage with early initiation of AP or AC therapy (<24 h) following IV alteplase or EVT compared to initiation >24 h • Limitations include generalizability and selection bias

Abbreviations: AC indicates anticoagulant; AIS, acute ischemic stroke; AP, antiplatelet; d, days; EVT, endovascular therapy; h, hours; IV, intravenous; mRS, modified Rankin Scale; and sICH, symptomatic intracerebral hemorrhage.
Literature search topic: Intravenous Fibrinolysis

Table XXXIX. Randomized Clinical Trials Evaluating Intravenous Fibrinolytics Other Than Alteplase for Treatment of Acute Ischemic Stroke

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
NOR-TEST Logallo N, et al.[170] 28780236	**Aim:** To establish superiority of tenecteplase 0.4 mg/kg (single bolus) as compared with alteplase 0.9 mg/kg (10% bolus + 90% infusion/60 minutes) for patients with acute ischemic stroke **Study Type:** multicenter, prospective, open-label, blinded endpoint, phase 3 RCT **Size:** N=1107	**Major Inclusion criteria:** Age 18 years or older; Ischemic stroke with measurable deficit on NIHSS); treatment within 4½ hours of stroke onset, or Wake-Up Stroke-Treatment within 4½ hours after awakening based on FLAIR-DWI mismatch on MRI; eligible for bridging therapy before thrombectomy	**Intervention:** IV tenecteplase 0.4 mg/kg (single intravenous bolus) n=549 **Comparator:** IV alteplase 0.9 mg/kg (10% bolus + 90% infusion/60 minutes) n=551	**1° end point::** mRS 0-1 at 3 months: tenecteplase : 354/549 (64%) alteplase: 345/551 (63%) OR 1.08; 95% CI, 0.84 - 1.38; *P*=.52 **Safety endpoint:** Symptomatic ICH at 24-36 hrs: tenecteplase: 3% alteoplase: 2% OR, 1.16; 95% CI, 0.51 - 2.68; *P*=0.70	NIHSS score of 0 or improvement of ≥4 at 24 h: tenecteplase: 41.7% alteplase 38.8% OR, 1.12 (95% CI, 0.89-1.43; *P*=0.97)	• Only mild strokes: Median NIHSS 4 (IQR 2-8) •18% stroke mimics • 4% had symptoms on awakening and had positive DWI-FLAIR mismatch • given its superiority design to detect a 9% difference in the primary end point, this trial was not designed to establish noninferiority	•Tenecteplase at a dose of 0·4 mg/kg has a similar safety and efficacy profile to alteplase in a stroke population predominantly composed of patients with minor neurological impairment and no major intracranial occlusion.

		<u>Major Exclusion Criteria:</u> Premorbid mRS ≥3; Seizure at stroke onset and no visible occlusion on baseline CT; large areas of hypodense ischaemic changes on baseline CT; systolic blood pressure >180 mm Hg or diastolic blood pressure >110 mm Hg despite of blood pressure lowering therapy; other usual IV alteplase exclusions					
DIAS 4 von Kummer R, et al.[167] 2016 27803391	**Aim:** Assess the safety and efficacy of desmoteplase between 3 h and 9 h after stroke onset in patients with occlusion or high-grade	**Inclusion criteria:** NIHSS 4–24; within 3–9 h of symptom onset; occlusion or high-grade stenosis of a	**Intervention:** Desmoteplase, 90 mcg/kg (n=124) **Comparator:** Placebo (n=128)	**1° end point:** mRS 0–2 at 90 d*: 42% vs. 36%; adjusted OR, 1.45; 95% CI, 0.79–2.64; *P*=0.23 **Safety end point:** sICH: 5% vs. 2%	Desmoteplase increased the recanalization rate at 12 to 24 h by an absolute difference of 22.8% (*P*=0.02)	• Terminated after enrollment of 270 of 400 planned patients following the results of DIAS 3	• Desmoteplase was not superior to placebo • Patients recruited from North America,

	stenosis in major cerebral arteries **Study type:** RCT **Size:** N=270	major cerebral artery on MRA/CTA **Exclusion criteria:** Age>85 y; hemorrhage on CT or MRI; infarction >1/3 of MCA territory or >1/2 of ACA or PCA territory; high risk of bleeding				• No safety concerns	Latin America and Europe
DIAS 3 Albers GW, et al.[168] 2015 25937443	**Aim:** Assess the safety and efficacy of desmoteplase between 3 h and 9 h after stroke onset in patients with occlusion or high-grade stenosis in major cerebral arteries **Study type:** RCT **Size:** N=492	**Inclusion criteria:** NIHSS 4–24; within 3–9 h of symptom onset; occlusion or high-grade stenosis of a major cerebral artery on MRA/CTA **Exclusion criteria:** Age>85 y; hemorrhage on CT or MRI; infarction >1/3 of MCA territory or >1/2 of ACA or PCA territory; high risk of bleeding	**Intervention:** Desmoteplase, 90 mcg/kg (N=247) **Comparator:** Placebo (N=245)	**1° end point:** mRS 0–2 at 90 d*: 51% vs. 50%; adjusted OR, 1.20; 95% CI, 0.79–1.81; *P*=0.40. **Safety end point:** sICH: 3% vs. 2%	No differences in mortality (10% in both groups)	No safety concerns	• Desmoteplase was not superior to placebo • Patients recruited from Asia and Europe
ATTEST Huang X, et al.[89] 2015 25726502	**Aim:** Assess the efficacy and safety of tenecteplase vs. alteplase within 4·5 h of stroke onset	**Inclusion criteria:** Indication for alteplase; within 4.5 h of	**Intervention:** Tenecteplase, 0.25 mg/kg single bolus, up to 25 mg (N=52)	**1° end point:** Percentage of penumbral tissue salvaged at 24–48 h: 68% vs. 68%; *P*=0.81	• No differences in mRS at 30 or 90 d	• Analysis was per protocol • Extracranial bleeding: 8% vs. 0%	Tenecteplase 0.25 mg/kg appears to be as safe as

	Study type: RCT (Phase II) **Size:** N=104	symptom onset; available CTP at baseline **Exclusion criteria:** Any contraindications for alteplase GFR<30 ml/min	**Comparator:** Alteplase, 0.9 mg/kg infusion, up to 90 mg (N=52)	**Safety end point:** sICH: 2% vs. 4%	• No difference in mortality at 90 d		standard-dose alteplase
DIAS-J Mori E, et al.[380] 2015 [26251244](26251244)	**Aim:** Assess the safety and tolerability of desmoteplase within 3 to 9 h of stroke onset in Japanese patients **Study type:** RCT (Phase II dose ranging) **Size:** N=193	**Inclusion criteria:** NIHSS 4–24; within 3–9 h of symptom onset; occlusion or high-grade stenosis of a major cerebral artery on MRA/CTA **Exclusion criteria:** Age>85 y; hemorrhage on CT or MRI; infarction >1/3 of MCA territory or >1/2 of ACA or PCA territory; high risk of bleeding	**Intervention:** Desmoteplase, 70 mcg/kg (N=16); 90 mcg/kg (n=16) **Comparator:** Placebo (n=16)	**1° end point:** sICH within 72 h: 6% with 70 mcg/kg vs. 0% with 90 mcg/kg vs. 13% with placebo **Safety end point:** Primary end point was the safety end point	No increase in brain edema or other major adverse events	Dose ranging trial	Desmoteplase in doses of 70 mcg/kg or 90 mcg/kg appeared safe
Parsons M, et al.[91] 2012 [22435369](22435369)	**Aim:** Compare the effectiveness of two different doses of tenecteplase vs. alteplase in acute stroke patients within 6 h of symptom onset and selected by CTP	**Inclusion criteria:** Indication for alteplase; within 6 h of symptom onset; ≥20% mismatch by DWI/PWI or CTP; large intracranial	**Intervention:** Tenecteplase, 0.1 mg/kg single bolus, up to 10 mg (N=25) or 0.25 mg/kg single bolus, up to 25 mg (n=25)	**Co-primary end points:** • Percentage of perfusion lesion that was reperfusion at 24 h on MRI: 79% with tenecteplase (both doses combined) vs. 55% with alteplase; *P*=0.004 • NIHSS improvement at 24 h: 8±5 with	mRS 0–1 at 90 d: 72% with tenecteplase 0.25 mg/kg vs. 40% with alteplase	No differences in ICH or other serious adverse events	Both tenecteplase doses appeared superior to standard-dose alteplase for the studied end points

	Study type: RCT (phase IIb) **Size:** N=75	artery occlusion on CTA **Exclusion criteria:** Any contraindications for alteplase	**Comparator:** Alteplase, 0.9 mg/kg infusion, up to 90 mg (n=25)	tenecteplase (both doses combined) vs. 3±6 with alteplase **Safety end point:** No sICH cases			
Haley EC, et al.[169] 2010 20185783	**Aim:** Compare the effectiveness of three different doses of tenecteplase vs. alteplase in acute stroke patients within 3 h of symptom onset **Study type:** RCT (phase IIb/III) **Size:** N=112	**Inclusion criteria:** Indication for alteplase; within 3 h of symptom onset **Exclusion criteria:** Any contraindications for alteplase	**Intervention:** Tenecteplase, 0.1 mg/kg (N=31), 0.25 mg/kg (N=31), and 0.4 mg/kg (n=19) **Comparator:** Alteplase 0.9 mg/kg infusion, up to 90 mg (n=31)	**1° end point:** mRS 0–1: 45% with 0.1 mg/kg, 48% with 0.25 mg/kg, 37% with 0.4 mg/kg and 42% with placebo; *P*>0.3 for all comparisons **Safety end point:** Total of 6 symptomatic ICHs: 3 of 19 (15.8%) in the 0.4 mg/kg group, 2 of 31 (6.5%) in the 0.25 mg/kg tenecteplase group, and none (0 of 31) in the 0.1 mg/kg tenecteplase group; by comparison, there was 1 of 31 (3.2%) symptomatic ICH in the rtPA group	N/A	Prematurely terminated due to slow recruitment	The 0.4 mg/kg dose was inferior; the other two doses appeared to be similar to standard dose alteplase
DIAS 2 Hacke W, et al.[92] 2009 19097942	**Aim:** Assess the safety and efficacy of two doses of desmoteplase between 3–9 h after stroke onset in patients with radiological penumbra **Study type:** RCT (phase II dose-ranging) **Size:** N=193	**Inclusion criteria:** NIHSS 4–24; ≥20% mismatch by DWI/PWI or CTP; within 3–9 h of symptom onset **Exclusion criteria:** Age>85 y; hemorrhage on CT or MRI; infarct core >1/3	**Intervention:** Desmoteplase, 90 mcg/kg (n=57) or 125 mcg/kg (N=66) **Comparator:** Placebo (n=63)	**1° end point:** Favorable clinical outcome at 90 d*: 47% with 90 mcg/kg vs. 36% with 125 mcg/kg vs. 46% with placebo; *P*=0.47 **Safety end point:** sICH: 3.5% with 90 mcg/kg vs. 4.5% with 125 mcg/kg vs. 0% with placebo	• Median changes in lesion volume: 90 mcg/kg desmoteplase 14% (0.5 cm^3), 125 mcg/kg desmoteplase 11% (0.3 cm^3), placebo 10% (–0.9 cm^3) • Mortality rate was 5% for 90 mcg/kg	Dose-ranging trial	The investigated doses of desmoteplase did not improve outcomes in patients with acute stroke and tissue-at-risk within 3–9 h from symptom onset

		of MCA territory on DWI or CTP; high risk of bleeding; ICA occlusion			desmoteplase, 21% for 125 mcg/kg desmoteplase, and 6% for placebo		
DEDAS Furlan AJ, et al.[94] 2006 16574922	**Aim:** Assess the safety and efficacy of two doses of desmoteplase between 3–9 h after stroke onset in patients with radiological penumbra **Study type:** RCT (Phase II, dose-escalation) **Size:** N=104	**Inclusion criteria:** NIHSS 4–20; DWI/PWI mismatch; within 3–9 h of symptom onset **Exclusion criteria:** Age>85 y; hemorrhage on MRI; infarction >1/3 of MCA territory on DWI; high risk of bleeding	**Intervention:** Desmoteplase, 90 mcg/kg (n=14) or 125 mcg/kg (n=15) **Comparator:** Placebo (n=8)	**1° end point:** Rate of reperfusion on MRI after 4–8 h: favorable clinical outcome at 90 d*: 18% with 90 mcg/kg vs. 53% with 125 mcg/kg vs. 38% with placebo **Safety end point:** sICH: 0% in all groups	Favorable clinical outcome at 90 d*: 29% with 90 mcg/kg vs. 60% with 125 mcg/kg vs. 25% with placebo; *P*=0.02 in favor of the 125 mcg/kg dose	Dose-escalation trial	Desmoteplase in doses of 90 mcg/kg or 125 mcg/kg appeared safe
DIAS Hacke W, et al.[95] 2005 15569863	**Aim:** Assess the safety and efficacy of various doses of desmoteplase between 3–9 h after stroke onset in patients with radiological penumbra **Study type:** RCT (Phase II, dose-finding) **Size:** N=104	**Inclusion criteria:** NIHSS 4–20; DWI/PWI mismatch; within 3–9 h of symptom onset **Exclusion criteria:** Age>85 y; hemorrhage on MRI; infarction >1/3 of MCA territory on DWI; high risk of bleeding	**Intervention:** Desmoteplase, multiple doses (n=75) **Comparator:** Placebo (n=27)	**1° end point:** Rate of reperfusion on MRI after 4–8 h: 71% vs. 19%; *P*=0.001 (125 mcg/kg dose) **Safety end point:** sICH: 26.7% with fixed doses (i.e., not weight-adjusted) and 2.2% with weight-adjusted doses vs. 0% with placebo	Favorable clinical outcome at 90 d*: 60% vs. 47%; *P*=0.009 (125 mcg/kg dose)	Dose-finding trial	• Acceptable rate of sICH with doses of up to 125 mcg/kg • Desmoteplase may confer improved rates of reperfusion by MRI criteria

*Defined as ≥8 points improvement on NIHSS (or 0 to 1), mRS (0 to 2), and Barthel Index (75 to 100).

Abbreviations: ACA indicates anterior cerebral artery; CI, confidence interval; CT, computed tomography; CTA, computed tomography angiogram; CTP, computed tomography perfusion; DWI, diffusion weighted imaging; GFR, glomerular filtration rate; h, hours; ICA, internal carotid artery; ICH, intracerebral hemorrhage; MRA, magnetic resonance angiogram;

MRI, magnetic resonance imaging; mRS, modified Rankin scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NS, not significant; OR, odds ratio; PCA, posterior cerebral artery; PWI, perfusion weighted imaging; RCT, randomized clinical trial; sICH, symptomatic intracerebral hemorrhage; y, years.
Literature search topic: IV lysis

Table XL. Randomized Clinical Trials Of Adjuvant Sonothrombolysis (since 2013 AIS Guidelines)

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
NOR-SASS Nacu A, et al.[171] 27980128	**Aim:** to demonstrate superiority of contrast-enhanced ultrasound treatment (sonothrombolysis) versus sham ultrasound treatment in consecutively admitted patients with acute ischemic stroke within 4.5 hours after stroke onset **Study Type:** multicenter, prospective, open-label, blinded endpoint, phase 3 RCT **Size:** N=183	**Major Inclusion Criteria:** Acute ischemic stroke patients ≥ 18 years, with or without visible arterial occlusion on computed tomography angiography (CTA) and treatable ≤ 4(½) hours after symptom onset **Major Exclusion Criteria:** Premorbid mRS ≥3; Primary endovascular treatment; Recent or unstable coronary ischemia or resting angina <7 days; Acute	**Intervention:** Contrast Enhanced Sonothrombolysis with 2 MHz pulse-wave transcranial Doppler (TCD) ultrassund for 60 minutes and microbubbles plus alteplase/tenecteplase (n=93) **Comparator:** sham ultrasound, sham microbubbles (NaCl 0.9%) plus alteplase/tenecteplase (n=90)	**6 1° end points defined in different ways:** neurological improvement at 24 hours (3) and functional handicap at 90 days (3): All *P* 0.05 **Safety end point:** sICH 2/93 vs 4/90; *P*=0.13		Stopped prematurely (183 of planned 276) for lack of funding	Sonothrombolysis was safe among unselected ischemic stroke patients with or without a visible occlusion on computed tomography angiography and with varying grades of clinical severity. There was no statistically significant clinical effect of sonothrombolysis in this prematurely stopped trial.

		cardiac insufficiency, cardiac insufficiency class III/IV; serious cardiac arrhythmias; Any right-left-shunt, severe pulmonary hypertension (PAP >90 mmHg) Moderate to severe chronic obstructive pulmonary disease (COPD), baseline O2 saturation <80 %)					

Table XLI. Nonrandomized Trials, Observational Studies, and/or Registries of Endovascular Therapy

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Coutinho JM, et al.[381] 2017 28097310	**Study type:** Post hoc-analysis **Size:** N=291 (N=160 ET and IV alteplase, N=131 ET alone)	**Inclusion criteria:** Two multicenter, prospective clinical trials using the Solitaire device: SWIFT and STAR registry **Exclusion criteria:** Patients in dataset	**1° end point:** • Reperfusion • 90 d mRS 0–2 • Mortality **Results:** • No clinically meaningful differences between groups • TICI 2b/3: ET+IV alteplase 84.1%, ET alone 84.7%. • 90 d mRS 0–2: ET+IV alteplase 57.7%, ET alone 47.7% (*P*=0.1)	• Similar treatment times, device passes, and emboli to new territory between groups • Non-randomized patient sample, with local site variation in treatment protocols • Approximately 1/4 of patients in ET+IV alteplase group were treated with reduced dose alteplase (0.6 mg/kg), although sensitivity analysis

		treated with Merci device	• Mortality: ET+IV alteplase 8.1%, ET alone 12.2%	excluding these patients found similar results • Findings suggest that IV alteplase does not provide additional benefit in endovascular treatment of acute ischemic stroke from large vessel occlusion
Bush CK, et al.[174] 2016 26807742	**Study type:** Meta-analysis **Size:** N=1287	**Inclusion criteria:** Meta-analysis of contemporary ET with stent retrievers vs. standard care for patients with acute ischemic anterior circulation stroke: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Non-randomized trials, studies not reporting ORs or variances, studies where ET with new generation thrombectomy devices was not part of intervention	**1° end point:** Day 90 mRS 0–2 **Results:** OR for ET: 2.2 (95% CI, 1.66–2.98; *P*<0.0001)	• Improved functional outcomes and greater chance of functional outcome after ET with new generation thrombectomy devices • Similar complication profiles and mortality between ET and standard care • Treatment effect independent of IV alteplase administration • Findings underscore impact of time dependence on treatment outcome but cannot provide precise time-point after onset of symptoms for futility • Homogenous benefit across subgroups • Findings strongly support recommendations for early ET for acute ischemic stroke patients with LVO, using new thrombectomy devices
SEER Campbell BC, et al.[173] 2016 26888532	**Study type:** Meta-analysis **Size:** N=787	**Inclusion criteria:** Meta-analysis (patient-level data) of acute ischemic stroke trials in which Solitaire stent retriever was the only or the predominant device used:	**1° end point:** Day 90 mRS ordinal analysis **Results:** • mRS score improvement OR, 2.7 (95% CI, 2.0–3.5; $P \leq 1 \times 10^{-10}$) • NNT of 2.5 for improvement in 1 grade of mRS score	• No difference in secondary end points of sICH or mortality • NNT of 4.25 for independent functional outcome, homogeneity of benefit across subgroups • Revascularization rates 77% with Solitaire • Reduced mortality after ET in patients ≥80 y 20% vs. 40%, adjusted OR: 3.7 (1.3–10.6) *P*=0.01,

		SWIFT PRIME, ESCAPE, EXTEND-IA, REVASCAT **Exclusion criteria:** Non-randomized trials, trials without imaging confirmation of LVO, trials where Solitaire was not the dominant device utilized initially, and others		despite overall equivalence for mortality as a secondary outcome • Study details results with Solitaire and does not evaluate other devices for thrombectomy • Identifies robust benefit for Solitaire thrombectomy in acute ischemic stroke patients
HERMES Goyal M, et al.[172] 2016 26898852	**Study type:** Meta-analysis **Size:** N=1287	**Inclusion criteria:** Meta-analysis (patient level data) of ET vs. medical management for acute ischemic stroke due to LVO: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Trials other than the 5 recent randomized trials listed	**1° end point:** Day 90 mRS shift analysis **Results:** • Adjusted cOR: 2.49 (95% CI, 1.76–3.53; *P*<0.0001) • NNT for 1 point reduced disability on mRS is 2.6	• Shows clinical benefit from thrombectomy across wide range of age and stroke severity • 71% with TICI 2b/3 result after ET • Mortality, sICH, and parenchymal hematoma equivalent between groups • Homogeneous benefit across pre-specified subgroups, including age>80 y, tandem occlusions, ASPECTS or NIHSS score • Benefit irrespective of IV alteplase administration • Patient-level data utilized for analysis from studies utilizing current clinical practice patterns. • Consistency of benefit suggests that results likely apply to broader patient range after acute ischemic stroke from LVO
Grech R, et al.[382] 2016 26597570	**Study type:** Meta-analysis **Size:** Solitaire N=762, Trevo N=210	**Inclusion criteria:** Meta-analysis of studies utilizing Solitaire or Trevo in the treatment of acute ischemic stroke	**1° end point:** • Recanalization rates • 90 d mRS 0–2 • sICH **Results:**	• Aggregates information from studies regarding stent retrievers to increase statistical power • Evaluates only Solitaire and Trevo devices

		Exclusion criteria: Case reports or series, patients treated without ET, trails utilizing pooled data from other sources, animal studies, and others	• No clinically meaningful differences between Solitaire and Trevo groups • Recanalization 86.7% vs. 80.8% (Solitaire vs. Trevo) • Weighted mean 1.9 passes vs. 2.5 passes (Solitaire vs. Trevo) • Functional outcome in 52.1% vs. 47.6% (Solitaire vs. Trevo) • sICH 7% vs. 8.5% (Solitaire vs. Trevo)	• Only two RCTs included; remainder are observational or non-RCT designs • Includes trials utilizing TIMI 2/3 recanalization targets • Supports the use of stent retrievers to achieve functional outcomes with good safety profiles, without clear differences between Solitaire and Trevo
Rodrigues FB, et al.[383] 2016 27091337	**Study type:** Meta-analysis **Size:** N=2925	**Inclusion criteria:** Meta-analysis of ET vs. medical management for acute ischemic stroke due to LVO: IMS II, MR RESCUE, SYNTHESIS Expansion, MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-IA, THERAPY, THRACE **Exclusion criteria:** Observational studies, non-controlled or non-randomized interventional studies, studies without mechanical thrombectomy in intervention arm or IV alteplase in control arm	**1° end point:** • 90 d mRS 0–2 • Mortality **Results:** • ET functional outcome risk ratio: 1.37 (95% CI, 1.14–1.64) • No mortality differences risk ratio: 0.9 (95% CI, 0.76–1.06) •Analysis restricted to MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-IA, THERAPY, THRACE: functional outcome risk ratio: 1.56 (95% CI, 1.38–1.75), mortality risk ratio: 0.86 (95% CI, 0.69–1.06)	• Provides evidence for the benefit of ET, particularly stent retriever thrombectomy, over medical management alone for treatment of acute ischemic stroke from LVO • Includes both THERAPY and THRACE but only data from results presented in press or meetings • Heterogeneous group of studies included, with variable endovascular treatment methods. Analyzed further as studies published prior to 2015 and those published during or after 2015
Saver JL, et al.[32] 2016 27673305	**Study type:** Meta-analysis **Size:** N=1287	**Inclusion criteria:** Meta-analysis of time to treatment of ET vs. medical management	**1° end point:** 90 d mRS ordinal shift **Results:** • ET mRS 2.9 (95% CI, 2.7–3.1);	• Defines a time window of <7.3 h to arterial puncture for benefit of ET for acute ischemic stroke patients with LVO

		for acute ischemic stroke due to LVO: MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Trials other than the 5 recent randomized trials listed	standard care mRS 3.6 (95% CI, 3.5–3.8) • mRS scale distribution declined with longer time to treatment. • Absolute risk difference for reduced disability 39.2% at 3 h, 30.2% at 6 h, 15.7% at 8 h; benefit absent after 7.3 h	• No sub group analysis by trial to determine which imaging criteria selected patients who benefitted after 6 h most accurately • Time dependence for therapy highlights need for initiation of therapy as rapidly as possible after onset of symptoms, with benefit greatest for treatment initiation <2 h from symptom onset • In hospital processes directly associated with improved functional outcome • Mortality, sICH, and parenchymal hematoma rates did not vary with longer delay to reperfusion
Touma L, et al.[384] 2016 26810499	**Study type:** Systematic review and meta-analysis **Size:** N=1287	**Inclusion criteria:** Systematic review and meta-analysis to quantify benefits and risks of using stent retrievers with alteplase compared to alteplase alone for acute ischemic stroke from large vessel occlusion, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Observational studies, case reports, reviews, abstracts, and others	**1° end point:** 90 d mRS 0–2 **Results:** Stent retriever patients: • Greater functional outcome, RR: 1.72 (95% CI, 1.48–1.99) • Greater odds of 1-unit decrease in 90 d mRS, pooled OR: 2.03 (95% CI, 1.65–2.50)	• Mortality, sICH, parenchymal hematoma inconclusive between groups (wide CI), no detectable differences between groups • Asserts the benefit of stent retriever thrombectomy for treatment of acute ischemic stroke patients with LVO
Badhiwala JH, et al.[385] 2015 26529161	**Study type:** Meta-analysis **Size:** N=2423	**Inclusion criteria:** Meta-analysis of ET vs. medical management for	**1° end point:** • Day 90 mRS 0–2 • Ordinal mRS improvement • Revascularization at 24 h	• Confirms improved functional outcomes and higher rates of angiographic revascularization at 24

		acute ischemic stroke: IMS II, MR RESCUE, SYNTHESIS Expansion, MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-IA **Exclusion criteria:** Non-randomized studies, retrospective series, pilot studies, abstracts, studies that did not include IV alteplase for controls or ET for interventions, and others	• sICH within 90 d • All-cause mortality at 90 d **Results:** • mRS score 0–2: 44.6% for ET vs. 31.8% for standard care, OR, 1.71 (95% CI, 1.18–2.49; *P*=.005) • ET treatment benefit across all mRS scores, OR, 1.56 (95% CI, 1.14–2.13; *P*=.005) • ET higher rates of angiographic revascularization at 24 h (75.8% vs. 34.1%; OR, 6.49 (95% CI, 4.79–8.79; *P*<.001)) • Similar sICH and mortality	h for ET compared to IV alteplase alone • No clinically meaningful difference between groups in symptomatic intracranial hemorrhage or all-cause mortality at 90 d • Confirmation of LVO pre-procedurally increased chance of improved functional outcome after ET • Benefit of ET was increased by concomitant use of IV alteplase
Chen CJ, et al.[386] 2015 26537058	**Study type:** Meta-analysis **Size:** N=2423	**Inclusion criteria:** Meta-analysis of outcomes in RCT of acute ischemic stroke patients undergoing ET: IMS II, MR RESCUE, SYNTHESIS Expansion, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Single center, non-randomized trials, failure to compare ET to standard care directly	**1° end point:** Day 90 mRS 0–2 **Results:** • OR for ET, 1.71; *P*=0.005 • Subgroup analysis of 6 trials with LVO criteria: OR, 2.23 for d 90 mRS 0–2; *P*<0.00001	• Subgroup analysis of 2 trials without LVO selection criteria failed to demonstrate difference between groups in functional independence • Angiographic revascularization achieved in 565 (56%) of 1,005 patients • Similar sICH and mortality rates • Heterogeneous treatment methods in ET group
Elgendy IY, et al.[387]	**Study type:** Meta-analysis	**Inclusion criteria:** Meta-analysis of	**1° end point:** 90 d mRS 0–2	• ET associated with 45% relative and 13% absolute higher likelihood

2015 26653623	**Size:** N=2410	outcomes in RCT of ET for patients presenting within 4.5 h of symptom onset: IMS II, MR RESCUE, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Trials that prohibited IV alteplase before thrombectomy, non-randomized studies, retrospective series, and others	**Results:** For ET RR, 1.45 (95% CI, 1.22–1.72; *P*<0.0001)	of mRS 0–2 compared to standard care alone • Demonstrates the efficacy and safety of ET compared to standard care for acute ischemic stroke patients • Similar rates of sICH but a trend towards decreased mortality with ET (RR: 0.86, 95% CI: 0.72–1.02; *P*=0.09)
Fargen KM, et al.[388] 2015 25432979	**Study type:** Meta-analysis **Size:** N=183/N=1903	**Inclusion criteria:** Meta-analysis of outcomes in RCT of ET in acute ischemic stroke patients with LVO criteria and without LVO criteria: PROACT II, MELT, IMS III, SYNTHESIS, MR RESCUE, MR CLEAN **Exclusion criteria:** Non-randomized studies, retrospective series, comparison to historical controls	**1° end point:** Day 90 mRS 0–2 shift analysis **Results:** • LVO confirmation: OR, 1.67 (95% CI: 1.29–1.16, *P*=0.0001) • No LVO confirmation: OR, 1.27 (95% CI, 1.05–1.54; *P*=0.019)	• Identifies superior outcomes in patients undergoing ET, particularly with LVO demonstrated pre-procedurally • Does not include contemporary ET trials, with the exception of MR CLEAN
Kumar G, et al.[389] 2015 25271064	**Study type:** Meta-analysis **Size:** N=2056 (IA N=1715, IV N=341)	**Inclusion criteria:** Meta-analysis of published studies on stroke therapy for basilar artery occlusion	**1° end point:** Death or dependency (DoD), mortality **Results:** • For entire population Recanalization decreased: DoD RR: 0.67 (95% CI, 0.63–0.72)	• Included endovascular and IV cases of basilar occlusion • Suggests equivalence between endovascular therapies and IV treatment, but supports the benefit

		Exclusion criteria: Studies of LVO other than basilar artery, abstracts, case reports, reviews, meta-analyses, studies lacking outcome data, and others	Mortality RR: 0.49 (95% CI, 0.44–0.55) • For IA patients recanalized: DoD RR: 0.67; mortality RR: 0.53	of recanalization in patients with acute basilar occlusion
Marmagkiolis K, et al.[390] 2015 26476611	**Study type:** Meta-analysis **Size:** N=1287	**Inclusion criteria:** Meta-analysis of ET for ICA and M1 occlusions vs. standard care: MR CLEAN, ESCAPE, REVASCAT, SWIFT PRIME, EXTEND-IA **Exclusion criteria:** Non-randomized studies, retrospective series, and others	**1° end point:** Day 90 mRS 0–2 **Results:** ET 42.6% vs. standard care 26.1% (*P*<0.0001), OR, 2.43 (95% CI, 1.9–3.09)	• Analysis restricted to acute ischemic stroke therapy in contemporary trials • sICH and 90-d mortality equivalent between groups • Confirms safety and efficacy of stent retriever use for ischemic stroke after large vessel occlusion
Yarbrough CK, et al.[391] 2015 26396032	**Study type:** Systematic review and meta-analysis **Size:** N=2049	**Inclusion criteria:** Systematic review and meta-analysis to evaluate effect of ET on outcome for LVO patients: IMS II, MR RESCUE, SYNTHESIS Expansion, MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT **Exclusion criteria:** Non-randomized studies, case reports or series, and others	**1° end point:** 90 d mRS 0–2 **Results:** • All trials: pooled OR: 1.75 (95% CI: 1.2–2.54) • All trials requiring LVO confirmation: OR, 2.0 (95% CI, 1.48–2.71)	• Confirms benefit of ET for acute ischemic stroke patients compared to standard care alone • Use of IV alteplase associated with improved outcomes (OR: 1.83, 95% CI: 1.46–2.31), no IV alteplase also increased odds for good outcome, but not statistically significant (OR: 1.59, 95% CI: 0.86–2.95) • Effect of ET greater in subgroup with higher NIHSS • Trend towards decreased mortality in ET group; similar sICH rates • Treatment benefit if ET commenced before 6-8 h from onset

				• Heterogeneous ET techniques in studies included
Almekhalfi MA, et al.[392] 2013 22837311	**Study type:** Meta-analysis **Size:** N=925 (MERCI N=357, Penumbra N=455, stent retriever N=113)	**Inclusion criteria:** Meta-analysis of device-based trials to assess impact of recanalization on the outcome of ET **Exclusion criteria:** Studies investigating devices other than MERCI, Penumbra, or stent retrievers	**1° end point:** TICI 2b/3, day 90 mRS 0–2 **Results:** • Successful recanalization in 59.1% MERCI studies (95% CI, 49.3–77.7), 86.6% Penumbra studies (95% CI, 84.1–93.8), and 92.9% stent retriever studies (95% CI, 90.9–99.9) • mRS 0–2 in 31.5% MERCI, 36.6% Penumbra, and 46.9% stent retriever	• Analyzes comparative recanalization rates, procedural timing, and outcomes between various devices based on published trials • Minimal data available for procedure times for MERCI device, but Penumbra and stent retriever comparable in treatment times • References first generations of stent retrievers, and earlier generations of aspiration systems; does not reflect current practice patterns
Fields JD, et al.[393] 2011 21990808	**Study type:** Meta-analysis **Size:** N=334	**Inclusion criteria:** Meta-analysis of IA thrombolytics for MCA occlusion vs. placebo: PROACT, PROACT II, MELT **Exclusion criteria:** Studies utilizing mechanical thrombectomy techniques	**1° end point:** Day 90 mRS 0–1, 0–2; sICH **Results:** • IAT day 90 mRS 0–1: 31% vs. 20%, OR, 2.0 (95% CI, 1.2–3.4; *P*=0.01) • IAT mRS 0–2: 43% vs. 31%, OR, 1.9 (95% CI, 1.2–3.0; *P*=0.01) • sICH: 11% vs. 2%, OR, 4.6 (95% CI, 1.3–16; *P*=0.02)	• Estimates benefit of endovascular therapy from intra-arterial lytic administration • Endovascular therapy improved all functional outcome measures with similar mortality despite increased risk of sICH • Supports efficacy and safety within 6 h of intra-arterial lytic therapy for MCA occlusions • Heterogeneity in sample; MELT (compared to PROACT and PROACT II) treated patients earlier and with more mild strokes, and permitted guidewire maceration • Urokinase not available in the US since October 2010 • Many control patients would now receive IV alteplase; effect of intra-arterial thrombolytic compared to contemporary stroke therapy therefore uncertain

Abbreviations: ASPECTS indicates Alberta Stroke Program Early CT Score; CI, confidence interval; DoD, death or dependency; ET, endovascular therapy; GA, general anesthesia; IAT, internal carotid artery; IV, intravenous; LVO, large vessel occlusion; MCA, middle cerebral artery; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; NNT, number needed to treat; OR, odds ratio; sICH, symptomatic intracerebral hemorrhage; TICI, thrombolysis in cerebral infarction; TIMI, thrombolysis in myocardial infarction; RCT, randomized clinical trial; RR, relative risk; and y, years.
Literature search topic: Endovascular interventions

Table XLII. Randomized Clinical Trials Comparing General Anesthesia to Conscious Sedation for Endovascular Stroke Therapy

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
AnSTROKE Lowhagen Henden P et al.[181] 28522637	**Aim:** null hypothesis was that the anesthesia technique does not have an impact on neurological outcome, as long as severe hypotension during the procedure is avoided **Study type:** single-center, open-label, blinded end-point RCT **Size**: 90	**Major Inclusion criteria:**) ≥18 years of age; proven occlusion in anterior cerebral circulation by CT angiography; NIHSS ≥10 (iright-sided occlusion) or ≥14 (left-sided occlusion; treatment initiated within 8 hours after onset of symptoms. **Major Exclusion criteria:** anesthesiological concerns (airway, agitation, etc) at the discretion of	**Intervention:** General anesthesia (GA) by propofol and remifentanil, maintained with sevoflurane and remifentanil, (n=45) **Comparator:** Conscious sedation (CS) by remifentanil infusion (n=45)	**1° end point:** mRS 0-2 at 3 months: GA: 19/45 (42.2%) CS: 18/45 (40.0%) (*P*=1.00) **Safety end point:** • Symptomatic ICH 22-36 hrs: GA: 0/45 (0%) CS: 3/45 (7%) *P*=0.24	mTICI 2b–3 GA: 41/45 (91%0 CS: 40/45(89%) *P*=1.00	• single-center study • size of the study limited •superiority design not designed to establish noninferiority	•In this small, single center study no statistically significant difference was found between GA and CS in neurological outcome 3 months after stroke or in mTICI 2b/3 recanalization.

		the attending anesthetist;) premorbidity mRS ≥4 or other comorbidity contraindicating embolectomy.					
SIESTA Schonenberger S, et al.[182] 2016 [27785516](27785516)	**Aim:** To assess whether conscious sedation is superior to general anesthesia for early neurological improvement among patients receiving acute ischemic stroke thrombectomy **Study type:** RCT **Size:** N=150	**Inclusion criteria:** NIHSS>10, IC ICA, M1, <9 h **Exclusion criteria:** Aspiration risk, severe agitation, difficult airway access, and many more	**Intervention:** GA during procedure (n=73) **Comparator:** Conscious sedation during procedure (n=77)	**1° end point:** NIHSS improvement after 24 h: -3.2 NIHSS points GA group, -3.6 NIHSS points conscious sedation group; mean difference 0.4 points (95% CI, -3.4 to 2.7; *P*=0.82) **Safety end point:** • Death 24.7% vs. 24.7% • Vessel perforation/SAH 1.4% vs. 2.6% (*P*=0.59)	• TICI 2b/3: 89% GA vs. 80% conscious sedation group (not clinically meaningful) • No clinically meaningful differences in mRS or mortality at 3 mo between groups • No clinically meaningful differences in process time points or duration of endovascular therapy	Single center; experienced with general anesthesia pre-trial initiation, small sample size, early primary end point assessment (24 h)	Trial findings do not support an advantage for conscious sedation over GA in acute endovascular ischemic stroke intervention

Abbreviations: CI indicates confidence interval; ICA, internal carotid artery; GA, general anesthesia; NIHSS, National Institutes of Health Stroke Score; RCT, randomized clinical trial; SAH, subarachnoid hemorrhage; and TICI, thrombolysis in cerebral infarction.

Literature search topics: Endovascular interventions

Table XLIII. Nonrandomized Trials, Observational Studies, and/or Registries Comparing General Anesthesia to Conscious Sedation for Endovascular Stroke Therapy

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Berkhemer OA, et al.[180] 2016 27421546	**Study type:** Post hoc analysis of MR CLEAN **Size:** GA N=79, CS N=137, control N=267	**Inclusion criteria:** Post hoc analysis comparing the clinical and angiographic outcomes of GA vs. CS for all patients allocated to ET in MR CLEAN **Exclusion criteria:** Inability to undergo ET (1 patient)	**1° end point:** 90 d mRS 0–2 **Results:** • GA with 51% lower chance of mRS 0–2 (95% CI: 31%–86%), absolute risk difference 19% for mRS 0–2 in favor of CS group compared to control (adjusted OR, 2.96; 95% CI, 1.78–4.92) • Greater infarct growth in GA group. Door to groin time 32 min longer in GA group (*P*=0.001) • Similar safety outcomes and procedural duration between GA and CS	• Conversion to GA occurred in 4.4% • No data on type of anesthesia collected in MR CLEAN • Limited details about procedural BP changes • Results challenge routine use of GA
Brinjkji W, et al.[394] 2015 25395655	**Study type:** Systematic review and meta-analysis **Size:** N=1956	**Inclusion criteria:** Systematic review and meta-analysis comparing the clinical and angiographic outcomes of GA vs. CS **Exclusion criteria:** Case reports, non-comparative studies, studies that failed to separate outcome by anesthesia type, and others	**1° end point:** 90 d mRS 0–2 **Results:** GA with lower odds of mRS 0–2 (OR, 0.43; 95% CI, 0.35–0.53) and TICI 2b/3 (OR, 0.54; 95% CI, 0.37–0.80); higher odds of death (OR, 2.59; 95% CI; 1.87–3.58) and respiratory complications (OR, 2.09; 95% CI; 1.36–3.23).	• No included studies were randomized trials • Higher rates of both recanalization and good functional outcomes for patients treated with conscious sedation • Decreased rates of mortality and respiratory complications for patients treated with conscious sedation • Similar procedural time-points between groups

Abbreviations: CI indicates confidence interval; CS, conscious sedation; ET, endovascular therapy; GA, general anesthesia; mRS, modified Rankin Scale; OR, odds ratio; and TICI, thrombolysis in cerebral infarction.
Literature search topic: Endovascular interventions

Table XLIV. Nonrandomized Studies of Antiplatelet Therapy in Patients with Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Li W, et al.[395] 2016 27608821	**Study type:** Single-arm, open label, propensity matched **Size:** N=41	**Inclusion criteria:** IV alteplase + tirofiban infusion **Exclusion criteria:** alteplase exclusions	**1° end point:** 90 d mRS (favorable 0–1) **Results:** 70.7% vs. 46.2% (*P*=0.026)	Interpretation limited by generalizability; warrants a prospective randomized trial
Wada T, et al.[396] 2016 27567296	**Study type:** Retrospective, observational, propensity matched **Size:** N=2726 (LAA), N=1612 (SVD)	**Inclusion criteria:** AIS in Japan treated with ozagrel (subtyped LAA, SVD) **Exclusion criteria:** Age<40 y, atrial fibrillation or other indication for AC	**1° end point:** mRS at discharge **Results:** • LAA, OR, 0.99 (0.88–1.11); SVD, OR, 1.99 (0.87–1.16) • sICH no difference	Limited by generalizability; warrants further study in a prospective randomized trial
CLEAR-ER Adeoye O, et al.[189] 2015 25523054	**Study type:** Post hoc, propensity matched analysis of data from 3 prior trials **Size:** 85 vs. 169 matched controls (IMS III, ALIAS Part 2)	**Inclusion criteria:** 0.6 mg/kg IV alteplase <3 h, + eptifibatide infusion **Exclusion criteria:** alteplase exclusions	**1° end point:** Severity-adjusted mRS at 90 d (favorable outcome mRS 0–2) **Results:** 45% vs. 36% unadjusted RR, 1.24 (0.91–1.69)	0.6 mg/kg IV alteplase + eptifibatide in AIS warrants a prospective randomized trial
CLEAR-FDR Adeoye O, et al.[190] 2015 26243231	**Study type:** Single-arm, open-level, multicenter **Size:** N=27	**Inclusion criteria:** Full dose IV alteplase <3 h, + eptifibatide infusion **Exclusion criteria:** alteplase exclusions	**1° end point:** sICH within 36 h **Results:** 3.7% sICH	Full dose IV alteplase + eptifibatide appears safe and warrants a prospective randomized trial

Abbreviations: AC indicates anticoagulation; AIS, acute ischemic stroke; CI, confidence interval; IV, intravenous; LAA, large-artery atherosclerosis; OR, odds ratio; RR, relative risk; sICH, symptomatic intracerebral hemorrhage; and SVD, small vessel disease.
Literature search topic: Antiplatelet

Table XLV. Randomized Clinical Trials Comparing Antiplatelet to Control

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
SOCRATES Johnston SC and Amarenco P[196] 2016 [27705253](27705253)	**Aim:** To determine the efficacy of ticagrelor vs. ASA in minor stroke or high-risk TIA **Study Type:** Randomized, double-blind, placebo-controlled trial **Size:** N=13,199 (674 centers, 33 countries)	**Inclusion criteria:** Acute minor stroke (NIHSS≤5) or TIA (ABCD2≥4), age>40, ability to start study drug within 24 h onset **Exclusion criteria:** Clear indication or contraindication for specific antiplatelet therapy; thrombolytic or EVT; numerous others	**Intervention:** Ticagrelor (180 mg day 1, 90 mg BID × 90 d) + placebo (n= 6589) **Comparator:** ASA (300 mg day 1, 100 mg daily × 90 d) + placebo (n=6610)	**1° end point**: Time to composite stroke, MI, or death up to 90 d: ticagrelor 442 (6.7%) vs. ASA 497 (7.5%); HR, 0.89 (0.78–1.01); *P*=0.07 **Safety end point**: Time to first bleeding event up to 90 d: no difference	• Ischemic stroke: 385 (5.8) vs. 441 (6.7), HR, 0.87 (0.76–1.00); *P*=0.046 • All stroke: 390 (5.9) vs. 450 (6.8) HR, 0.86 (0.75–0.99); *P*=0.03; p-values considered non-significant	• Low enrollment of high-risk patients (e.g., symptomatic carotid) • Low event rates in TIA group • More patients had premature discontinuation in the ticagrelor group due to adverse events (e.g., dyspnea)	Ticagrelor not recommended
Ciccone A, et al.[191] 2014 [24609741](24609741)	**Aim:** To assess safety and efficacy of glycoprotein GP IIb-IIIa inhibitors in AIS **Study Type:** Cochrane review **Size:** N=1365 (4 trials)	**Inclusion criteria:** Randomized, unconfounded trials, started treatment within 6 h of stroke onset **Exclusion criteria:** Nonrandomized, risk of bias at	**Intervention:** IV GP IIb-IIIa inhibitor (abciximab, tirofiban) either alone or in combination with IV thrombolytic agents (n=685) **Comparator:** (n=680)	**1° end point**: Death or dependency at follow-up: abciximab vs. placebo: OR: 0.97 (0.77–1.22); tirofiban vs. ASA: OR, 1.00 (0.52–1.92) **Safety end point**: sICH: abciximab vs. placebo, OR, 4.6 (95% CI, 2.01–10.54); tirofiban vs. ASA, OR, 0.32 (95% CI, 0.03–3.19)	Non-significant difference in risk of extracranial hemorrhage: abciximab (OR, 1.81; 95% CI: 0.96–3.41); tirofiban (OR, 3.04, 95% CI, 0.12–75.83)	• Abciximab contributed 89% of the total study participants considered • Heterogeneity between trials • Only 2 new trials (abESTT-II and SETIS) included since 2006 review	Supports current LOE

		discretion of reviewers				• Excluded CLEAR trials (2008, 2013) due to lower dose of IV alteplase in the intervention group compared to control	
Sandercock PA, et al.[186] 2014 [24668137](24668137)	**Aim:** To assess the safety and efficacy of oral antiplatelet therapy in AIS started within 14 d from onset **Study Type:** Cochrane review **Size:** N=41,483 (8 trials)	**Inclusion criteria:** Randomized, unconfounded trials of oral antiplatelet therapy in AIS started within 14 d from onset **Exclusion criteria**: Nonrandomized, treatment allocation not concealed from enrolling investigator	**Intervention:** Antiplatelet therapy (4 studies tested ASA, 3 tested ticlopidine, and 1 tested ASA / dipyridamole); *2 trials (IST, CAST) testing ASA 160–300 mg daily, started within 48 h, contributed 98% of the data (n=20,647) **Comparator:** (n=20,644)	**1° end point**: Death or dependency at follow-up: ASA vs. control, OR, 0.95 (0.91–0.99); *P*=0.01 **Safety end point**: sICH: ASA vs. control, OR: 1.23 (1.00–1.50), *P*=0.04	Significant reduction in recurrent ischemic stroke, PE	• 98% of data contributed by 2 trials published in 1997 (IST, CAST) • No new trials included since 2008 • Trial data limited primarily to conclusions about ASA • Excluded IV antiplatelet agents	Supports current LOE
CHANCE Wang Y, et al.[193] 2013 [23803136](23803136)	**Aim:** To determine the efficacy of ASA/clopidogrel vs. ASA alone in patients with minor stroke or high-risk TIA **Study Type:** Randomized, double-blind, placebo-controlled trial	**Inclusion criteria:** Acute minor stroke (NIHSS ≤3) or TIA (ABCD2 ≥4), age>40, ability to start study drug within 24 h onset	**Intervention**: Open label ASA (75–300 mg day 1, 75 mg day 2–21) + clopidogrel (300 mg day 1, 75 mg daily day 2–90) (n=2584) **Comparator**: Open label ASA (75–300 mg day	**1° end point:** New stroke (ischemic or hemorrhagic at 90 d): ASA/clopidogrel 212 (8.2%) vs. ASA/placebo 303 (11%), HR, 0.68 (0.57–0.81); *P*<0.001 **Safety end point:** Moderate to severe	• Stroke, MI, vascular death: 216 (8.4%) vs. 307 (11.9%), HR, 0.69 (0.58–0.82); *P*<0.001 • Ischemic stroke 204 (7.9%) vs. 295 (11.4%), HR, 0.67 (0.56–0.81); *P*<0.001	• Stratified randomization by site and time of randomization • Intervention group received placebo ASA d 21–90 • Questionable external validity in non-Asian populations and	Adds to current LOE; awaiting definitive RCT (POINT)

	Size: N=5170 (114 centers in China)	**Exclusion criteria**: Isolated sensory, visual symptoms, dizziness without evidence of infarct on MRI, a clear indication for AC, history of GIB or surgery within previous 3 mo, numerous other exclusions	1, 75 mg day 2–90 + placebo (n=2586)	bleeding event: no difference	• No difference in hemorrhagic stroke	outside of Chinese healthcare system: POINT trial ongoing in the US	
CHANCE-1 YEAR Wang Y, et al.[194] 2015 25957224	**Aim:** To determine the efficacy of ASA/clopidogrel vs. ASA alone in patients with minor stroke or high-risk TIA **Study Type:** Randomized, double-blind, placebo-controlled trial **Size:** N=5170 (114 centers in China)	**Inclusion criteria:** Acute minor stroke (NIHSS ≤3) or TIA (ABCD2 ≥4), age>40, ability to start study drug within 24 h onset **Exclusion criteria**: Isolated sensory, visual symptoms, dizziness without evidence of infarct on MRI, a clear indication for AC, history of GIB or surgery within previous 3 mo, numerous other exclusions	**Intervention**: Open label ASA (75–300 mg day 1, 75 mg day 2–21) + clopidogrel (300 mg day 1, 75 mg daily day 2–90) (n=2584) **Comparator**: Open label ASA (75–300 mg day 1, 75 mg day 2–90 + placebo (n=2586)	**1° end point:** New stroke (ischemic or hemorrhagic **1° end point at 1 year** ASA/clopidogrel 275 (10.6%) vs. ASA/placebo 362 (14.0%), HR, 0.78 (0.65–0.93); *P*<0.001 **Safety end point:** Moderate to severe bleeding event: no difference	• Stroke, MI, vascular death at 1 yr: 282 (10.9%) vs. 370 (14.3%), HR, 0.78 (0.65–0.93); *P*=0.005 • Ischemic stroke at 1 yr: 263 (10.2%) vs. 349 (13.5%), HR, 0.77 (0.64–0.93); *P*=0.006 • No difference in hemorrhagic stroke	• Stratified randomization by site and time of randomization • Intervention group received placebo ASA d 21–90 • Questionable external validity in non-Asian populations and outside of Chinese healthcare system: POINT trial ongoing in the US	The early benefit of clopidogrel-aspirin treatment in reducing the risk of subsequent stroke persisted for the duration of 1-year of follow-up. Adds to current LOE; awaiting definitive RCT (POINT)

Abbreviations: AC indicates anticoagulation; ASA, acetylsalicylic acid; BID, twice a day; CI, confidence interval; EVT, endovascular therapy; GIB, gastrointestinal bleeding; HR, hazard ratio; IV, intravenous; LOE, level of evidence; MI, myocardial infarction; MRI, magnetic resonance imaging; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PE, pulmonary embolus; RCT, randomized clinical trial; sICH, symptomatic intracerebral hemorrhage; sx, symptoms; and TIA, transient ischemic attack.
Literature search topic: Antiplatelet

Table XLVI. Randomized Clinical Trials Comparing Anticoagulant to Control

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
ARTSS-2 Barreto AD, et al.[206] 2017 28507269	**Aim:** To assess safety of argatroban as adjunct therapy in patients with AIS treated with alteplase **Study Type:** Randomized controlled trial **Size:** N=90	**Inclusion criteria:** AIS patients receiving IV alteplase within 4.5 h, age≥18 y, NIHSS≥10 or proximal LVO **Exclusion criteria:** • Planned EVT • Full listing in data supplement	**Intervention:** Argatroban (100 µg/kg bolus) followed by infusion of either 1 (low dose) (N=30) or 3 µg/kg per min (high dose) (n=31) for 48 h **Comparator:** No argatroban (n=29)	**1° end point** Probability of a clinical benefit (mRS 0–1 at 90 d) RR>1.0: • Low dose: 1.17 (0.57–2.37), 0.67 • High dose: 1.27 (0.63–2.53), 0.74 • Low + high dose: 1.34 (0.68–2.76), 0.79 **Safety end point**: Incidence of sICH: • Control: 3/29 (10%) • Low-dose: 4/30 (13%) • High-dose: 2/31 (7%) Probability RR>1.0: • Low dose: 1.55 (1.07–2.25), 0.99 • High dose: 1.73 (1.04–2.89), 0.98	Recanalization at 2–3 h, neurological improvement by NIHSS, QOL at 90 d: no clinically meaningful differences	• No formal sample size estimation • Study not powered to determine differences in end points • Open label design	Supports the safety of adjunctive argatroban + IV alteplase at the doses assessed to proceed with a Phase III efficacy trial
Sandercock PA, et al.[198] 2015 25764172	**Aim:** To assess the efficacy and safety of early AC in first 14 d from AIS	**Inclusion criteria:** Randomized trials of early AC started within 14	**Intervention:** UFH, LMWH, oral AC, thrombin	**1° end point**: Death or disability at the end of follow-up (8 trials, n=22,125): OR, 0.99 (95% CI, 0.93–1.04)	• Recurrent IS: OR, 0.76 (95% CI, 0.65–0.88)	• Heterogeneity (intervention, stroke populations,	Supports current LOE

	Study Type: Cochrane review of randomized trials **Size:** N=23,748	d from onset of acute ischemic stroke (>90% trials AC started in first 48 h) **Exclusion criteria:** Non-randomization, no control group, confounded studies	inhibitors (n=11,613) **Comparator:** Control (n=11,613)	**Safety end point**: sICH: OR, 2.55 (95% CI, 1.95–3.33)	• PE: OR, 0.60 (95% CI, 0.44–0.81) • Extracranial hemorrhage: OR, 2.99 (95% CI, 2.24–3.99)	intervention, follow-up) • No additional studies included since 2008 review	
Yi X, et al.[199] 2014 24656240	**Aim:** To investigate the efficacy of LMWH compared to aspirin in preventing END in acute stroke patients **Study Type:** Unblinded RCT **Size:** N=1368 (2 Chinese hospitals)	**Inclusion criteria:** Age 18–85 y; diagnosis of ischemic stroke as defined by CT and MRI; LAA or SVD by TOAST criteria; symptoms of stroke <48 h before receiving the first dose of trial medication; presence of motor deficit as a result of acute stroke **Exclusion criteria:** • NIHSS score >15 • History of ICH; known	**Intervention:** Enoxaparin (40 mg, 4000 IU) started <48 h onset and continued for 10 d (n=683) **Comparator:** ASA (200 mg) started <48 h onset and continued for 10 d (n=685)	**1° end point**: END (≥4 pts on NIHSS) at 10 d after admission: END: LMWH, 27 (3.95%) vs. ASA, 81 (11.82%), *P*<0.001 **Safety end point**: Time to first bleeding event up to 90 d: no difference	• Early recurrent ischemic stroke, VTE, or myocardial infarction at 10 d after admission; 6 mo mRS (good outcome 0–2) • DVT: LMWH 10 (1.46%) vs. 29 (4.23%), *P*=0.003 • ERIS, MI: no difference • 6 mo mRS 0–2: LMWH 64.2% vs. ASA 6.52% *P*=0.33 • Symptomatic basilar artery - LMWH 41 (82.00%) vs. ASA 25	• Unblinded • Excluded cardioembolic etiologies • Questionable generalizability	Does not add to current LOE

		contraindication for the use of LMWH or aspirin • Patient on anticoagulation therapy before the onset of stroke; sustained hypertension (BP >200/110 mmHg) immediately before randomization • Coexisting terminal disease or dementia, atrial fibrillation on ECG, chronic rheumatic heart disease, or metallic heart valve • Thrombo-cytopenia			(48.08%), *P*=0.001		
Whiteley WN, et al.[197] 2013 23642343	**Aim:** To investigate targeted heparinoids in AIS for patients at high risk of DVT and/or lower risk for hemorrhagic events **Study Type**: Meta-analysis of randomized trials **Size:** N=22,655	**Inclusion criteria:** Individual patient data from 5 randomized control trials: IST, TOAST, FISS-tris, HAEST, TAIST **Exclusion criteria:** n<100, non-	**Intervention:** UFH, heparinoid, LMWH (n=N/A) **Comparator:** ASA/placebo (n=N/A)	**1° end point**: Composite of thrombotic events within 14 d (any fatal or non-fatal pulmonary embolism, deep vein thrombosis, myocardial infarction, or recurrent ischemic stroke [not stroke extension alone): heparin vs. control ARR: 1.4% **Safety end point**: Composite of hemorrhagic events within 14 d (any	• Dead or dependent at 3–6 mo (trial defined); predictive modeling to define parameters that might help target heparin regimen for specific patient groups (e.g., age, presence of	• Results driven by IST (83% of outcomes, source of derivation set for predictive modeling) • Models only modestly predictive for thrombotic and hemorrhagic events	Supports current LOE

		randomized, data not available (excluded 22 trials		recorded fatal or non-fatal intracranial hemorrhage, or extracranial hemorrhages that led to death, transfusion, or surgery: control vs. heparin ARR: 1.6%	atrial fibrillation, NIHSS) • No group showed benefit of heparins over aspirin or placebo for the prevention of death or disability at the time of last follow-up	• Generaliz-ability limited to stroke subtypes predominant in the included trials • Heterogeneity between trials • Trials identified from Cochrane review[397]	
FISS-tris Study Wang Q, et al.[398] 2012 22893265 Wang QS, et al.[399] 2012 22076004	**Aim:** To investigate the efficacy of LMWH vs. ASA in patients with LAOD subgroups **Study Type:** Unblinded RCT **Size:** N=353 (11 hospitals Hong Kong, Singapore)	**Inclusion criteria:** Age 18–90 y; diagnosis of ischemic stroke and vascular imaging to confirm LAOD (intracranial and extracranial) **Exclusion criteria:** Patients with pre-existing disability (defined as prestroke mRS 1) and severe stroke (defined as a NIHSS 22)	**Intervention:** Nadroparin (3800 IU) started <48 h onset and continued for 10 d (n=180) **Comparator:** ASA (160 mg) started <48 h onset and continued for 10 d (n=173)	**1° end point**: • END at 10 d defined by progressive stroke, ERIS, sICH • "Progressive stroke" was defined as stroke events of END without evidence of ERIS or sICH: dichotomized Barthel Index 6 mo (good >85) END (progressive stroke) - LMWH better than ASA: (5.0% [9 of 180] vs. 12.7% [22 of 173]; OR, 0.36 [95% CI, 0.16–0.81]); no difference in ERIS or sICH 6 mo Barthel Index: >68 y (*P*=0.043; OR, 1.86 [95% CI, 1.02–3.41]); without ongoing antiplatelet treatment on admission (*P*=0.029; OR, 1.85 [95% CI, 1.06–3.21]), and with symptomatic posterior circulation arterial disease (*P*=0.001; OR, 5.76 [95% CI, 2.00–16.56])	• mRS 0–2 at 6 mo LMWH better than ASA: >68, no antiplatelet on admission • All other subgroups no difference	• "Progressive stroke" poorly defined • Different primary outcomes compared to main FISS-tris trial • Exploratory subgroup analysis • Questionable generalizability	Does not add to current LOE

Abbreviations: AC indicates anticoagulation; AIS, acute ischemic stroke; ARR, absolute risk reduction; ASA, acetylsalicylic acid; BP, blood pressure; CI, confidence interval; CT, computed tomography; DVT, deep vein thrombosis; ECG; electrocardiogram; END, early neurologic deterioration; ERIS, early recurrence of ischemic stroke; EVT, endovascular therapy; h, hours; IU, international units; IV, intravenous; LAA, large-artery atherosclerosis; LAOD, large artery occlusive disease; LMWH, low-molecular-weight heparin; LOE, level of evidence; LVO, large vessel occlusion; MI, myocardial infarction; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PE, pulmonary embolus; QOL, quality of life; RCT, randomized clinical trial; RR, relative risk; sICH, symptomatic intracerebral hemorrhage; SVD, small vessel disease; UFH, unfractionated heparin; VTE, venous thromboembolism, and y, years.
Literature search topic: Anticoagulation

Table XLVII. Nonrandomized Studies of Anticoagulation in Patients with Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Wada T, et al.[200] 2016 26670085	**Study type:** Retrospective, observational **Size:** N=2289	**Inclusion criteria:** AIS in Japanese hospitals treated with argatroban **Exclusion criteria:** • Age<40 y • Pregnancy • Pre-preexisting comorbidities of malignancy coagulopathy, preexisting atrial fibrillation • Receipt of oral anticoagulants including warfarin and dabigatran during hospitalization • Liver failure • IV antihypertensive therapy or heparin on admission • Alteplase or endovascular	**1° end point:** mRS at discharge (propensity matched) **Results:** • OR, 1.01 (0.88–1.16) • ICH 3.5% vs. 3.8%	Interpretation limited by generalizability and selection bias

		therapy during hospitalization		
Kate M, et al.[201] 2015 26304866	**Study type:** Open-label, single-arm safety trial of dabigatran in AIS **Size:** N=53	**Inclusion criteria:** TIA or stroke NIHSS≤3; dabigatran started <24 h LKW and continued for 30 d **Exclusion criteria:** GFR<30, alteplase or EVT, clear indication for AC	**1° end point:** sICH **Results:** 0% sICH	Dabigatran appears safe in AIS with minor stroke or TIA and provides preliminary data for a larger randomized trial
RAF Study Paciaroni M, et al.[202] 2015 26130094	**Study type:** Prospective cohort **Size:** N=1029 (multicenter Europe and Asia)	**Inclusion criteria:** Known or newly diagnosed atrial fibrillation **Exclusion criteria:** Contraindication to AC	**1° end point:** Composite stroke, TIA, systemic embolism, sICH, major extracranial bleeding within 90 d **Results:** • 12.6% primary outcome • HR, 0.53 (0.30–0.93) starting AC 4–14 d compared to <4 d	• Initiating AC 4–14 d from stroke onset in patients with atrial fibrillation had better outcomes • High CHA_2DS_2-VASc, NIHSS, large ischemic lesions, and type of AC associated with composite outcome • Study limited by non-randomization
Mokin M, et al.[203] 2013 22345142	**Study type:** Retrospective, observational **Size:** N=18	**Inclusion criteria:** Non-occlusive intraluminal thrombus of intracranial and extracranial arteries confirmed by CTA, treated with IV heparin **Exclusion criteria:** alteplase or EVT	**1° end point:** Follow-up recanalization (range treatment 1–8 d) **Results:** • 9 pts complete, 9 pts partial • No ICH	Numbers too small to draw any meaningful conclusions; short duration of treatment and follow-up
Vellimana AK, et al.[204] 2013 23061393	**Study type:** Retrospective, observational **Size:** N=24	**Inclusion criteria:** TIA or stroke, intraluminal thrombus CCA, ICA treated with AC	**1° end point:** Recurrent ischemic events; TIA **Results:** No recurrent ischemic events; one TIA (mean follow-up 16.4 mo	Numbers too small to draw any meaningful conclusions; 10 patients underwent delayed revascularization

		Exclusion criteria: Intracranial thrombus, trauma/dissection, ipsilateral CAS, ICH		
ARTSS-1 Barreto AD, et al.[205] 2012 22223235	**Study type:** Open-label, pilot safety study of argatroban infusion + IV alteplase **Size:** N=65	**Inclusion criteria:** Age 18–65 y, <3 to 4.5 h LKW, complete or partially occlusive thrombus on TCD, eligible for IV alteplase **Exclusion criteria:** NIHSS >17 right MCA, >22 left MCA	**1° end point:** sICH or PH-2 **Results:** • 6.2% sICH • TCD recanalization 61%	Argatroban infusion + IV alteplase potentially safe and feasible for Phase III trial

Abbreviations: AC indicates anticoagulation; CAS, carotid artery stenting; CI, confidence interval; CCA, common carotid artery;CTA, computed tomography angiography; EVT, endovascular therapy; HR, hazard ratio; ICA, internal carotid artery; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; LKW, last known well; sICH, symptomatic intracerebral hemorrhage; MCA, middle cerebral artery; PH-2, parenchymal hematoma type 2; TIA, transient ischemic attack; and TCD, transcranial Doppler.
Literature search topic: Anticoagulation

Table XLVIII. Randomized Clinical Trials Comparing Other Treatments for Acute Ischemic Stroke

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
ALIAS Martin RH, et al.[210] 2016 (Parts I & II combined data) 27462118 Ginsberg MD, et al.[209] 2013 (Part II) 24076337	**Aim:** To determine the safety and efficacy of albumin infusion in AIS **Study Type:** Randomized, double-blinded, placebo-controlled trial **Size:** N=1275 combined (NETT)	*Combined dataset from ALIAS Parts I & II trials **Inclusion criteria:** AIS, age 18–83 y, NIHSS>6, initiation of infusion within 5 h LKW and	**Intervention**: 25% albumin infusion (2 g/kg) (n=637) **Comparator:** Saline placebo (1:1) (n=638)	**1° end point:** 90 d disability (proportion of favorable outcomes defined by mRS 0–1, NIHSS 0–1, or both): • Combined: proportion of good outcomes identical (41%) between groups • Part II: RR, 0.96 (0.84–1.10)	Secondary efficacy, death (30 & 90 d), ICH within 24 h: no differences between groups	Part I stopped early for safety; Part II stopped early for futility; saline group in Part II did better than expected, stratified randomization by thrombolysis; differences in alteplase rates	High-dose albumin is not recommended

		within 90 min of alteplase (if treated) **Exclusion criteria:** CHF or other cardiac/systemic conditions exacerbated by volume expansion; numerous other exclusions listed[209]		**Safety end point**: CHF, pulmonary edema within 48 h: CHF within 48 h: RR, 7.76 (3.87–15.57) (combined)		and age between Parts I & II	
FAST-MAG, Saver JL, et al.[400] 2015 25651247	**Aim:** To determine the efficacy of magnesium infusion, initiated early, on stroke outcomes **Study Type:** Randomized, double-blind, placebo-controlled trial **Size:** N=1700 (multiple CA sites)	**Inclusion criteria:** Age 40–95 y, + LAPSS, treatment initiation within 2 h LKW, deficit >15 min **Exclusion criteria:** Patient unable to provide informed consent or enrollment under EFIC; otherwise standard exclusions (NEJM appendix)	**Intervention:** Magnesium sulfate 4 g bolus + 16 g infusion × 24 h (n=857) **Comparator:** Placebo (n=843)	**1° end point:** 90 d disability (shift in mRS): no significant shift (*P*=0.28) **Safety end point**: 90 d: Mortality (*P*=0.95); sICH (*P*=0.12), SAEs (*P*=0.67)	• NIHSS, Barthel Index, GOS: no differences • SAEs, sICH, death: no differences	• Long enrollment period • Higher ICH rate than predicted (22%) • 4% mimic rate • 33%–38% alteplase treatment rate in eligible patients	Magnesium infusion is not recommended

Chang TS and Jensen MB[208] 2014 25159027	**Aim:** To assess the effects of hemodilution in AIS **Study Type:** Cochrane review **Size:** N=4174 (21 trials)	**Inclusion criteria:** Randomized trials of hemodilution treatment in AIS, treatment started w/in 72 h **Exclusion criteria:** No details of intervention, incomplete outcomes data, no control group, lack of randomization	**Intervention**: Plasma volume expansion vs (plasma, dextran 40, HES, albumin, ± venesection) **Comparator**: Control	**1° end point:** Death or dependency at 3-6 mo: risk ratio: 0.96 (95% CI, 0.85–1.07) **Safety end point**: Serious cardiac events: Overview analysis (OR, 0.99; 95% CI, 0.66–1.50)	• Early and late mortality, venous thromboembolic events, serious cardiac events, anaphylactoid reactions: no significant differences in secondary outcomes • Cardiac events at 3–6 mo, OR, 0.99 (0.66–1.50)	• Heterogeneity, isovolemic vs. hypervolemic intervention • Risk of bias • Treatment effect (reduced HCT) delayed >6 h in most participants • Small numbers to assess some interventions (e.g., HES)	Hemodilution is not recommended

Abbreviations: ADL indicates activities of daily living; AIS, acute ischemic stroke; ATA, arterial transit artifact; CHF, chronic heart failure; CI, confidence interval; CT, computed tomography; EVT, endovascular therapy; g, gram; GOS, Glasgow Outcome Scale; h, hours; HCT, hematocrit; HES, hydroxyethyl starch; ICH, intracranial hemorrhage; LAPSS, Los Angeles Prehospital Stroke Screen; LKW, last known well; MRI, magnetic resonance imaging; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; OTT, onset to treatment; RCT, randomized clinical trial; RR, relative risk; SAE, serious adverse event; sICH, symptomatic intracranial hemorrhage; TLT, transcranial laser therapy; and y, years.

Literature search topic: Neuroprotection

Table XLIX. Randomized Clinical Trials Comparing Transcranial Laser Therapy for Stroke

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
NEST-3 Hacke W, et al.[401] 2014 25293665	**Aim**: To investigate benefit of TLT for acute ischemic stroke **Study type:** Prospective randomized clinical trial **Size:** N=1000	**Inclusion criteria:** Ischemic stroke within 24 h, NIHSS 7–17, ≤80 y **Exclusion criteria:** IV alteplase	**Intervention:** Transcranial laser therapy (TLT) between 4.5–24 h of stroke onset (n=288) **Comparator:** Sham TLT (n=288)	**1° end point:** Disability 90 d mRS (success 0–2, failure 3–6) **Safety end point:** N/A	N/A	Potential non-standardization of TLT between animal models and human trials (not taking skull thickness into account)	• Terminated due to futility; analysis after 566 subjects •No benefit of NILT over sham procedure •Terminated after inclusion of 2/3 of planned patient number

Abbreviations: h indicates hours; IV, intravenous; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NILT, near infrared laser therapy; OR, odds ratio; TLT, transcranial laser therapy; y, year.
Literature search topic: Transcranial laser therapy AND transcranial near-infrared laser therapy

Table L. Randomized Clinical Trials Comparing Early Versus Delayed Initiation of Treatment for Blood Pressure Reduction in Patients with Acute Ischemic Stroke

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
ENOS ENOS Trial Investigators[228] 2015 25465108	**Aim:** To assess the efficacy and safety of BP reduction with transdermal glyceryl nitrate within 48 h of an acute stroke	**Inclusion criteria:** • Acute ischemic stroke (or ICH) within previous 48 h	**Intervention:** Transdermal glyceryl nitrate 5 mg/d for 7 d (n=2000)	**1° end point:** mRS distribution at 90 d: OR for worse outcome: 1.01 (95% CI, 0.91–1.13; *P*=0.83) for the active arm	• 90-d Barthel Index, mini-mental state score, HRQOL, and depression	• Subset of patients previously on antihypertensive s were also randomized to	• Early treatment of hypertension with transdermal glyceryl nitrate was safe but

	Study type: RCT **Size:** N=4011	• SBP 140–220 mmHg **Exclusion criteria:** • Coma • Minor stroke • Hypertensive emergency • SBP>220 mmHg • Premorbid disability	**Comparator:** Placebo (n=2011)	**Safety end points:** All cause-mortality, early neurological decline, recurrent stroke within 7 d, symptomatic hypotension, and serious systemic events: *P*>0.1 for all comparisons	score: *P*>0.1 for all comparisons • Post-hoc subgroup analysis (Woodhouse et al. 2015) of patients started on treatment within 6 h of stroke onset (N=273) showed benefit (improved mRS at 90 d on ordinal shift analysis) from the intervention: common OR: 0.51 (95% CI: 0.32–0.80)	continue (n=1053) or stop (n=1044) those drugs: there were no differences in the comparison of those two groups either (OR, 1.05; 95% CI, 0.90–1.22; *P*=0.55) • Results were similar when the analysis was restricted to patients with ischemic stroke	ineffective to prevent death or dependency • Early reinitiation of antihypertensive s was ineffective to prevent death or dependency • Treatment within 6 h was safe and may be beneficial to improve functional outcomes
Lee M, et al.[229] 2015 26022636	**Aim:** Assess the effect of BP reduction within 72 h of an acute ischemic stroke on functional outcomes at 3 mo **Study type:** Meta-analysis of RCTs **Size:** N=12,703 (13 trials)	**Inclusion criteria:** As per individual trials; only including acute ischemic stroke **Exclusion criteria:** As per individual trials	**Intervention:** Treatment started for BP reduction within the first 72 h (n=6392) **Comparator:** No new treatment started for BP reduction within the first 72 h (n=6311)	**1° end point:** Death or dependency (mRS 3–6) at 90 d: RR, 1.04 (95% CI, 0.96–1.13; *P*=0.35) **Safety end point:** Serious adverse events (as per each trial definition): *P*>0.05 for all comparisons	Recurrent vascular events, all-cause mortality, disability, recurrent stroke: *P*>0.05 for all comparisons	Heterogeneity across trials	Early BP reduction was safe but ineffective to prevent death or dependency
VENTURE Oh M, et al.[227] 2015 25580869	**Aim:** To assess the efficacy and safety of modest blood pressure reduction with valsartan within 48 h after symptom	**Inclusion criteria:** • Acute ischemic stroke	**Intervention:** Oral valsartan 80 mg/d for 7 d (n=195)	**1° end point:** Death or major disability (mRS 3–6) at 90 d: OR, 1.11; 95% CI, 0.69–1.79; *P*=0.667	Major vascular events within 90 d: OR, 1.41; 95% CI, 0.44–4.49; *P*=0.771	Early termination due to futility determined on interim analysis	Early reduction of BP with valsartan did not reduce death or dependency and

	onset in patients with acute ischemic stroke and high BP **Study type:** RCT **Size:** N=393	within previous 48 h • SBP 150–185 mmHg **Exclusion criteria:** • Impaired level of consciousness • NIHSS ≥22 • Pre-existent disability • Coexistent vascular emergency • Severe comorbidities	**Comparator:** Placebo (n=198)	**Safety end point:** Early neurological deterioration (within 7 d): OR, 2.43; 95% CI, 1.25–4.73; *P*=0.008		(target size=289 per group)	major vascular events at 90 d but increased the risk of early neurological deterioration
COCHRANE Bath PM and Krishnan K [226] 2014 25353321	**Aim:** To assess the clinical effectiveness of altering blood pressure in people with acute stroke, and the effect of different vasoactive drugs on blood pressure in acute stroke **Study type:** Meta-analysis of RCTs **Size:** N=17,011 (from 26 trials)	**Inclusion criteria:** • As per individual trials • In acute ischemic stroke and ICH • Age ≥18 y **Exclusion criteria:** As per individual trials	**Intervention:** Treatment started for BP reduction within the acute phase (n=8497) **Comparator:** No new treatment started for BP reduction within the acute phase (n=8514)	**1° end point:** • Death or dependency (mRS >2 or 3) ≥ 1 mo after the stroke: OR, 0.98; 95% CI, 0.92-1.05 • Blood pressure lowering did not reduce death or dependency either by drug class (OR, 0.98; 95% CI, 0.92–1.05), stroke type (OR, 0.98; 95% CI, 0.92–1.05), or time to treatment (OR, 0.98; 95% CI, 0.92–1.05) **Safety end points:** Early neurological decline: OR, 1.07; 95% CI, 0.92–1.24	Treatment within 6 h of stroke appeared effective in reducing death or dependency (OR: 0.86, 95% CI: 0.76–0.99) but not death (OR: 0.70, 95% CI: 0.38–1.26) by the end of the trial	Great heterogeneity across included trials	Early treatment of hypertension was safe but ineffective to prevent death or dependency

CATIS He J, et al.[225] 2014 24240777	**Aim:** Evaluate whether immediate blood pressure reduction in patients with acute ischemic stroke would reduce death and major disability at 14 d or hospital discharge **Study type:** RCT **Size:** N=4071	**Inclusion criteria:** • Age >22 y • Acute ischemic stroke within previous 24 h **Exclusion criteria:** • Impaired level of consciousness • Hypertensive emergency • BP >220/120 • Atrial fibrillation • Intravenous alteplase	**Intervention:** Antihypertensive medication to maintain BP <140/90 for the first wk (n=2038) **Comparator:** No antihypertensive medication for the first wk (n=2033)	**1° end point:** Death or major disability (mRS 3–6) at 14 d: OR, 1.0 (95% CI, 0.88–1.14; *P*=0.98) **Safety end point:** • Vascular disease events *P*=0.28 • Recurrent stroke *P*=0.07	• Death or major disability (mRS 3–5) at 90 d: OR, 0.99 (95% CI, 0.86–1.15; *P*=0.93) • Lower blood pressure at 14 d (mean difference of -8.6 mmHg in SBP and -3.9 mmHg in DBP; *P*<0.001) and at 90 d (mean difference of -2.9 mmHg in SBP and -1.4 mmHg in DBP; *P*<0.001) in the active arm	Antihypertensive regimen was not standardized	• Early treatment of hypertension was safe but ineffective to prevent death or dependency • Early initiation of anti-hypertensives was associated with better BP control at 2 wk
SCAST Sandset EC, et al.[224] 2011 21316752	**Aim:** Examine whether blood-pressure lowering treatment candesartan is beneficial in patients with acute stroke and hypertension **Study type:** RCT **Size:** N=2029	**Inclusion criteria:** • Acute ischemic stroke (or ICH) within previous 30 h • SBP >140 mmHg • Age >18 y **Exclusion criteria:** • Impaired level of consciousness • Hypertensive emergency	**Intervention:** Candesartan 4–16 mg/d for 7 d (n=1017) **Comparator:** Placebo (n=1004)	**1° end point:** • mRS at 6 mo: OR for worse outcome: 1.17 (95% CI, 1.00–1.38; *P*=0·048) • Vascular death or MI or recurrent stroke within 6 mo: HR, 1.09 (95% CI, 0.84–1.41; *P*=0.52) **Safety end point:** • Stroke progression: RR, 1.47 in favor of placebo; 95% CI, 1.01–2.13; *P*=0.04 • Symptomatic hypotension: no difference; *P*=0.29	• Death from any cause, vascular death, ischemic stroke, hemorrhagic stroke, MI, stroke score, and Barthel Index at 7 d and 6 mo: *P*>0.1 for all comparisons	Mean BPs were similar in both groups after the first 7 d	Early initiation of candesartan was safe but ineffective to prevent death or dependency

		• Premorbid disability		• Renal failure: no difference; *P*=0.37			
COSSACS Robinson TG, et al.[223] 2010 [20621562](20621562)	**Aim:** Assess the efficacy and safety of continuing or stopping pre-existing antihypertensive drugs in patients with acute stroke **Study type:** RCT **Size:** N=763	**Inclusion criteria:** Acute ischemic stroke (or ICH) within previous 48 h **Exclusion criteria:** • Impaired level of consciousness • Unable to swallow • Hypertensive emergency • BP >200/120 mmHg • Premorbid disability • Intravenous alteplase	**Intervention:** Continue previous antihypertensive medication/s (n=379) **Comparator:** Stop previous antihypertensive medication/s (n=384)	**1° end point:** Death or major disability (mRS 3–6) at 14 d: RR, 0.86 (95% CI, 0.65–1.14; *P*=0.3) **Safety end point:** Adverse events, minor and serious: *P*>0.05 for all	• 2-week NIHSS: *P*=0.46 and 2-week Barthel Index: *P*=0.30 • 2-week BP: significantly lower in the continue arm (mean difference of -13 mmHg in SBP and -8 mmHg in DBP) *P*<0.0001 • 6-month mortality: *P*=0.98; 6-month disability *P*<0.05	• Trial was terminated early because of slow recruitment, and consequently it was underpowered • Treatment was not homogeneous (different drugs, no specific BP target) • No differences when analysis restricted to patients with ischemic stroke	• Early reinitiation of antihypertensive medications was safe but ineffective to prevent death or dependency • Early reinitiation of antihypertensives was associated with better BP control at 2 wk
PRoFESS Bath PM, et al.[221] 2009 [19797187](19797187)	**Aim:** Assess the safety and efficacy of lowering blood pressure with telmisartan (on top of standard poststroke antihypertensive treatment) in patients with acute ischemic stroke **Study type:** RCT **Size:** N=1360	**Inclusion criteria:** • Age >55 or 50–54 y with multiple vascular risk factors • Acute ischemic hemispheric stroke within 72 h of onset **Exclusion criteria:**	**Intervention:** Oral telmisartan 80 mg/d (n=647) **Comparator:** Placebo (n=713)	**1° end point:** Death or dependency at 30 d: OR, 1.03; 95% CI, 0.84–1.26; *P*=0.81 **Safety end point:** Serious adverse events: *P*>0.05	• Death or dependency at 7 and 90 d: *P*>0.05 • Composite recurrent vascular events at 90 d: *P*=0.40 • Mini-Mental State Examination at 90 d: *P*>0.05	• Pre-specified analysis of a larger trial with factorial design • Trial evaluated mild strokes (mean NIHSS=3)	Early treatment of hypertension with telmisartan was safe but ineffective to prevent death or dependency

		• Inability to swallow • Pre-existent disability • Renal failure or renal artery stenosis • Hyperkalemia • Recent myocardial infarction or severe coronary artery disease					
CHHIPS Potter JF, et al.[222] 2009 19058760	**Aim:** Assess the feasibility, safety, and effects of two regimens for lowering blood pressure in patients with acute stroke **Study type:** RCT **Size:** N=179	**Inclusion criteria:** • Acute ischemic stroke (or ICH) within previous 36 h • SBP >160 mmHg **Exclusion criteria:** • Coma • Hypertensive emergency • BP >200/120 mmHg • Premorbid disability	**Intervention:** Labetalol (n=58) or lisinopril (n=58), titrated to keep SBP <160 mmHg for 2 wk **Comparator:** Placebo (n=63)	**1° end points:** Death or major disability (mRS 3–6) at 14 d: RR, 1.03, 95% CI, 0.80–1.33; *P*=0.82 **Safety end point:** • Early neurological decline: RR, 1.22; 95% CI, 0.33–4.54; *P*=0.76 • Serious systemic adverse events: RR, 0.91; 95% CI, 0.69–1.12; *P*=0.50	Mortality at 3 mo lower in active arm (9.7% vs. 20.3%, HR: 0.40 (95% CI: 0.2–1.0; *P*=0.05)	Pilot trial with small sample size	Early treatment of hypertension was safe but ineffective to prevent death or dependency
Eveson DJ, et al.[220] 2007 17324738	**Aim:** Explore the hemodynamic effect and safety of oral lisinopril initiated within 24 h after an acute stroke	**Inclusion criteria:** • Acute ischemic stroke within 24 h of onset	**Intervention:** Oral lisinopril 5–10 mg for 14 d (n=18) **Comparator:** Placebo (n=22)	**1° end point:** Functional outcomes at 3 mo: *P*=0.7 **Safety end point:** • Excessive drop in BP: *P*>0.05	N/A	• Single center • Designed to evaluate safety	Early initiation of lisinopril was safe

	Study type: RCT (phase II) **Size:** N=40	• SBP >140 mmHg or DBP >90 mmHg **Exclusion criteria:** • Coma • Re-existent disability • Inability to swallow • Severe carotid stenosis • Advanced heart failure • Acute myocardial infarction within 6 mo • Severe aortic stenosis		• Doubling in serum creatinine concentration: *P*>0.05			
ACCESS Schrader J, et al.[219] 2003 12817109	**Aim:** Assess the safety of modest blood pressure reduction in the early treatment of stroke **Study type:** RCT (phase II) **Size:** N=339	**Inclusion criteria:** • Age 18–85 y • Acute ischemic hemispheric stroke within 36 h of onset • Severe hypertension (SBP ≥200 mmHg or DBP ≥110 mmHg within 6–24 h after admission, or SBP ≥180 mmHg or DBP ≥105 mmHg	**Intervention:** Oral candesartan 4–16 mg/d titrated to keep BP <160/100 for 7 d (n=173) **Comparator:** Placebo (n=166)	**1° end points:** Barthel Index at 3 mo: 87.0±22.9 vs. 88.9±19.9; *P*>0.05 **Safety end point:** • Cerebral complications at 7 d: *P*>0.05 • Cardiac complications at 7 d: *P*>0.05	• Combined mortality, cerebrovascular and cardiovascular events at 12 mo: OR, 0.475 (95% CI, 0.252–0.895) • BP at 3, 6, and 12 mo: *P*>0.05	• Terminated early (planned size 500) • Designed to evaluate safety	• Early initiation of oral candesartan was safe but not associated with reduction in disability. • Oral candesartan was associated with reduced rates of mortality and cardiovascular events at 12 mo despite similar long-term control of BP

		within 24–36 h after admission **Exclusion criteria:** • Coma • Severe carotid stenosis • Advanced heart failure • Unstable angina • Severe aortic or mitral stenosis					
VENUS Horn J, et al.[218] 2001 11157183	**Aim:** Determine the safety and efficacy of nimodipine on the functional outcome of acute ischemic stroke **Study type:** RCT **Size:** N=454	**Inclusion criteria:** • Age 18–85 y Acute ischemic or hemorrhagic stroke within 6 h of onset **Exclusion criteria:** • Coma • Minor deficits • Inability to swallow pills • Severe comorbidity • Pre-existent disability • SBP <130 or >220 mmHg	**Intervention:** Oral nimodipine 30 mg four times/d for 10 d (n=225) **Comparator:** Placebo (n=229)	**1° end points:** Death or dependency at 3 mo: 32% vs. 27% (RR, 1.2; 95% CI, 0.9–1.6; NS) **Safety end point:** Major adverse events: *P*>0.1	Change in neurological status at 24 h: *P*=0.35 Mortality at 10 d: RR, 0.7; 95% CI, 0.4–1.4	Study rationale was based on presumed neuroprotective effect of nimodipine rather than solely its antihypertensive effect	Early oral nimodipine was associated with worse outcomes after acute ischemic stroke

Kaste M, et al.[216] 1994 8023348	**Aim:** Determine the safety and efficacy of nimodipine on the functional outcome of acute ischemic stroke **Study type:** RCT **Size:** N=350	**Inclusion criteria:** • Age 16–69 y •Acute ischemic hemispheric stroke within 48 h of onset **Exclusion criteria:** • Coma • TIA • Severe comorbidity	**Intervention:** Nimodipine 120 mg/d for 21 d (n=174) **Comparator:** Placebo (n=176)	**1° end points**: All at 12 mo: • Rankin score: scores 1–2 in 96 patients of both groups (*P*>0.5) • Neurological score: median 28 vs. 25 (*P*>0.5) • Mobility: unaided in 117 vs. 126 patients (*P*>0.5) **Safety end point**: None specified	Functional outcome at 3 mo, mortality at 3 and 12 mo, and residence at 12 mo: all *P*>0.5	Study rationale was based on presumed neuroprotective effect of nimodipine rather than solely its antihypertensive effect	• No functional benefit from the early initiation of antihypertensive therapy with nimodipine • Greater fatality rates on the nimodipine arm during the first 3 mo
INWEST Wahlgren NG, et al.[217] 1994 Link to article	**Aim:** Determine the safety and efficacy of nimodipine on the functional outcome of acute ischemic stroke **Study type:** RCT **Size:** N=295	**Inclusion criteria:** • Age ≥40 y • Acute ischemic stroke in carotid territory within 24 h of onset • Stable hemiparesis **Exclusion criteria:** • Coma • Pre-existent disability • Unstable cardiac disease • Severe comorbidity	**Intervention:** Intravenous nimodipine 1 mg/h (n=101) or 2 mg/h (n=94) for 5 d followed by oral nimodipine 30 mg four times/d for 16 d **Comparator:** Placebo (n=100)	**1° end points:** • Neurological outcome by the Orgogozo scale at 21 d: significantly worse in the 2 mg/h nimodipine arm (*P*=0.0005) • Functional outcome by Barthel Index at 21 d: significantly worse in the 2 mg/h nimodipine arm (*P*=0.0033) **Safety end point:** Mortality: *P*>0.1	Neurological outcome by the Orgogozo and Mathew scales and functional outcome by Barthel Index at 12 and 24 wk: all markedly worse in the 2 mg/h nimodipine arm (*P*<0.001)	•Study rationale was based on presumed neuroprotective effect of nimodipine rather than solely its antihypertensive effect • Trial terminated early because of worse outcomes in the high-dose active arm (planned size=600 patients) • Trial terminated early because of futility determined in an interim analysis (planned	Early IV nimodipine was associated with worse outcomes after acute ischemic stroke in a dose-dependent manner

						size=1500 patients)	

Abbreviations: BP, blood pressure; CI, confidence interval; DBP, diastolic blood pressure; h, hour; HR, hazard ratio; HRQOL, health-related quality of life; ICH, intracerebral hemorrhage; IV, intravenous; MI, myocardial infarction; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; RCT, randomized clinical trial; RR, relative risk; SBP, systolic blood pressure; and y, year.
Literature search topic: Blood pressure II

Table LI. Deleted

Table LII. Deleted

Table LIII. Randomized Clinical Trials of Nutrition

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point	Study Limitations; Adverse Events	Summary Conclusions Comments
Geeganage C, et al.[236] 2012 23076886	**Aim:** To assess the effectiveness of interventions for treatment of dysphagia and nutritional and fluid supplementation in patients with acute and subacute (within 6 mo from onset) stroke **Study type:** Cochrane review RCT **Size:** N=6779 participants (33 studies)	**Inclusion criteria:** Participants recruited with a clinical diagnosis of stroke within 6 mo **Exclusion criteria:** Studies with no control group, not randomized, or no relevant outcome data available	**Intervention:** Interventions for dysphagia; feeding strategies and timing (early – within 7 d) vs. later); fluid supplementation; swallowing therapy (n=967), feeding (route, timing, supplementation (n=5812) **Comparator:** N/A in review	**1° end point:** Functional outcome: death or dependency, or death or disability, at the end of the trial; results related to PEG vs. NG supplemental feeding: • PEG was associated with fewer treatment failures (t=3; n=72; OR, 0.09; 95% CI, 0.01–0.51; *P*=0.0007; 1^2=0% • PEG was associated with fewer GI bleeding events (t=1; n=321; OR, 0.25%; 95% CI, 0.09–0.69; *P*=0.0007)	• Case fatality at the end of the trial • Neurological deterioration within 4 wk • Late disability or dependency at the end of the trial • Proportions with dysphagia at the end of the trial • Improvement in dysphagia	The Cochrane Collaborative assessed the risk of bias in the included trials using the "Risk of Review of Intervention"; the assessment included: sequence generation, allocation concealment, blinding of participants and personnel, blinding of	• Continues to be insufficient data on the effect of swallowing therapy, feeding, and nutritional and fluid supplementation on functional outcome and death in dysphagic patients with acute stroke • Behavioral interventions and acupuncture

				• PEG was associated with higher feed delivery (t=1; n=30; MD=22.00; 95% CI, 16.15–27.85; *P*<0.000001) • PEG was associated with fewer pressure sores (t=1; n=321; OR, 3.10; 95% CI, 0.98–9.83; *P*=0.05) • PEG and NG tube feeding did not differ for end-of-trial case fatality (t=5; n=455; OR, 0.81; 95% CI, 0.42–1.56) **Safety end point:** N/A		outcomes assessment, incomplete outcome data, and selective outcome reporting	reduced dysphagia • PEG reduced treatment failures and gastrointestinal bleeding, and had higher feed delivery and albumin concentration • Reduced pressure sores was associated with nutritional supplementation
FOOD Trial Collaboration Dennis M, et al.[235] 2006 16409880	**Aim:** To determine whether routine oral nutritional supplementation of a normal hospital diet improves outcome after stroke **Study type:** RCT – three pragmatic multicenter randomized **Size:** N=5033 patients (131 hospitals in 18 countries)	**Inclusion criteria:** Stroke patients with dysphagia **Exclusion criteria:** SAH, TIA, coma patients; or patients already entered into the same FOOD Trial	**Trial 1** • **Intervention:** Normal hospital diet (n=2007) • **Comparator:** Normal hospital diet plus oral nutritional supplements (equivalent to 360 ml of 1.5 kcal/ml, 20 g protein per d) until hospital discharge (n=2016) **Trial 2** • **Intervention:** Early enteral tube (n=429) • **Comparator:** No tube feeding	**1° end point:** • **Trial 1**: Normal vs normal plus supplements: the supplemented diet was associated with an absolute reduction in risk of death of 0.7% (95% CI, -1.4–2.7; *P*=0.5) and a 0.7% (95% CI, -2.3 to 3.8, *P*=0.6) increased risk of death or poor outcome • **Trial 2**: Early enteral vs. no tube feeding for more than 7 d: early tube feeding was associated with an absolute reduction in risk of death of 5.8% (95% CI, -0.8 to 12.5; *P*=0.09) and a reduction in death or poor outcome of 1.2% (95% CI, -4.2 to 6.6; *P*=0.7)	None	• Failure to reach sample sizes in all: Trial 1, 67%; Trial 2, 43%; Trial 3, 32% • Stopping recruitment prior to sample sizes being achieved can lead to bias in RCTs	• Trial 1 unable to confirm the expected 4% absolute benefit for death or poor outcome from routine oral nutritional supplements; did not support supplementation of hospital diet for unselected stroke patients who are predominantly well nourished on admission • Trial 2 suggests that a policy of early tube feeding may

			for more than 7 d (avoid) (n=430) **Trial 3** • **Intervention:** Tube feeding via PEG (n=162) • **Comparator:** Tube feeding via NG tube (n=159)	• **Trial 3**: Tube feeding via PEG or NG tube: PEG was associated with an increase in absolute risk of death of 1.0% (95% CI, -10.0 to 11.9; *P*=0.9) and an increased risk of death or poor outcome of 7.8% (95% CI, 0.0–15.5; *P*=0.05) **Safety end point:** N/A			substantially reduce the risk of dying after stroke but it is very unlikely the alternative policy of avoiding early tube feeding would improve survival • Trial 3 data suggest that in the first 2–3 wk after stroke better functional outcomes result from feeding via NG tube than PEG tube

Abbreviations: CI indicates confidence interval; GI, gastrointestinal; HR, hazard ratio; MD, mean difference; N/A, not available; NG, nasogastric; OR, odds ratio; PEG, percutaneous endoscopic gastrostomy; RCT, randomized clinical trial; SAH, subarachnoid hemorrhage; TIA, transient ischemic attack.
Literature search topic: Nutrition

Table LIV. Nonrandomized Trials, Observational Studies, and/or Registries of Oral Hygiene

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Seedat J and Penn C[402] 2016 26974243	**Study Type:** Quantitative, quasi-experimental parallel group design **Size:** There were two groups of participants with oropharyngeal dysphagia: • Group one (study group, N=23) was recruited by	**Inclusion criteria:** Diagnosed with either stroke or traumatic brain injury as their primary medical diagnosis with a confirmed diagnosis of oropharyngeal dysphagia	**1° end point:** Aspiration pneumonia **Results**: The Fisher's exact test showed that there was a significant, moderate association between the occurrence of aspiration pneumonia and group: all seven were participants from the comparison group (*P*=0.0092)	• No participant from either group presented with aspiration pneumonia at the initiation of dysphagia intervention (entry into the study), although signs of aspiration were observed and aspiration pneumonia developed over the course of intervention in the comparison group, but there was no diagnosis of aspiration in the study group

	consecutive sampling, received regular oral care and were not restricted from drinking water; however, all other liquids were restricted • Group two (comparison group, N=23) was recruited via a retrospective record review, received inconsistent oral care and were placed on thickened liquids or liquid-restricted diets	**Exclusion criteria**: N/A		• A limitation of the current study was the exclusion of videofluoroscopy pre-intervention for each participant in the study group to confirm swallowing function • It is possible to reduce adverse medical effects of aspiration including fatality by implementing a cost-effective and low resource oral care protocol for patients with dysphagia • Further studies should be completed
Wagner C, et al.[239] 2016 26584429	**Study Type:** Cohort study compared the proportion of pneumonia cases in hospitalized stroke patients before and after implementation of a systematic intervention **Size**: N=1656 admissions (707 formed historical controls; 949 were in the intervention group)	**Inclusion criteria:** All patients hospitalized with acute ischemic stroke or intracerebral hemorrhage admitted to a large, urban academic medical center in Boston, MA, USA from May 31, 2008, to June 1, 2010 (epoch prior to implementation of OHC), and from January 1, 2012, to December 31, 2013 (epoch after full implementation of OHC), who were 18 y of age and hospitalized for ≥2 d	**1° end point:** Hospital-acquired pneumonia **Results**: • The unadjusted incidence of hospital-acquired pneumonia was lower in the group assigned to OHC compared to controls (14 vs. 10.33%; *P*=0.022), unadjusted OR, 0.68 (95% CI, 0.48–0.95; *P*=0.022) • After adjustment for influential 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)	In this large hospital-based cohort of patients admitted with acute stroke, systematic OHC use was associated with decreased odds of hospital-acquired pneumonia

		were eligible for inclusion **Exclusion criteria**: N/A		
Sorensen RT, et al.[237] 2013 23636069	**Study type:** Controlled trial cohort study **Size:** N=146 hospitalized acute stroke patients included in three groups: an intervention group (N=58), one internal control group (N=58, retrospectively selected from same clinic), and one external control group (N=30) from a comparable stroke unit in a neighboring hospital	**Inclusion criteria:** Hospitalized acute stroke patients with moderate or severe dysphagia **Exclusion criteria:** Active metastatic cancer, severe liver or kidney failure, and terminal illness including cancellation of active treatment within 3 d after admission at the stroke unit	**1° end point:** The intervention consisted of early screening with a clinical method of dysphagia screening, the Gugging Swallowing Screen, and intensified oral hygiene; investigate whether the incidence of aspiration pneumonia could be reduced in such patients by an early screening for dysphagia **Results**: • The incidence of x-ray verified pneumonia was 4 of 58 (7%) in the intervention group compared with 16 of dysphagia and intensified oral hygiene • 58 (28%) in the internal control group (*P*<0.01) and with 8 of 30 (27%) in the external control group (*P*<0.05)	• Cohort studies have shown that oral hygiene protocols may help reduce aspiration pneumonia after stroke • The intervention group received early and systematic dysphagia screening (which indicated recommendations for diet administrated orally or by tube) together with intensified oral hygiene • The control group contained patients who were not systematically screened for dysphagia within 24 h and who received unsystematic and arbitrary oral hygiene without the use of antibacterial mouth rinse with chlorhexidine • Pneumonia was reduced in the intervention group (7% vs. 28%) • The efficacy of oral hygiene portion cannot be separated from the combination

Abbreviations: CI indicates confidence interval; OHC, oral health care; and OR, odds ratio.
Literature search topic: Oral care

Table LV. Randomized Clinical Trials of Oral Care

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
Brady MC, et al.[238] 2006 17054189	**Aim:** To compare the effectiveness of staff led OHC interventions with standard care for ensuring oral hygiene for individuals affected after a stroke (post stroke) **Study type:** Intervention review of RCT that evaluated one or more interventions designed to improve oral hygiene **Size:** N=470 patients (3 studies)	**Inclusion criteria:** • RCTs evaluating one or more interventions designed to improve oral health • Recruited from a health care setting with a mixed population of individuals post-stroke **Exclusion criteria:** Studies that did not have patient specific data	**Interventions:** • OHC education training program: staff trained (n=40), patients receiving OHC interventions (n=132) • Decontami-nation gel (n=103) • Ventilator-associated pneumonia bundle of care augmented with an OHC (n=100) **Comparators:** • OHC education training program: untrained staff (n=27), standard oral care (n=129) • Placebo gel (n=103) • Standard VAP bundle no	**1° end point:** Dental plaque (plaque scale and denture cleanliness scale): • OHC demonstrated significant reduction in denture plaque score (*P*<0.0000.1) • No difference in dental plaque (DMS, -0.25; 95% CI, -0.77 to 0.28) **Safety end point**: None	• Patient satisfaction care received, oral comfort and appearance: result not reported • Staff knowledge on oral care (*P*=0.0008) • Staff attitude toward oral care (*P*=0.0001) • Presence of oral disease: no evidence of a difference in gingivitis between groups (DMS, -1.57, 95% CI, -2.23 to 0.92; *P*<0.00001)	• Blinding of participants impossible for some OHC, recorded when that happened • Incomplete outcome data, selective outcome reporting, sample size calculations, comparability of groups at baseline, reliability of measures used, and evidence of intention-to-treat analysis	• Evidence with review indicates the potential benefits of decontamination gel on the incidence of pneumonia, but further investigation is needed • Was not an outcome, but patients receiving the decontamination gel had fewer incidences on pneumonia (one incident) over the course the trial period than those that used the placebo gel (100 participants; seven incidents of pneumonia) (OR, 0.20, CI 95%, 0.05–0.84, *P*=0.03)

			augmented OHC (n=100)				

Abbreviations: CI indicates confidence interval; DMS, difference in mean score; HR, hazard ratio; N/A, not available; OHC, oral health care; OR, odds ratio; RCT, randomized clinical trial; and RR, relative risk.
Literature search topic: Oral care

Table LVI. Randomized Clinical Trials Comparing Deep Vein Thrombosis Prophylaxis

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
European Stroke Organisation (ESO) guidelines for prophylaxis for VTE Dennis M, et al.[240] 2016 Link to article	**Aim:** Focused on both non-pharmacological and pharmacological interventions given with the primary objective of reducing the risk of VTE **Study type:** RCTs and systematic reviews/meta-analyses **Size**: 24 RCT's reviewed, total (N=22,700)	**Inclusion criteria:** RCTs and systematic reviews evaluating GCS, IPC, and prophylactic anticoagulation with UFH, LMWH and heparinoids, but no randomized trials evaluating NES **Exclusion criteria:** Did not include trials that directly compared anticoagulants with antiplatelet medications	**Intervention:** Pharmacologic or non-pharmacologic interventions: 1. GSC (n=1256) 2. IPC (n=1438) 3. Anti-coagulants UFH (n=5363) 4.LMWH or heparinoid (n=876) **Comparator:** Care which did not include specific VTE prophylactic intervention: 1. No GCS (n=1262) 2. No IPC (n=1438)	**1° end point:** • Death or dependency at follow-up • Survival (or its reciprocal – mortality) • Functional status (mRS, the Oxford handicap scale, the International Stroke trial simple questions, or the Barthel Index) • ICH • Symptomatic PE (fatal and non-fatal) • Major (or serious) extracranial hemorrhages • Symptomatic DVT • Asymptomatic DVT • Fractures secondary to falls due to mechanical devices or osteoporosis secondary to prolonged heparin use	Other outcomes were fatal PE and HRQOL-adjusted survival	• Risk of bias due to limitations in study design and inconsistency of results, indirectness of evidence, imprecision, reporting bias, magnitude of the treatment effect, evidence of a dose–response relationship, and the effect of all plausible confounding • The quality of evidence was judged to be moderate and strength of recommendation	ESO recommendation s: • GCS should not be used in patients with ischemic stroke • Thigh-length IPC should be used for immobile patients •Prophylactic anticoagulation with UFH (5000U × 2, or × 3 daily) or LMWH or heparinoid should be considered in immobile patients with

			3. No anticoagulants (n=10,197) 4.Only UFH (n= 870	• Any hemorrhage including minor bruising • Skin breaks which may be caused by stockings and IPC sleeves **Results:** • GCS had no significant effect on death (*P*=0.41) • IPC had no significant effect, despite a strong trend on deaths during treatment period (OR, 82; 95% CI, 0.66–1.02) but improved survival to 6 mo (HR, 0.86; 95% CI, 0.74–0.99) • Anticoagulants were associated with a reduction in DVT (OR, 0.21; 95% CI, 0.15–0.29); there were also statistically significant increases in sICH (OR, 1.68; 95% CI. 1.11–2.55) and symptomatic extracranial hemorrhages (OR, 1.65; 95% CI, 1.0–2.75) • For LMWHs of heparinoids or UFH, there were nonsignificant trends towards reduction in PE (*P*=0.81) and sICH (*P*=0.84) • There was a statistically significant increase in major extracranial hemorrhage (OR, 3.79; 95% CI, 1.30–11.03; *P*=0.01) with LMWH		weak due to lack of blinding • The strength of recommendation was weak	ischemic stroke in whom the benefits of reducing the risk of VTE is high enough to offset the increased risks of ICH and extracranial bleeding associated with their use •If prophylactic anticoagulation is indicated, LMWH or heparinoid should be considered instead of UFH because of its greater reduction in risk of DVT, the greater convenience, reduced staff costs, and patient comfort associated with single daily dose vs. multiple daily injections, but these advantages should be weighed against the higher risk of extracranial bleeding, higher drug costs and

				• The use of LMWH was associated with a statistically significant reduction in DVTs (OR, 0.55; 95% CI, 0.44–0.70), which were mostly asymptomatic **Safety end point:** None			risks in elderly patients with poor renal function
Sandercock et al.[198] 2015 25764172	**Aim:** To assess the effectiveness and safety of anticoagulation within 14 days of ischemic stroke onset **Study Type:** Meta-analysis **Size:** N=22,544 (from 14 trials) for PE analysis N=916 (from 10 trials) for DVT analysis N=22,943 (from 16 trials) for ICH analysis N=22,255 (from 18 trials) for major ECH	**Inclusion criteria:** Patients with confirmed or suspected ischemic stroke within the previous 14 days	Not specified	**End points:** • PE (symptomatic): OR, 0.60; 95% CI, 0.44-0.81) with anticoagulation vs no anticoagulation • DVT (symptomatic or asymptomatic): OR, 0.21; 95% CI, 0.15-0.29 with anticoagulation vs no anticoagulation	•Symptomatic ICH: OR, 2.55; 95% CI, 1.95-3.33 for anticoagulation vs no anticoagulation • Major ECH: OR, 2.99; 95% CI, 2.24-3.99	• Different forms of anticoagulation • Various forms of defining and assessing the endpoints	• Benefit of anticoagulation in the reduction of VTE are offset by the increased risk of bleeding
CLOTS 3 CLOTS Trials Collaboration Dennis M et al.[403] 2013 23727163	**Aim:** Establish whether routine application of IPC to the legs of immobile patients who had a stroke reduced their risk of DVT **Study type:** Multicenter parallel group randomized trial **Size:** N=2876	**Inclusion criteria:** Admitted within 3 d of acute stroke and be immobile **Exclusion criteria:** Age <16 y, SAH, or contraindications	**Intervention:** Routine care plus IPC (thigh high length) (n=1438) **Comparator:** Routine care and no IPC (n=1438)	**1° end point:** • Symptomatic or asymptomatic DVT in the popliteal or femoral veins detected on a screening within 30 d of randomization: • An absolute reduction in risk of 3.6% (95% CI, 1.4–5.8)	• 30- and 60-d death • DVT (including symptomatic or asymptomatic calf, popliteal or femoral) • Symptomatic DVT, PE confirmed on	•Moderate adherence to IPC •Masking poor at times: patient went for screening with device on	• IPC, UFH, or LMWH and heparinoids can reduce the risk of VTE in immobile patients with acute ischemic stroke, but further research is required to

		to IPC		• The adjusted OR for the comparison of 122 of 1267 patients vs. 174 of 1245 patients was 0.65 (95% CI, 0.51–0.84; *P*=0.001) • Deaths in the treatment period occurred in (11%) allocated IPC and (13%) allocated no IPC within the 30 d of treatment period (*P*=0.057) • Skin breaks on the legs were reported in (3%) patients allocated IPC and in 20 (1%) patients allocated no IPC (*P*=0.002) • Falls with injury were reported in (2%) patients in the IPC group and in (2%) patients in the no-IPC group (*P*=0.221) **Safety end point:** None	imaging or autopsy • Complications of IPC association with days worn (i.e., end date minus start date) divided by the number of days it should have been worn		test whether NES is effective • The strongest evidence is for IPC • Better methods are needed to help stratify patients in the first few wks after stroke onset by their risk of VTE and their risk of bleeding on anticoagulants
Geeganage CM, et al.[404] 2013 22516428	**Aim**: To assess the effect of heparin and other antithrombotic therapies in patients with acute/early ischemic stroke **Study type**: Systematic review and meta-analysis of RCTs **Size**: 15 RCTs that fulfilled the selection criteria (N=8045 patients)	**Inclusion criteria**: RCT assessing anticoagulation (UFH, LMWH, and heparinoid in adults>18 y and within 14 d of acute stroke **Exclusion criteria**: If trial did not record information on PE and sICH	**Intervention**: LMWH (n=18,29), heparinoids (n=341), and UFH (n=5875) **Comparator**: Same as above	**1° end point:** The ratio of sICH to sPE was increased with LMWH (RR: 2.1; 95% CI: 1.03–4.28), but was in approximated unity with heparinoids (RR, 1.27; 95% CI, 0.31–5.17) and UFH (RR, 0.99; 95% CI, 0.65–1.52)	Insufficient data were obtained for other outcomes, precluding further analysis	• Trials were excluded because data on both sICH and sPE were unavailable in the primary publications • Many of the included trials did not primarily focus on sICH and PE and so only collected symptomatic and fatal events	Routine acute use was not recommended but may still be relevant in patients at very high risk of PE (e.g., morbid obesity, previous VTE, and inherited thrombophilia) or if started later, although trials have not assessed these issues

						• Definition of sICH also varied widely among trials • The trials used different types and doses of low-dose anticoagulation	
Whiteley W, et al.[197] 2013 23642343	**Aim:** To test the hypothesis that a policy of using clinical data to target heparins in patients with ischemic stroke who have a high risk of venous or arterial thromboembolism, and avoiding heparins in patients with a high risk of bleeding, leads to overall better outcomes **Study type:** Meta-analysis **Size:** N=22,655 patients; 5 RCTs using UFH, heparinoids and LMWH in acute ischemic stroke included: IST, TOAST, TAIST, HAEST, FISS-tris	**Inclusion criteria:** Patients with baseline diagnosis of probable or definite ischemic stroke **Exclusion criteria:** Excluded 22 other trials of heparins because they were small (<100 patients), and were not clearly randomized, or data not readily available	**Intervention:** RCTs (5) compared heparins (UFH or LMWH) (n=11,478) **Comparator:** Aspirin (n=10,941)	**1° end point**: Prediction of thrombotic events (MI, stroke, deep VTE, or PE) and hemorrhagic events (symptomatic intracranial or extracranial in the first 14 d after stroke: • No group had a statistically significant benefit of heparins over aspirin or placebo in an ordinal logistic regression model (*P*=0.43) for the prevention of death or disability at the time of last follow-up • In none of the 16 groups was there evidence of heterogeneity between the risk differences from the different trials • There was no visible pattern or trend of increasing benefit or harm across the groups **Safety end point:** None	The state of being dead or dependent at final follow-up	• Predictive variable missing in dataset that may impact predictive models • Random error in variable due to data defined and obtained differently (particularly measures of stroke severity) • Large RCTs collection of data for death or dependence at end of follow-up rather than data on recurrent events or VTE	In view of the lack of evidence for heparin prophylaxis in reducing mortality in other categories of high-risk medical patients and in stroke, these data suggest current guideline recommendation s for routine or selective use of heparin in stroke (and perhaps other patients) should be revised

ACP Clinical Guidelines Qaseem A, et al.[405] 2011 22041951	**Aim**: To assess the benefits and harms of prophylaxis in hospitalized adult medical patients and those with acute stroke **Study type**: Systematic evidence review **Size**: Ten trials (N=20,717) evaluated medical patients without stroke, 8 trials (N=15,405) of patients with acute stroke	**Inclusion criteria**: English-language randomized trials were included if they provided clinical outcomes and evaluated therapy with low-dose heparin or related agents or mechanical measures compared with placebo, no treatment, or other active prophylaxis in the target population **Exclusion criteria**: Surgical hospitalized patients	1. Heparin prophylaxis vs. no heparin prophylaxis in medical patients without stroke (n=20,717) and with stroke (n=15,405) 2. LMWH vs. UFH in medical patients without stroke (n=11,650) and with stroke (n=2785) 3. Medical device for BTE prophylaxis vs. no mechanical devices in medical patients with and without stroke (n=2518)	**1° end point:** Mortality up to 120 d after enrollment: 1. Medical patients without stroke: compared with no heparin prophylaxis, heparin prophylaxis was not associated with a statistically significant reduced risk for mortality (risk ratio: 0.94; 95% CI, 0.84–1.04; I^2=0%; absolute reduction); acute stroke patients: LMWH with UFH in patients with acute stroke did not show statistically significant differences for mortality (risk ratio: 1.00; 95% CI, 0.81–1.22; I^2=1%; absolute reduction) 2. Medical patients without stroke showed no statistically significant difference in mortality (risk ratio: 0.91; 95% CI, 0.73–1.13; I^2=25%; absolute reduction); stroke patients did not show statistically significant differences for mortality (risk ratio: 1.00; 95% CI, 0.81–1.22; I^2=1%; absolute reduction 3. Medical results showed no statistically significant difference in risk for mortality (risk ratio: 1.11; 95% CI, 0.87–1.42)	• Symptomatic DVT: in medical patients: not statistically significant (RR, 0.78; CI, 0.45–1.35); in stroke patients: no statistically significant symptomatic DVT, or PE (risk ratio: 1.11; 95% CI, 0.87–1.42) • All PE, fatal PE: in medical patients, heparin was associated with reduced risk for PE (risk ratio: 0.69; 95% CI, 0.52–0.90; I^2=0%; absolute reduction); in stroke patients, heparin had no statistically significant effect on PE (risk ratio: 0.70; 95% CI, 0.44–1.11; I^2=0%; major bleeding events (risk ratio: 0.89; 95% CI, 0.70–1.15; I^2=0%; • Bleeding events: in medical patients risk for major	None reported	• In patients with acute stroke, there was no statistically significant benefit from heparin prophylaxis but there was increased risk for major bleeding • In both groups, low-dose heparin prophylaxis may have reduced PE and increased risk for bleeding and major bleeding events and had no statistically significant effect on mortality • The conclusion of findings indicate little or no net benefit • No significant differences in clinical benefits or harms were found between UFH and LMWH

				Safety end point: None	bleeding events increased but did not reach statistical significance (risk ratio: 1.49; 95% CI, 0.91–2.43; I^2=16%; absolute increase); in stroke patients heparin associated with statistically significant increase in major bleeding events (risk ratio: 1.66; 95% CI, 1.20–2.28; I^2=0%; absolute increase); in 14-day hemorrhagic stroke or serious extracranial hemorrhage (1.3% vs. 0.80%; OR, 1.73; 95% CI, 1.22–2.46) • Mechanical prophylaxis effect on skin in medical and stroke patients (statistically significantly increased among patients treated with compression stockings (risk		

					ratio: 4.02; 95% CI, 2.34–6.91) (risk ratio: 1.11; 95% CI, 0.87–1.42); risk for lower-extremity skin damage statistically significantly increased among patients treated with compression stockings (risk ratio: 4.02; 95% CI, 2.34–6.91)		

Abbreviations: CI indicates confidence interval; DVT, deep vein thrombosis; ECH, extracranial hemorrhage; ESO, European Stroke Organisation; GCS, graduated compression stockings; HR, hazard ratio; HRQOL, health-related quality of life; ICH, intracranial hemorrhage; IPC, intermittent pneumatic compression; LMWH, low-molecular–weight heparin; MI, myocardial infarction; mRS, modified Rankin Scale; N/A, not available; NES, neuromuscular electrical stimulation; OR, odds ratio; PE, pulmonary embolism; RCT, randomized clinical trial; RR, relative risk; SAH, subarachnoid hemorrhage; sICH, symptomatic intracerebral hemorrhage; UFH, unfractionated heparin; and VTE, venous thromboembolism.
Literature search topic: Stroke, DVT prophylaxis

Table LVII. Nonrandomized Studies of Depression Screening in Patients with Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Meader N, et al.[241] 2014 23385849	**Study type:** Meta-analysis **Size:** N=2907 (24 studies)	**Inclusion criteria:** Validation studies of mood questionnaires from inception to 2012 **Exclusion criteria:** Studies not clearly stating diagnostic status of depression or insufficient data for extraction	**1° end points:** Sensitivity and specificity for diagnosis of post-stroke depression; ROC meta-analysis **Results**: • CESD: sensitivity: 0.75 (95% CI, 0.60–0.85); specificity: 0.88 (95% CI, 0.71–0.95) • HDRS: sensitivity: 0.84 (95% CI, 0.75–0.90); specificity:0.83 (95% CI, 0.72–0.90) • PHQ-9: sensitivity: 0.86 (95% CI, 0.70–0.94); specificity: 0.79 (95% CI, 0.60–0.90)	Several tools have optimal ROC characteristics for detecting post-stroke depression including the CESD, HDRS, and PHQ-9; however, further research is needed to determine the optimal screening method and timing to diagnose and treat PSD[242]

Abbreviations: CESD indicates Center of Epidemiological Studies-Depression Scale; HDRS, Hamilton Depression Rating Scale; PHQ-9, Patient Health Questionnaire-9; PSD, poststroke depression; and ROC, receiver operating curve.
Literature search topic: Depression

Table LVIII. Randomized Clinical Trials of Mobility Intervention

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
SEVEL Herisson F, et al.[406] 2016 27023901	**Aim:** To test the hypothesis that early sitting could be beneficial to stroke patient outcome **Study type:** RCT **Size:** N=138	**Inclusion criteria:** Age >18 y **Exclusion criteria:** Massive infarct or contraindication for sitting	**Intervention:** Early-sitting group patients were seated out of bed at the earliest possible time but no later than one calendar day after stroke onset (n=63) **Comparator:** Progressively-sitting group was first seated out of bed on the third calendar day after stroke onset (n=75)	**1° end point:** Primary outcome measure was the proportion of patients with a mRS [0–2] at 3 mo post stroke: there was no difference regarding outcome of people with stroke, with a proportion of mRS [0–2] score at 3 mo of 76.2% and 77.3% of patients in the early- and progressive-sitting groups, respectively (*P*=0.52) **Safety end point:** N/A	• Prevalence of medical complications • Length of hospital stay • Tolerance to the procedure	• Slow enrollment, could detect beneficial/detrimental effects of ± 15% of the early sitting procedure on stroke outcome with a realized 37% power; however, enrollment was sufficient to rule out effect sizes >25% with 80% power • No blinded assessment of the primary outcome	There was also no difference between groups for secondary outcome measures, and the procedure was well tolerated in both arms
Morreale M, et al.[407] 2016 26220327	**Aim:** To compare PNF and CTE methods in two different time settings (early vs. standard approach) to evaluate different role of time and techniques in functional	**Inclusion criteria:** First ever sub-cortical ischemic stroke in the MCA territory and contralateral hemiplegia	**Intervention:** • All patients were randomly assigned by means of a computer-generated randomization	**1° end point:** Disability at 3–12 mo (disability measures: mRS and Barthel Index): disability was not different between groups at 3 mo but Barthel Index significantly changed between early	• Six-Minute Walking Test, Motricity Index, MMSE, Beck Depression Inventory: Six-Minute Walking Test (*P*=0.01)	Homogenous population that may not reflect other strokes; moderate stroke severity in population	A time-dependent effect of rehabilitation on post stroke motor recovery was observed, particularly in

	recovery after acute ischemic stroke **Study type:** We designed a prospective multicenter blinded interventional study of early vs. standard approach with two different methods by means of both PNF and CTE **Size:** N=340	admitted within 6 and 24 h from symptoms onset **Exclusion criteria:** NIHSS<2, aphasia, visual disturbances, neglect and/or other spatial representation defects, disorientation or confusion, ongoing seizures, MMSE<26, cardiovascular or neurological instability, hemorrhagic transformation, prior diagnosed neurological disease, chronic inflammatory disease, psychiatric disease, amputation, fractures or neoplasms	sequence in blocks of 4 to one to the 4 interventional groups: early groups: early PNF (n=110), delayed PNF (n=60), early CTE (n=110), delated CTE (n=60) • Patients in both delayed group underwent to a standard protocol in the acute phase **Comparator:** Standard approach delayed PNF (n=60), delayed CTE (n=60)	vs. delayed groups at 12 mo (*P*=0.01) **Safety end point:** Safety outcome: immobility-related adverse events	and Motricity Index in both upper (*P*=0.01) and lower limbs (*P*=0.001) increased in early vs. delayed groups regardless rehabilitation schedule		lower limb improvement. According to our results, rehabilitation technique seems not to affect long-term motor recovery
AVERT AVERT Trial Collaboration Group[243] 2015 25892679	**Aim:** Compare the effectiveness of frequent, higher dose, very early mobilization with usual care after stroke	**Inclusion criteria:** • Age ≥18 y, with confirmed first (or recurrent) stroke (infarct or	**Intervention:** High-dose, very early mobilization protocol interventions included:	**1° end point:** Favorable outcome 3 mo after stroke, defined as a mRS of 0–2: patients in the high-dose, very early mobilization group has less favorable outcomes	Outcomes included an assumption free ordinal shift of the mRS across the entire range of the scale;	• A limitation of large trials is the small amount of information that can be obtained about potential confounding	Early mobilization after stroke is recommended in many clinical practice guidelines

	Study type: RCT parallel-group, single-blind **Size:** N=2104 patients of 56 acute stroke units	intracerebral hemorrhage) • Admitted to a stroke unit within 24 h of stroke onset • Treatment with alteplase **Exclusion criteria:** • mRS >2, early deterioration, direct admission to the ICU, documented palliative treatment, immediate surgery, another serious medical illness or unstable coronary condition, coma, SBP <110 mmHg or >220 mmHg, oxygen saturation <92% with oxygen supplementation, resting heart rate of <40 beats/min or >110 beats/min, temperature >38.5°C • SAH	beginning mobilization within 24 h of stroke onset whereas usual care typically was 24 h after onset of stroke; there was a focus on sitting, standing and walking activity; and at least three additional out-of-bed sessions (n=1054) **Comparator:** Standard of care (n=1054)	(46% vs. 50%) than those in the usual care group; 8% vs. 7% of patients died in the very early mobilization group, and 19% vs. 20% had a non-fatal serious adverse event with high-dose, very early mobilization **Safety end point:** N/A	time taken to achieve unassisted walking over 50 m and the proportion of patients achieving unassisted walking by 3 mo; and deaths and the number of non-fatal serious adverse events at 3 mo	factors (e.g., physiological variables) and about each staff–patient interaction • Not prescriptive about usual care mobilization practices, which changed during the trial; usual care clinicians started mobilization earlier each year, with the result that roughly 60% of patients receiving usual care had started out-of-bed therapy within 24 h of stroke onset • Whether this result was a consequence of contamination from the trial protocol, a response to changes in attitudes to early mobilization over time as reflected in recent clinical	worldwide, and our findings should affect clinical practice by refining present guidelines; however, clinical recommendation s should be informed by future analyses of dose–response associations

						guidelines, or both, is uncertain	

Abbreviations: CTE indicates cognitive therapeutic exercise; h, hours; HR, hazard ratio; ICU, intensive care unit; MCA, mean cerebral artery; min, minutes; MMSE, Mini-Mental State Examination; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; OR, odds ratio; PNF, proprioceptive neuromuscular facilitation; RCT, randomized clinical trial; RR, relative risk; SAH, subarachnoid hemorrhage; SBP, systolic blood pressure; and y, year.
Literature search topic: Early mobility

Table LIX. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Hemispheric Stroke				
Sundseth J, et al.[251] 2017 27942881	**Study type:** Retrospective cohort **Size:** N=45	**Inclusion criteria:** MCA infarction with cerebral edema and decompressive craniectomy **Exclusion criteria:** N/A	**1° end point:** Early death (during primary hospitalization) **Results:** MCA infarct with additional anterior or posterior cerebral artery territorial involvement only clinically significant predictor of early in-hospital death	No age-related impact on early death after decompression for MCA infarct
Alexander P, et al.[250] 2016 27884858	**Study type:** Meta-analysis of RCTs **Size:** N=338 patients (7 RCTs)	**Inclusion criteria:** RCTs comparing conservative vs. DHC for ischemic MCA infarct syndrome **Exclusion criteria:** N/A	**1° end point:** Death and disability mRS **Results:** • DHC reduced death 69% vs. 30% • Severe disability (mRS=4), 32% and very severe disability (mRS=5), 11%	• Quality of evidence high for death; low for functional outcome mRS 0–3; moderate for mRS 0–4 (wide CIs and problems in concealment, blinding of outcome assessors, stopping early • DHC left 34% with mRS 4–5 and 11% mRS 5

Yang MH, et al.[249] 2015 25661677	**Study type:** Meta-analysis **Size:** N=314 patients (6 studies)	**Inclusion criteria:** RCTs of DHC for stroke **Exclusion criteria:** N/A	**1° end point:** N/A **Results:** DHC reduces mortality, death or major disability (mRS>3) and death or severe disability (mRS>4); associated with slightly higher proportion of major disability (mRS4–5) in survivors	• Compared to conservative treatment DHC decreased mortality and improved functional outcome in a clinically meaningful manner • Increase in the proportion of survivors with major disability was not clinically meaningful
Agarwalla PK, et al.[245] 2014 24402484	**Study type:** Literature review **Size:** N/A	**Inclusion criteria:** N/A **Exclusion criteria:** N/A	**1° end point:** N/A **Results:** N/A	• Review of literature on craniotomy in acute stroke • Supports current guidelines as written
Suyama K, et al.[252] 2014 25045787	**Study type:** Retrospective cohort **Size:** N=355	**Inclusion criteria:** DHC **Exclusion criteria:** N/A	**1° end point:** 30-d mortality and functional outcome (mRS) at 3 mo **Results:** Overall mortality 18.6%; only 5% with favorable functional outcome (mRS<4); Poor outcome associated with GCS<6 and midbrain compression	• Only 8.7% of patients with malignant MCA infarction underwent DHC in Japan • Mean age 67; patients aged >60 y comprised 80% of cohort • 22% of patients had mRS=4; 26.9% with mRS=5 • Age not found to be independent risk factor of poor outcome
Yu JW, et al.[253] 2012 23210030	**Study type:** Retrospective cohort **Size:** N=131	**Inclusion criteria:** Malignant MCA infarction, age>18 y, decompressive hemicraniectomy within 48 h of stroke onset; NIHSS>or=18 for right-sided infarction, NIHSS>or=20 for left-sided infarction	**1° end point:** Mortality at 30 d and six mo; outcome ("good" outcome mRS≤3; "poor" outcome mRS>3) **Results:** Reduction in mortality in craniectomy group vs conservative care group (29.3% vs 58.9% at 30 days and 48.3% vs 71.2% at six months). Death rate at six mo was not statistically different between age groups (>or=70 y vs <70 y) nor was rate of favorable outcome (*P*=0.137, *P*=0.077) High preoperative NIHSS was associated with higher rate of six-month mortality (*P*=0.047)	• Decompressive craniectomy reduced mortality and improved rate of good outcomes • Age was not independently associated with death at six months or poor outcome.

		Exclusion criteria: Preexisting significant disability (mRS>vs=4), pupils fixed and dilated, hemorrhagic infarction >50% MCA territory on CT		
Cerebellar Stroke				
Agarwalla PK, et al.[245] 2014 24402484	**Study type:** Comprehensive literature review **Size:** 12 Sigle institution and multi-institution series, N=283	**Inclusion criteria:** e Sigle institution and multi-institution series in which suboccipital decompression was used in the treatment of cerebellar infarct **Exclusion criteria:** N/A	**1° end point:** N/A **Results:** Suboccipital decompression is a life-saving procedure in patients with massive cerebellar infarctions. Ventriculostomy was commonly performed either in isolation as treatment of hydrocephalus or as adjunctive treatment to suboccipital decompression (60%, n=172); Several studies identify progressive decline in level of consciousness as indication for decompression or ventriculostomy. Long term functional outcomes after suboccipital decompression for massive cerebellar infarctions are correlated with immediate preoperative level of consciousness.	• Non-randomized studies, with a mix of retrospective series of various sizes • Cerebellar infarction with symptomatic edema and mass effect may be indicated before neurological deterioration, but the timing is unclear • Ventriculostomy is commonly performed; very rare mention of upward herniation only in setting of aggressive cerebrospinal fluid diversion without suboccipital decompression
Mostofi K[246] 2013 23532804	**Study type:** Retrospective series **Size:** N=53	**Inclusion criteria:** Massive cerebellar stroke **Exclusion criteria:** N/A	**1° end point:** Morbidity and mortality (GCS at 1 mo) **Results:** Clinically meaningful improvement in outcomes/GCS in surgical group	• Suboccipital craniectomy improves outcome over medical management • Only 3% of patients received ventriculostomy

Raco A, et al.[244] 2003 14580272	**Study type:** Retrospective cohort **Size:** N=44	**Inclusion criteria:** Cerebellar infarct **Exclusion criteria:** Deep coma	**1° end point:** mRS and death **Results:** 20/25 patients without decompression with good outcomes; 13/17 with ventriculostomy or decompression with good outcomes; overall mortality 13.6%	• Most patients treated conservatively did well • 8 patients were treated with ventriculostomy only • Only 3 patients were treated with ventriculostomy plus decompression • One patient treated with decompression only • Recommend ventriculostomy for hydrocephalus and worsening consciousness; decompression reserved for worsening despite ventricular drainage

Abbreviations: CI indicates confidence interval; DHC, decompressive hemicraniectomy; GCS, Glasgow Coma Score; MCA, middle cerebral artery; N/A, not available; and RCT, randomized controlled trial.

Literature search topics: cerebral edema, surgical decompression suboccipital AND Cerebral edema, impact of age AND Cerebral edema, hypothermia, corticosteroids AND Cerebral edema, decompression timing AND Cerebral edema, ventriculostomy, hydrocephalus AND Cerebral edema, barbiturates AND Cerebral edema, corticosteroids AND Cerebral edema, cerebellar decompression

Table LX. Randomized Clinical Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction

Study Acronym; Author; Year Published	Aim of Study; Study Type; Study Size (N)	Patient Population	Study Intervention (# patients) / Study Comparator (# patients)	End Point Results (Absolute Event Rates, *P* value; OR or RR; & 95% CI)	Relevant 2° End Point (if any)	Study Limitations; Adverse Events	Summary Conclusions Comments
DESTINY II Juttler E, et al.[254] 2014 24645942	**Aim:** To determine impact of decompressive craniotomy on patients aged >60 y **Study type:** RCT **Size:** N=112	**Inclusion criteria:** Malignant MCA infarct randomized within 48 h **Exclusion criteria:** Age <60	**Intervention:** Decompressive hemicraniectomy (n=49) **Comparator:** Conservative treatment in the ICU (n=63)	**1° end point:** Survival without severe disability (mRS <5) at 6 mo: proportion who survived mRS 0-4 was 38% in hemicraniectomy group vs. 18% in control group (CI, 1.06–7.49; *P*=0.04); mRS 3 7% surgery group vs. 3% control group	Death at 6 mo	N/A	• Hemi-craniectomy improved primary end point (38% vs. 18%; OR, 2.91; 95% CI, 1.06–7.49; *P*=0.04) • None with mRS<3; 35% vs.

		y, intracerebral hemorrhage		**Safety end point:** N/A			15% with mRS=4; 28% vs. 18% with mRS=5 • Improved survival in pts aged >60 y; most patients are disabled
ChiCTR Zhao J, et al.[255] 2012 22528280	**Aim**: To assess effectiveness of DHC on patients ≤80 y **Study type:** RCT **Size:** N=47	**Inclusion criteria:** Patients aged18–80 y with malignant MCA infarct **Exclusion criteria:** Age >80 y; DHC > 48 h of stroke onset	**Intervention:** DHC (n=24) **Comparator:** Medical management (n=23)	**1° end point:** mRS at 6 mo: DHC reduced mortality significantly at 6 and 12 mo (33.3 vs. 82.6%, *P*=0.001); significant reduction in poor outcome (mRS>4) in 36 patients after 6 mo (*P*<0.001) **Safety end point:** Significant reduction (*P*<0.001) in mortality after 36 patients completed 6 mo follow up	• 6- and 12-month mortality and mRS after 1 y • Subgroup analysis performed for patients aged 60–80 y	• Stopped early • Concluded that DHC <48 h reduced death and severe disability even in patients aged 60–80 y	• DHC reduced mortality in all subgroups at 6 and 12 mo (12.5% vs. 60.9% and 12.5 vs. 60.9%) • Fewer patients had mRS>4 (33.3 vs. 82.6%)
DESTINY, DECIMAL, HAMLET; Vahedi, et al.[247] 2007 17303527	**Aim:** Analyze effectiveness of decompressive craniectomy in malignant MCA infarction **Study type**: Pooled analysis of three RCTs **Size:** N=93	**Inclusion criteria:** age 18-80 y with MCA malignant infarction, enrolled in HAMLET, DECIMAL, or DESTINY trials; treated within 48 h after stroke **Exclusion criteria:** Age>60; failed enrollment	**Intervention:** Decompressive hemicraniectomy **Comparator:** Conservative treatment in the ICU	**1° end point:** mRS at 1 year dichotomized between favorable (0-4) and unfavorable (5 or death); more patients in decompressive group had mRS≤4 (75% vs 24%; aRR 51%; 95% CI, 34-69), an mRS≤3 (43% vs 21%; aRR 23%) and survived (78% vs 29%; aRR 50%) **Safety end point:** N/A	Case fatality rate at 1 year, mRS dichotomized between 0-3 and 4 to death.	N/A	• Decompressive hemicraniectomy within 48 hours of malignant MCA infarction reduces mortality and increases numbers of patients with favorable outcome (mRS 0-4) • Numbers needed to treat of two for survival with

		in any of the RCTs					mRS≤4, four for survival with mRS≤3, and two for survival irrespective of functional outcome

Abbreviations: CI indicates confidence interval; DHC, decompressive hemicraniectomy; h, hour; HR, hazard ratio; mRS, modified Rankin Scale; N/A, not available; OR, odds ratio; RCT, randomized clinical trial; and y, year.
Literature search topics: Cerebral edema, surgical decompression suboccipital AND Cerebral edema, impact of age AND Cerebral edema, hypothermia, corticosteroids AND Cerebral edema, decompression timing AND Cerebral edema, ventriculostomy, hydrocephalus AND Cerebral edema, barbiturates AND Cerebral edema, corticosteroids AND Cerebral edema, cerebellar decompression

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Table LXXVII. Nonrandomized Studies of Early Secondary Prevention in Patients with Acute Ischemic Stroke

Study Acronym; Author; Year Published	Study Type/Design; Study Size	Patient Population	Primary End Point and Results (*P* value; OR or RR; & 95% CI)	Summary Conclusions Comments
Anticoagulation				
Gioia LC, et al.[207] 2016 27222524	**Study type:** Prospective open-label **Size:** N=60	**Inclusion criteria:** Patients with AF treated with rivaroxaban ≤14 d of TIA or ischemic stroke (NIHSS <9) **Exclusion criteria:** GFR <30 ml/min, contraindication to MRI	**1° end point:** Symptomatic HT at day 7 (defined as PH2 with ≥4-point increase in NIHSS score) **Results:** No patients developed symptomatic HT	• Rivaroxaban may be safe for initiation ≤14 d of TIA or minor to moderate severity ischemic stroke in patients with AF • Study limited by small sample size and observational design
VISTA analysis Abdul-Rahim AH, et al.[419] 2015 25319957	**Study type:** Retrospective cohort **Size:** N=644 (individual patient data from neuroprotection trials in AIS)	**Inclusion criteria:** AIS with known h/o AF or on baseline ECG; patients randomized to placebo or any drug with no known action on stroke outcome **Exclusion criteria:** Lacking data on relevant baseline and outcomes data	**1° end point:** Ordinal shift mRS at 90 d; recurrent stroke or sICH at 90 d (defined by ≥4-point increase on NIHSS **Results:** • Combined antithrombotic therapy (AC + AP) associated with more favorable ordinal mRS (OR, 1.79; 95% CI, 1.32–2.42) • Anticoagulation associated with fewer RS and sICH at 90 d compared to no antithrombotic therapy	• Initiation of anticoagulation therapy 2–3 d post-stroke associated with fewer events of recurrent stroke with no appreciable increase in rates of sICH; • Limitations: nonrandom selection of antithrombotic therapy subject to selection bias - patients in "no antithrombotic group" had higher baseline NIHSS and greater comorbidities; NOACs were not prescribed at the time of these data
RAF Study Paciaroni M, et al.[202] 2015 26130094	**Study type:** Prospective cohort **Size:** N=1029 (multicenter Europe and Asia)	**Inclusion criteria:** Known or newly diagnosed AF **Exclusion criteria:** Contraindication to AC	**1° end point:** Composite stroke, TIA, systemic embolism, sICH, major extracranial bleeding within 90 d **Results:** 12.6% primary outcome HR, 0.53 (0.30–0.93) starting AC 4–14 d vs. <4 d	• Initiating AC 4–14 d from stroke onset in patients with AF had better outcomes; high CHA_2DS_2-VASc, NIHSS, large ischemic lesions, and type of AC associated with composite outcome • Study limited by non-randomization

Antithrombotics after Hemorrhagic Transformation				
Kim JT, et al.[322] 2014 24587041	**Study type:** Retrospective analysis **Size:** N=222	**Inclusion criteria:** Patients with AIS and hemorrhagic transformation **Exclusion criteria:** • Early death or lost to f/u • Malignant infarction > 2/3 • Bleeding disorders • H/o recent hemorrhage • Brain surgery	**1° end point:** Neurological deterioration, vascular events, and death at 1 mo **Results:** Antithrombotics vs. no antithrombotics (1.6% vs 11.1%, *P*=0.041)	• Suggests patients with AIS and hemorrhagic transformation do better with early reinitiation of antithrombotics than not • Study limited by single-center, retrospective analysis
TAIST England TJ, et al.[323] 2010 21030711	**Study type:** Post-hoc analysis from RCT **Size:** N=1297	**Inclusion criteria:** Patients within 48 h of AIS, treated with medium and high dose tinzaparin (LMWH) vs. ASA **Exclusion criteria:** Presence of hemorrhagic transformation on prerandomization head CT	**1° end point:** Hemorrhagic transformation at 10 d and functional outcomes at 3 and 6 mo (mRS, BI) **Results:** No difference in hemorrhagic transformation on LMWH or functional outcomes in patients with HT	• LMWH is safe to administer in the acute stroke setting • Patients with sICH were excluded; post-hoc analysis subject to subject bias
Endovascular Therapy in CeAD				
CADISS subgroup Larsson SC et al.[325] 2017 28087823	**Study type:** Retrospective analysis of CeAD patients with and without DA **Size:** N=264	**Inclusion criteria:** CeAD patients within 7 d of symptom onset **Exclusion criteria** • Intracranial artery dissection	**1° end point:** Difference in recurrent stroke at 12 mo between CeAD patients with DA and without DA **Results**: DA vs. no DA: OR, 0.84 (95% CI, 0.10–7.31; *P*=0.88)	• Dissecting aneurysms have a benign natural history and endovascular therapy is not necessary in the majority of cases • Corroborated by accompanying systematic review • Study limited by possible selection and survival bias

		• Contraindications to antithrombotic therapy • Baseline antithrombotic therapy • Pregnancy		
Jensen J, et al.[420] 2016 27286992	**Study type:** Retrospective analysis **Size:** N=161	**Inclusion criteria:** CeAD patients managed with EVT (n=24) vs. no EVT **Exclusion criteria:** None listed	**1° end point:** No difference in 90-days mRS ≤2, adjusted OR, 0.62 (0.12–3.14; *P*=0.56) **Results**: Adjusted OR, 0.62 (95% CI, 0.12–3.14; *P*=0.56)	Retrospective analysis prone to selection bias. With medical therapy alone, the overall prognosis and natural history of CeAD, including dissecting aneurysms, is favorable[324,325]
Ahlhelm F, et al.[326] 2013 25187774	**Study type:** Retrospective case series **Size:** N=10	**Inclusion criteria:** CeAD patients managed with stenting due to 1) iatrogenic dissection or 2) recurrent ischemic events despite optimal antithrombotic treatment **Exclusion criteria:** N/A	**1° end point:** Technical success (8/10), complications (3/10), recurrent ischemic events **Results**: No recurrent ischemic events at mean f/u 47 mo	• Stenting is feasible for CeAD in patients with recurrent ischemic events despite optimal medical therapy but is rarely indicated • Limited by small sample size and selection bias

Abbreviations: AC indicates anticoagulant; AF, atrial fibrillation; AIS, acute ischemic stroke; AP, antiplatelet; CI, confidence interval; BI, Barthel Index; CeAD, cervical artery dissection; DA, dissecting aneurysm; ECG, electrocardiogram; EVT, endovascular therapy; f/u, follow-up; GFR, glomerular filtration rate; h, hour; h/o, history of; HR, hazard ratio; HT, hemorrhagic transformation; IV, intravenous; LMWH, low-molecular-weight heparin; mRS, modified Rankin Scale; N/A, not available; NIHSS, National Institutes of Health Stroke Scale; NOAC, new oral anticoagulant; OR, odds ratio; PH2, parenchymal hematoma type 2; RCT, randomized clinical trial; sICH, symptomatic intracerebral hemorrhage; RR, relative risk; RS, recurrent stroke; and TIA, transient ischemic attack.
Literature search topics: Antiplatelet AND Anticoagulation

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Table LXXXIII. Original Wording of Recommendations Reworded from Previous Guidelines and Statements

2018 AIS GL Section/Rec # or Table/Heading	Original Wording of Recommendation* Reworded for Clarity in 2018 AIS GL
1.2. Rec 1	The use of a stroke assessment system by first aid providers is recommended.
1.2. Rec 3	EMS personnel should provide prehospital notification to the receiving hospital that a potential stroke patient is en route so that the appropriate hospital resources may be mobilized before patient arrival.
1.3. Rec 1	EMS leaders in coordination with local, regional, and state agencies and in consultation with medical authorities and local experts should develop triage paradigms and protocols that ensure that all patients with a known or suspected stroke are rapidly identified and assessed by use of a validated and standardized instrument for stroke screening, such as the FAST (face, arm, speech test) scale, LAPSS, or the Cincinnati Prehospital Stroke Scale (CPSS).
1.3. Rec 2	Regional systems of stroke care should be developed. These should consist of the following: a. Healthcare facilities that provide initial emergency care, including administration of intravenous r-tPA, such as primary stroke centers, comprehensive stroke centers, and other facilities, and b. Centers capable of performing endovascular stroke treatment with comprehensive periprocedural care, including comprehensive stroke centers and other healthcare facilities, to which rapid transport can be arranged when appropriate.
1.3. Rec 3	Patients should be transported rapidly to the closest available certified PSC or CSC or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the statement.
1.6. Rec 2	When implemented within a telestroke network, teleradiology systems approved by the Food and Drug Administration (or equivalent organization) are useful in supporting rapid imaging interpretation in time for fibrinolysis decision making.
1.7. Rec 1	It may be useful for primary stroke centers and other healthcare facilities that provide initial emergency care, including administration of intravenous r-tPA, to develop the capability of performing emergency noninvasive intracranial vascular imaging to most appropriately select patients for transfer for endovascular intervention and to reduce the time to endovascular treatment
1.7. Rec 2	Endovascular therapy requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified neurointerventionalists. Systems should be designed, executed, and monitored to emphasize expeditious assessment and treatment. Outcomes for all patients should be tracked. Facilities are encouraged to define criteria that can be used to credential individuals who can perform safe and timely intra-arterial revascularization procedures.
2.1. Rec 1	The use of a stroke rating scale, preferably the National Institutes of Health Stroke Scale (NIHSS), is recommended.
2.2. Rec 8	If endovascular therapy is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient but should not delay intravenous r-tPA if indicated. For patients who qualify for intravenous r-tPA according to guidelines from professional medical societies, initiating intravenous r-tPA before noninvasive vascular imaging is recommended for patients who have not had noninvasive vascular imaging as part of their initial imaging assessment for stroke. Noninvasive intracranial vascular imaging should

	then be obtained as quickly as possible.
2.3. Rec 2	Baseline electrocardiogram assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA.
2.3. Rec 3	Baseline troponin assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA.
2.3. Rec 4	The 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 fibrinolysis.
3.2. Rec 2	Patients who have elevated blood pressure and are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered so that their systolic blood pressure is <185 mm Hg and their diastolic blood pressure is <110 mm Hg before fibrinolytic therapy is initiated.
3.5. Rec 1	Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke. Physicians should review the criteria outlined in Tables 10 and11 (which are modeled on those used in the NINDS Trial) to determine the eligibility of the patient.
3.5. Rec 2	Intravenous rtPA (0.9 mg/kg, maximum dose 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset. The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients >80 years old, those taking oral anticoagulants regardless of INR, those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the MCA territory, or those with a history of both stroke and diabetes mellitus.
3.5. Rec 8	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.
3.5. Rec 11	Treating clinicians should be aware that hypoglycemia and hyperglycemia may mimic acute stroke presentations and check blood glucose levels before intravenous initiation. Intravenous alteplase is not indicated for nonvascular conditions.
3.5. Rec 12	Because time from onset of symptoms to treatment has such a powerful impact on outcome, delaying treatment with intravenous alteplase to monitor for further improvement is not recommended.
3.5. Rec 13	In patients undergoing fibrinolytic therapy, physicians should be aware of and prepared to emergently treat potential side effects, including bleeding complications and angioedema that may cause partial airway obstruction.
3.5. Rec 14	Patients who have elevated blood pressure and are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered (Table 9) so that their systolic blood pressure is <185 mm Hg and their diastolic blood pressure is <110 mm Hg before fibrinolytic therapy is initiated. If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before beginning treatment with intravenous rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after intravenous rtPA treatment.
3.5. Rec 16	In patients eligible for intravenous rtPA, benefit of therapy is time dependent, and treatment should be initiated as quickly as possible. The door-to-needle time (time of bolus administration) should be within 60 minutes from hospital arrival.
3.7. Rec 1	Patients eligible for intravenous r-tPA should receive intravenous r-tPA even if endovascular treatments are being considered.
3.7. Rec 4	Although the benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.
3.7. Rec 5	Although the benefits are uncertain, the use of endovascular therapy with stent retrievers may be reasonable for carefully selected patients with acute ischemic stroke in whom treatment can be initiated (groin puncture) within 6 hours of symptom onset and who have causative occlusion of the M2 or M3 portion of the MCAs, anterior cerebral arteries, vertebral arteries, basilar artery, or posterior cerebral arteries.
3.7. Rec 9	The technical goal of the thrombectomy procedure should be a TICI grade 2b/3 angiographic result to maximize the probability of a good functional clinical outcome.

3.7. Rec 14	Use of salvage technical adjuncts, including intraarterial fibrinolysis, may be reasonable to achieve these angiographic results if completed within 6 hours of symptom onset.
3.8. Rec 2	Initial treatment with intra-arterial fibrinolysis is beneficial for carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA. However, these data are derived from clinical trials that no longer reflect current practice, including the use of fibrinolytic drugs that are not available. A clinically beneficial dose of intra-arterial r-tPA is not established, and r-tPA does not have US Food and Drug Administration approval for intra-arterial use. As a consequence, endovascular therapy with stent retrievers is recommended over intra-arterial fibrinolysis as first-line therapy
3.8. Rec 3	Intra-arterial fibrinolysis initiated within 6 hours of stroke onset in carefully selected patients who have contraindications to the use of intravenous r-tPA might be considered, but the consequences are unknown.
3.11. Rec 4	At present, use of devices to augment cerebral blood flow for the treatment of patients with acute ischemic stroke is not well established. These devices should be used in the setting of clinical trials.
3.12. Rec 1	At present, no pharmacological agents with putative neuroprotective actions have demonstrated efficacy in improving outcomes after ischemic stroke, and therefore, other neuroprotective agents are not recommended.
3.13. Rec 2	In patients with unstable neurological status (either stroke-in-evolution or crescendo TIA), the efficacy of emergent or urgent carotid endarterectomy is not well established.
4.2. Rec 3	Supplemental oxygen is not recommended in nonhypoxic patients with acute ischemic stroke.
4.6. Rec 2	Dysphagia screening is reasonable by a speech-language pathologist or other trained healthcare provider.
4.6. Rec 4	Selection of instrumental study (fiberoptic endoscopic evaluation of swallowing, videofluoroscopy, fiberoptic endoscopic evaluation of swallowing with sensory testing) may be based on availability or other considerations.
5.1. Rec 9	Osmotic therapy for patients with clinical deterioration from cerebral swelling associated with cerebral infarction is reasonable.
5.2. Rec 1	Recurrent seizures after stroke should be treated in a manner similar to other acute neurological conditions, and antiepileptic agents should be selected by specific patient characteristics.
5.2. Rec 2	Prophylactic use of anticonvulsants is not recommended.
Table 6: Within 3 h	Intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke. Physicians should review the criteria outlined in Tables 10 and 11 (which are modeled on those used in the 2 NINDS trials) to determine the eligibility of the patient.
Table 6: Age	For otherwise medically eligible patients ≥18 years of age, intravenous alteplase administration within 3 hours is equally recommended for patients <80 and >80 years of age. Older age is an adverse prognostic factor in stroke but does not modify the treatment effect of thrombolysis. Although older patients have poorer outcomes, higher mortality, and higher rates of sICH than those <80 years of age, compared with control subjects, intravenous alteplase provides a better chance of being independent at 3 months across all age groups.
Table 6: 3-4.5 h Table 6: Age, Diabetes mellitus, Prior stroke, Severity, OACs, Imaging	Intravenous alteplase (0.9 mg/kg; maximum dose, 90 mg) is recommended for administration to eligible patients who can be treated in the time period of 3 to 4.5 hours after stroke onset. The eligibility criteria for treatment in this time period are similar to those for people treated at earlier time periods within 3 hours, with the following additional exclusion criteria: patients >80 years old, those taking oral anticoagulants (OACs) regardless of international normalized ratio (INR), those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the middle cerebral artery (MCA) territory, or those with a history of both stroke and diabetes mellitus.
Table 6: Severity 0- to 3-h window	Within 3 hours from symptom onset, treatment of patients with milder ischemic stroke symptoms that are judged as nondisabling may be considered. Treatment risks should be weighed against possible benefits; however, more study is needed to further define the risk-to-benefit ratio.

Table 6: Severity 3- to 4.5-h window	The benefit of intravenous alteplase administration for acute stroke patients with a baseline NIHSS score >25 and presenting in the 3- to 4.5-hour window is uncertain.
Table 6: Preexisting disability	Preexisting disability does not seem to independently increase the risk of sICH after intravenous alteplase, but it may be associated with less neurological improvement and higher mortality. Thrombolytic therapy with intravenous alteplase for acute stroke patients with preexisting disability (mRS score ≥2) may be reasonable, but decisions should take into account relevant factors other than mRS (including quality of life, social support, place of residence, need for a caregiver after alteplase administration, patients' and families' preferences, and goals of care).
Table 6: Coagulopathy	Intravenous alteplase may be reasonable in patients who have a history of warfarin use and an INR ≤1.7.
Table 6: Menstruation	When there is a history of recent or active vaginal bleeding causing clinically significant anemia, then emergent consultation with a gynecologist is probably indicated before a decision about intravenous alteplase is made.
Table 6: Extracranial cervical dissections	Intravenous alteplase in acute ischemic stroke known or suspected to be associated with extracranial cervical arterial dissection is reasonably safe within 4.5 hours and is probably recommended.
Table 6: Recent MI	For patients presenting with acute ischemic stroke and a history of recent MI in the past 3 months, treating the ischemic stroke with intravenous alteplase is reasonable if the recent MI was non-STEMI, is reasonable if the recent MI was STEMI involving the right or inferior myocardium, and may be reasonable if the recent MI was STEMI involving the left anterior myocardium.
Table 6: Pregnancy	Intravenous alteplase administration for ischemic stroke may be considered in pregnancy when the anticipated benefits of treating moderate to severe stroke outweigh the anticipated increased risks of uterine bleeding.

*Original publication and date noted in 2018 AIS GL. Changes to Class and LOE, if any, are noted in the 2018 GL.

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Data Supplement 2

Literature Searches

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Public education, EMS assessment and management: recognize, call 911 Table 1. Nonrandomized Studies of Stroke Awareness and Emergency Medical Services Use Table 2. Randomized Controlled Trials for Improving Stroke Awareness Table 4. Nonrandomized Studies of Emergency Medical Services Use of Prehospital Stroke Severity Scales									
PubMed	10/25/2016	1/1/2012-10/25/2016	Humans, English only	None	public education stroke	468	61	22	0
clinicaltrials.gov	10/25/2016	No restrictions	N/A	None	public education stroke	40	40	N/A	0
PubMed	10/25/2016	1/1/2012-10/25/2016	English only	None	ems management stroke	66	66	23	0
PubMed	10/25/2016	1/1/2012-10/25/2016	English only	None	prehospital stroke management	116	116	40	0
clinicaltrials.gov	10/26/2016	No restrictions	N/A	None	ems stroke	45	45	N/A	0
clinicaltrials.gov	10/26/2016	No restrictions	N/A	None	Prehospital stroke	49	49	N/A	0
Emergency evaluation: benefit of stroke scale use Table 3. Nonrandomized Trials, Observational Studies, and/or Registries of Prediction Value of National Institutes of Health Stroke Scale									
PubMed	11/4/2016 (updated 2/4/2017)	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	NIH Stroke Scale, Use	276	276	2	0
PubMed	11/4/2016 (updated 2/4/2017)	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	NIH Stroke Scale, Benefit	31	31	0	0
PubMed	11/4/2016 (updated 2/4/2017)	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	NIH Stroke Scale, Emergency	151	151	2	0

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
CT attenuation IV alteplase interaction Table 17. Randomized Controlled Trials of Interaction of Baseline Imaging Computed Tomography Hypodensity with Treatment Effect for Intravenous Alteplase Table 18. Randomized Controlled Trials of Interaction of Baseline Computed Tomography Hyperdense Middle Cerebral Artery Sign with Treatment Effect for Intravenous Alteplase									
PubMed	10/30/2016	No limit (4/1/1990 - 2/28/2016 returned)	RCTs with interaction term calculated	Non-English	"tissue plasminogen activator"[MeSH Terms] AND ("brain ischemia/radiography"[Mesh Terms] OR "cerebrovascular disorders/radiography"[Mesh Terms] OR "stroke/radiography"[Mesh Terms]) AND ("randomized controlled trials as topic"[MeSH Terms] OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields]) OR ECASS[All Fields] OR "NINDS rt-PA Stroke Study"[All Fields] OR EPITHET[All Fields] OR "early ischemic changes"[All Fields] OR hypoattenuation[All Fields] OR "Alberta Stroke Program Early CT score"[All Fields])	82	82	7	5
EMBASE	10/30/2016	No limit (1/1/2004-12/30/2016 returned)	RCTs with interaction term calculated	Non-English	'tissue'/exp OR tissue AND ('plasminogen'/exp OR plasminogen) AND activator AND 'clinical' AND trial AND (early AND ischemic AND changes OR hypoattenuation OR 'alberta'/exp OR alberta) AND ('stroke'/exp OR stroke) AND program AND early AND ct AND score	21	21	1	0
Other	10/31/2016	N/A	RCTs with interaction term calculated	Non-English	Personal files, referenced by other studies	5	4	4	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
CT attenuation IAT interaction Table 17. Randomized Controlled Trials of Interaction of Baseline Imaging CT Hypodensity with Treatment Effect for IV alteplase									
PubMed	10/31/2016	1/1/2015 – 12/31/2016	RCTs with interaction term calculated	Non-English	stroke AND "Alberta Stroke Program Early CT score" AND (thrombectomy OR endovascular)	49	49	5	2
EMBASE	10/31/2016	No limit (1/1/2011 - 12/31/2016 returned)	RCTs with interaction term calculated	Non-English	thrombectomy AND 'clinical' AND trial AND (early AND ischemic AND changes OR hypoattenuation OR 'alberta'/exp OR alberta) AND ('stroke'/exp OR stroke) AND program AND early AND ct AND score	17	17	0	0
Other	10/31/2016	N/A	RCTs with interaction term calculated	Non-English	Personal files, referenced by other studies	1	1	1	1
Hyperdense MCA IV alteplase interaction Table 18. Randomized Controlled Trials of Interaction of Baseline Computed Tomography Hyperdense Middle Cerebral Artery Sign with Treatment Effect for Intravenous Alteplase									
PubMed	10/21/2016	No limit (1/1/2010 - 12/31/2016 returned)	RCTs with interaction term calculated	Non-English	"tissue plasminogen activator"[MeSH Terms] AND ("brain ischemia/radiography"[Mesh Terms] OR "cerebrovascular disorders/radiography"[Mesh Terms] OR "stroke/radiography"[Mesh Terms]) AND ("randomized controlled trials as topic"[MeSH Terms] OR ("randomized controlled trial"[Publication Type] OR "randomized controlled trials as topic"[MeSH Terms] OR "randomized controlled trial"[All Fields] OR "randomised controlled trial"[All Fields])) AND "hyperdense middle cerebral artery"[All Fields]	1 (and 16 cited by)	17	2	2

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
EMBASE	10/30/2016	No limit (1/1/1999 - 12/31/2016 returned)	RCTs with interaction term calculated	Non-English	'tissue'/exp OR tissue AND ('plasminogen'/exp OR plasminogen) AND activator AND 'clinical' AND trial AND hyperdense middle cerebral artery sign	4	34	3	1
Hyperdense MCA IV alteplase interaction II Table 19. Observational Studies of Interaction of Baseline Magnetic Resonance Imaging of Cerebral Microbleeds with Symptomatic Intracerebral Hemorrhage After Intravenous Alteplase									
PubMed	11/2/2016	No limit (1/1/2004 - 12/31/2015 returned)	RCTs with interaction term calculated	Non-English	Thrombectomy OR endovascular OR intra-arterial AND "hyperdense middle cerebral artery"[All Fields]	10	10	0	0
EMBASE	10/30/2016	No limit (1/1/2012- 12/31/2016 returned)	RCTs with interaction term calculated	Non-English	thrombectomy AND 'clinical' AND trial AND hyperdense middle cerebral artery sign	2	2	0	0
Door-to-imaging times achievable Table 16. Observational Studies of 2016 Door-to-Computed Tomography Times									
PubMed	10/31/2016	2016 publication date	US only, door-to-CT time	Non-English	("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND (door-to-CT[All Fields] OR (door-to-needle[All Fields] AND ("contraindications"[Subheading] OR "contraindications"[All Fields] OR "ct"[All Fields]))) 2014-2016	15	15	4	3
EMBASE	10/31/2016	2016 publication date	US only, door-to-CT time	Non-English	stroke AND 'door to ct'	25	25	0	0
Other	10/31/2016	2016 publication date	US only, door-to-CT time	Non-English	Personal files, referenced by other studies	1	1	1	1
Multimodal imaging Table 20. Randomized Controlled Trials of Intravenous Thrombolytics Employing Multimodal Imaging Table 21. Nonrandomized Trials, Observational Studies, and/or Registries of Intravenous Thrombolytics Employing Multimodal Imaging									
PubMed	10/10/2016 (updated 10/11/2016)	No range	None	None	acute ischemic stroke AND trial OR multimodal imaging OR penumbra OR mismatch OR imaging selection	357	274	27	8
Other	10/11/16	No range	None	None	Personal files	1	1	1	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Vessel and collateral status imaging Table 22. Nonrandomized Trials, Observational Studies, and/or Registries of Creatinine Testing Prior to Contrast Computed Tomography Table 24. Nonrandomized Trials, Observational Studies, and/or Registries of Collateral Status									
PubMed	10/10/2016 (updated 10/11/2016	No range	None	None	acute stroke AND CTA OR MRA OR vessel imaging OR collaterals	757	395	37	8
Interaction of baseline MRI microbleeds with IV alteplase Table 19. Observational Studies of Interaction of Baseline Magnetic Resonance Imaging of Cerebral Microbleeds with Symptomatic Intracerebral Hemorrhage After Intravenous Alteplase									
PubMed	11/16/2016	11/16/2016 -7/31/2013	English only, Adults, meta-analyses	abstracts, includes studies included in more recent meta-analyses	microbleeds AND stroke AND thrombolysis AND meta-analysis	6	6	2	2
Embase	11/16/2016	11/16/2016 -8/31/2004	English only, Adults, meta-analyses	abstracts, includes studies included in more recent meta-analyses	microbleeds AND stroke AND thrombolysis AND meta-analysis	17	17	0	0
Blood pressure Table 29. Nonrandomized Trials, Observational Studies, and/or Registries of Blood Pressure and Thrombolysis									
PubMed	10/28/2016 (updated 2/28/2017)	1/1/2010-2/28/2017	from 2010 on; English	pediatric, foreign lang	blood pressure and AIS; vasoactive agents and AIS	582	321	20	8
Oxygen supplementation Table 26. Randomized Controlled Trials Comparing Supplemental Oxygen									
PubMed	10/26/2016 (updated 10/27/2016)	1/1/2010-10/27/2016	from 2010 on; English	pediatric, foreign lang	oxygen supplementation and acute stroke	6	5	1	0
PubMed	10/28/2016 (updated 12/7/2016)	1/1/2010-12/7/2016	from 2010 on; English	pediatric, foreign lang	acute stroke and oxygen supplementation	18	10	4	4
Google	12/7/2016	1/1/2010-12/7/2016	from 2010 on; English	pediatric, foreign lang	singhal and oxygen and stroke	2	2	1	2

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Temperature Table 30. Nonrandomized Studies of Hyperthermia After Acute Ischemic Stroke Table 31. Randomized Controlled Trials of Normothermia Table 32. Nonrandomized Trials, Observational Studies, and/or Registries of Hypothermia Table 33. Randomized Controlled Trials of Hypothermia									
PubMed	11/21/2016	1/1/2010-11/21/2016	from 2010 on; English	pediatric, foreign lang	hypothermia and acute stroke	210	51	15	8
PubMed	10/27/2016	1/1/2010-10/27/2016	from 2010 on; English	pediatric, foreign lang	hyperthermia and acute stroke	202	50	0	0
PubMed	11/21/2016	1/1/2010-11/21/2016	from 2010 on; English	pediatric, foreign lang	normothermia and acute stroke	73	15	6	4
PubMed	11/21/2016	1/1/2010-11/21/2016	from 2010 on; English	pediatric, foreign lang	anti-pyretics and acute stroke	318	3	2	1
Blood Pressure and Endovascular Therapy Table 29. Nonrandomized Trials, Observational Studies, and/or Registries of Blood Pressure and Thrombolysis									
PubMed	10/28/2016	1/1/2010-10/28/2016	from 2010 on; English	pediatric, foreign lang	blood pressure and stroke and endovascular therapy	83	5	1	1
PubMed	10/28/2016	1/1/2010-10/28/2016	from 2010 on; English	pediatric, foreign lang	blood pressure and stroke and recanalization	43	3	0	0
Induced Hypertension Therapy									
PubMed	11/9/2016	1/1/2010-11/9/2016	from 2010 on; English	pediatric, foreign lang	induced HTN - therapy - stroke	297	1	0	0
Therapeutic Hypertension – Stroke									
PubMed	11/9/2016	1/1/2010-11/9/2016	from 2010 on; English	pediatric, foreign lang	therapeutic hypertension - stroke	373	1	1	0
PubMed	11/9/2016	1/1/2010-11/9/2016	from 2010 on; English	pediatric, foreign lang	ischemic stroke - vasopressors	120	0	0	0
Blood pressure and Thrombolysis Table 29. Nonrandomized Trials, Observational Studies, and/or Registries of Blood Pressure and Thrombolysis									
PubMed	11/22/2016	1/1/2010-11/22/2016	from 2010 on; English	pediatric, foreign lang	BP and thrombolysis and stroke	182	45	15	13
HBO Table 27. Nonrandomized Trials, Observational Studies, and/or Registries of Hyperbaric Oxygen									
PubMed	3/29/2017	1/1/2010 - 3/29/2017	from 2010 on; English	pediatric, foreign lang	HBO and acute ischemic stroke	20	20	4	1
PubMed	11/22/2016	1/1/2010-11/22/2016	from 2010 on; English	pediatric, foreign lang	cerebral air emboli and stroke and HBO	10	1	1	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
PubMed	11/22/2016	1/1/2010-11/22/2016	from 2010 on; English	pediatric, foreign lang	cerebral air emboli and stroke	67	6	0	0
Hypotension Table 23. Randomized Controlled Trials Comparing Endovascular Therapy									
PubMed	12/14/2016	1/1/2010-12/14/2016	from 2010 on; English	pediatric, foreign lang	hypotension and acute stroke and treatment	135	5	5	0
IV lysis Table 39. Randomized Controlled Trials Evaluating Intravenous Fibrinolytics Other Than Alteplase for Treatment of Acute Ischemic Stroke									
PubMed	12/16/2016	1/1/1980-11/30/2016	RCTs	Non RCTs	thrombolysis + stroke + randomized	1250	543	78	21
Alteplase, IV, stroke Table 34. Randomized Controlled Trials Evaluating Intravenous Alteplase for Treatment of Acute Ischemic Stroke									
MEDLINE	12/22/2016	1/1/1995–12/1/2016	Human, English, Adults	Non-RCTs	tissue plasminogen activator, rtPA, tPA, intravenous or IV alteplase, stroke or ischemic stroke or thrombosis or brain ischemia or cerebrovascular disorders	5134	879	269	87
Intravenous alteplase for mild stroke 3-4.5 hours Table 35. Randomized Controlled Trials of Intravenous Alteplase for Mild Stroke 3–4.5 Hours Table 36. Nonrandomized Trials, Observational Studies, and/or Registries of Intravenous Alteplase 3–4.5 Hours for Mild Stroke									
PubMed	4/16/2017	thru 12/31/2009	3-4.5 hours RCT subgroup analysis	English only	ECASS III AND subgroup	3	3	1	1
PubMed	4/16/2017	thru 9/30/2005	registry compare < 3 to 3-4.5	English only	alteplase AND mild stroke AND 4.5	19	19	1	1
PubMed	4/16/2017	Thru 5/30/2013	registry compare < 3 to 3-4.5	English only	alteplase AND mild stroke AND 3-4.5	2	2	1	1
PubMed	4/16/2017	thru 10/31/2008	registry compare < 3 to 3-4.5	English only	3-4.5 AND SITS-ISTR	5	5	1	0
Embase	4/16/2017	thru 12/31/2013	3-4.5 h data	English only	alteplase AND mild stroke AND 4.5 AND clinical trial	4	4	1	0
Intravenous Fibrinolysis Table 38. Nonrandomized Trials, Observational Studies of Antithrombotic Agents Given Within 24 Hours After Intravenous Alteplase for the Treatment of Acute Ischemic Stroke									
PubMed	12/16/2016	1/1/1995-12/16/2016	Adults - after 1995	case reports	thrombolysis + stroke + antithrombotics OR antiplatelets	952	252	15	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Endovascular interventions Table 23. Randomized Controlled Trials Comparing Endovascular Therapy Table 41. Nonrandomized Trials, Observational Studies, and/or Registries of Endovascular Therapy Table 42. Randomized Controlled Trials Comparing General Anesthesia to Conscious Sedation for Endovascular Stroke Therapy Table 43. Nonrandomized Trials, Observational Studies, and/or Registries Comparing General Anesthesia to Conscious Sedation for Endovascular Stroke Therapy									
PubMed	9/21/2016	1/1/1966-9/21/2016	humans, English-only, 10 or more patients	studies not regarding acute ischemic stroke, commentaries, editorials, letters to the editor	acute ischemic stroke AND thrombectomy OR endovascular OR intra-arterial OR stent retriever OR clot retrieval	42,251	42,251	585	32
Cochrane Central Register of Controlled Trials	9/25/2016	1/1/1966-9/25/2016	Humans, English-only. (Randomized trial, meta-analysis, systematic review, pooled analysis, or registry)	Studies not regarding acute ischemic stroke, commentaries, editorials, letters to the editor	acute ischemic stroke AND thrombectomy OR endovascular OR intra-arterial OR stent retriever OR clot retrieval	3445	3445	197	32
Anticoagulation Table 46. Randomized Controlled Trials Comparing Anticoagulant to Control Table 47. Nonrandomized Studies of Anticoagulation in Patients with Acute Ischemic StrokeTable 77. Studies of Early Secondary Prevention in Patients with Acute Ischemic Stroke									
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"anticoagulation", "acute ischemic stroke"	112	112	11	1
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans, Clinical Trial	None	"anticoagulation", "acute ischemic stroke"	5	5	1	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"enoxaparin", "acute ischemic stroke"	5	5	0	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"dalteparin", "acute ischemic stroke"	1	1	0	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"heparin", "acute ischemic stroke"	49	49	5	2

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"apixaban", "acute ischemic stroke"	12	12	2	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"rivaroxaban", "acute ischemic stroke"	20	20	2	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"dabigatran", "acute ischemic stroke"	30	30	3	1
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"argatroban", "acute ischemic stroke"	6	6	3	1
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"argatroban", "stroke"	38	38	2	2
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"edoxaban", "acute ischemic stroke"	4	4	0	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"fondaparinux", "acute ischemic stroke"	2	2	0	0
Antiplatelet Table 44. Nonrandomized Studies of Antiplatelet Therapy in Patients with Acute Ischemic Stroke Table 45. Randomized Controlled Trials Comparing Antiplatelet to ControlTable 77. Nonrandomized Studies of Early Secondary Prevention in Patients with Acute Ischemic Stroke									
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"aspirin", "acute ischemic stroke"	98	98	1	1
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans, Clinical Trial	None	"aspirin", "acute ischemic stroke"	33	33	1	1
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"clopidogrel", "acute ischemic stroke"	47	47	2	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans, Clinical Trial	None	"clopidogrel", "acute ischemic stroke"	12	12	2	0
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"ticagrelor", "acute ischemic stroke"	4	4	2	1
PubMed	7/4/2017	1/1/2010-7/4/2017	English & Humans	None	"prasugrel", "acute ischemic stroke"	0	0	0	0
PubMed	7/10/2017	1/1/2010-7/4/2017	English & Humans	None	"cilostazol", "acute ischemic stroke"	14	14	1	0
Neuroprotection Table 48. Randomized Controlled Trials Comparing Other Treatments for Acute Ischemic Stroke									
PubMed	7/10/2017	1/1/2010-7/10/2017	English & Humans	none	"neuroprotection", "acute ischemic stroke"	87	87	0	0

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Cost-effectiveness of CT/MRI in acute stroke Table 15. Nonrandomized Trials, Observational Studies, and/or Registries of Computed Tomography and Magnetic Resonance Imaging for Routine Stroke Care									
PubMed	11/21/2016	3/1/1985-11/30/2016	Formal cost-effectiveness analysis	Non-English	cost-effectiveness AND CT AND stroke	99	99	7	3
PubMed	11/22/2016	3/1/1985-11/30/2016	Formal cost-effectiveness analysis	Non-English	cost-effectiveness AND MRI AND stroke	70	70	1	0
Embase	12/5/2016	7/1/1999-12/31/2016	Formal cost-effectiveness analysis	Non-English	cost effectiveness':ti AND ('ct'/exp OR ct) AND ('stroke'/exp OR stroke)	60	60	4	0
Embase	12/5/2016	7/1/1999-12/31/2016	Formal cost-effectiveness analysis	Non-English	'cost':ti AND ('ct'/exp OR ct) AND ('stroke'/exp OR stroke)	104	104	0	0
Embase	12/5/2016	3/1/2003-12/31/2016	Formal cost-effectiveness analysis	Non-English	'cost':ti AND mri AND ('stroke'/exp OR stroke)	30	30	0	0
Blood pressure II Table 50. Randomized Controlled Trials Comparing Early Versus Delayed Initiation of Treatment for Blood Pressure Reduction in Patients with Acute Ischemic Stroke									
PubMed	11/20/2016	1/1/1999–11/20/2016	RCTs	Non RCTs	randomized controlled trials + acute ischemic stroke + blood pressure treatment	180	180	59	14
Treatment of hypotension Table 28. Nonrandomized Trials, Observational Studies, and/or Registries of Hypotension and Hypovolemia									
PubMed	4/30/2017	4/1/2017 - 12/31/1986	English only, association low blood pressure in acute ischemic stroke with outcome	Pediatric	Low blood pressure AND stroke	first 100 best match	13	13	8
Intravenous fluids and stroke Table 28. Nonrandomized Trials, Observational Studies, and/or Registries of Hypotension and Hypovolemia									
PubMed	4/30/2017	12/1/2016-7/31/1992	English only	Pediatric	Fluids AND acute stroke	first 100 best match	6	6	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Transcranial near-infrared laser therapy Table 49. Randomized Controlled Trials Comparing Transcranial Laser Therapy for Stroke									
PubMed	12/12/2016	1/1/2000 - 1/1/2016	English only, Adults>18	None	(transcranial[All Fields] AND near[All Fields] AND infrared[All Fields] AND ("lasers"[MeSH Terms] OR "lasers"[All Fields] OR "laser"[All Fields])) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])	26	26	4	2
Transcranial laser therapy Table 49. Randomized Controlled Trials Comparing Transcranial Laser Therapy for Stroke									
PubMed	12/12/2016	1/12000 - 1/1/2016	English only, Adults>18; RCTs	None	NEST-3[All Fields]	4	4	2	1
PubMed	12/12/2016	1/1/2000- 1/1/2016	English only, Adults>18	None	NILT[All Fields] AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])	7	7	1	0
Embase	12/12/2016	1/1/2000 - 1/1/2016	English only, Adults>18	None	NILT[All Fields]	21	21	0	0
Embase	12/12/2016	1/1/2000 - 1/1/2016	English only, Adults>18	None	NEST-3 AND "stroke"[All Fields]	8	8	2	1
Cerebral edema, surgical decompression suboccipital Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
Embase	1/20/2016	1/1/2014 - 1/1/2016	Cochrane review, Systematic review, Meta-analysis, controlled clinical trial	None	brain AND edema AND 'cerebrovascular accident' AND ([cochrane review]/lim OR [systematic review]/lim OR [meta analysis]/lim OR [controlled clinical trial]/lim) AND [2014-2016]/pi	48	48	1	1
Embase	1/20/2016	1/1/2013 - 1/1/2016	English speaking, adult >18	None	cerebral AND edema OR brain AND edema AND 'cerebrovascular accident' AND surgical AND decompression OR 'suboccipital craniotomy' OR 'suboccipital craniectomy' AND [2013-2016]/py	251	251	3	2

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Cerebral edema, impact of age Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	12/24/2016	1/1/2010 - 1/1/2016	RCTs and controlled trials	None	("decompressive craniectomy"[MeSH Terms] OR ("decompressive"[All Fields] AND "craniectomy"[All Fields]) OR "decompressive craniectomy"[All Fields]) AND (("Age"[Journal] OR "age"[All Fields] OR "Age (Omaha)"[Journal] OR "age"[All Fields] OR "Age (Dordr)"[Journal] OR "age"[All Fields] OR "Adv Genet Eng"[Journal] OR "age"[All Fields]) AND greater[All Fields] AND 60[All Fields]) OR ("aged"[MeSH Terms] OR "aged"[All Fields] OR "elderly"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("brain oedema"[All Fields] OR "brain edema"[MeSH Terms] OR ("brain"[All Fields] AND "edema"[All Fields]) OR "brain edema"[All Fields]) AND ((Clinical Trial[ptyp] OR Review[ptyp]) AND ("2014/01/01"[PDAT] : "2016/12/31"[PDAT]))	50	50	5	5
Depression Table 57. Nonrandomized Studies of Depression Screening in Patients with Acute Ischemic Stroke									
PubMed	7/10/2017	1/1/2010 - 7/10/2017	English & Humans	None	"depression", "screen", "stroke"	28	28	0	0

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Cerebral edema, hypothermia, corticosteroids Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	1/29/2016	1/1/2010 - 1/1/2017	English speaking, adult >18	None	("cerebral oedema"[All Fields] OR "brain edema"[MeSH Terms] OR ("brain"[All Fields] AND "edema"[All Fields]) OR "brain edema"[All Fields] OR ("cerebral"[All Fields] AND "edema"[All Fields]) OR "cerebral edema"[All Fields]) AND ("hypothermia"[MeSH Terms] OR "hypothermia"[All Fields]) AND ("adrenal cortex hormones"[Pharmacological Action] OR "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroids"[All Fields])	35	35	1	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Cerebral edema, decompression timing Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	12/24/2016	1/1/2014-1/1/2016	English speaking, adult >18	None	(severe[All Fields] AND ("brain oedema"[All Fields] OR "brain edema"[MeSH Terms] OR ("brain"[All Fields] AND "edema"[All Fields]) OR "brain edema"[All Fields])) AND (major[All Fields] AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) AND ("transfer (psychology)"[MeSH Terms] OR ("transfer"[All Fields] AND "(psychology)"[All Fields]) OR "transfer (psychology)"[All Fields] OR "transfer"[All Fields]) AND (("neurosciences"[MeSH Terms] OR "neurosciences"[All Fields] OR "neuroscience"[All Fields]) AND ("intensive care units"[MeSH Terms] OR ("intensive"[All Fields] AND "care"[All Fields] AND "units"[All Fields]) OR "intensive care units"[All Fields] OR ("intensive"[All Fields] AND "care"[All Fields] AND "unit"[All Fields]) OR "intensive care unit"[All Fields])) OR NSU[All Fields] AND ("2014/01/01"[PDAT] : "2016/12/31"[PDAT])	96	96	0	0

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Cerebral edema, ventriculostomy, hydrocephalus Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	12/12/2016	1/2014-1/2016	English speaking, adult >18	None	("cerebral oedema"[All Fields] OR "brain edema"[MeSH Terms] OR ("brain"[All Fields] AND "edema"[All Fields]) OR "brain edema"[All Fields] OR ("cerebral"[All Fields] AND "edema"[All Fields]) OR "cerebral edema"[All Fields]) AND ("hydrocephalus"[MeSH Terms] OR "hydrocephalus"[All Fields]) AND (("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) AND ("ventriculostomy"[MeSH Terms] OR "ventriculostomy"[All Fields])	3	3	2	1
Cerebral edema, barbiturates Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	1/29/2016	1/1/2014-1/1/2016	English speaking, adult >18	None	("cerebral oedema"[All Fields] OR "brain edema"[MeSH Terms] OR ("brain"[All Fields] AND "edema"[All Fields]) OR "brain edema"[All Fields] OR ("cerebral"[All Fields] AND "edema"[All Fields]) OR "cerebral edema"[All Fields]) AND (("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) AND ("barbiturates"[MeSH Terms] OR "barbiturates"[All Fields])	25	25	1	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Cerebral edema, corticosteroids Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	1/29/2016	1/1/2014-1/1/2016	English speaking, adult >18	None	("cerebral oedema"[All Fields] OR "brain edema"[MeSH Terms] OR ("brain"[All Fields] AND "edema"[All Fields]) OR "brain edema"[All Fields] OR ("cerebral"[All Fields] AND "edema"[All Fields]) OR "cerebral edema"[All Fields]) AND (("ischemia"[MeSH Terms] OR "ischemia"[All Fields] OR "ischemic"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) AND ("adrenal cortex hormones"[Pharmacological Action] OR "adrenal cortex hormones"[MeSH Terms] OR ("adrenal"[All Fields] AND "cortex"[All Fields] AND "hormones"[All Fields]) OR "adrenal cortex hormones"[All Fields] OR "corticosteroids"[All Fields])	47	47	2	1
Cerebral edema, cerebellar decompression Table 59. Nonrandomized Trials, Observational Studies, and/or Registries of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Stroke Table 60. Randomized Controlled Trials Comparing Impact of Treatment of Cerebral and Cerebellar Edema Following Acute Ischemic Infarction									
PubMed	1/24/2016	1/1/1985-1/1/2016	English speaking, adult >18	none	("cerebellum"[MeSH Terms] OR "cerebellum"[All Fields] OR "cerebellar"[All Fields]) AND ("infarction"[MeSH Terms] OR "infarction"[All Fields]) AND ("decompression"[MeSH Terms] OR "decompression"[All Fields])	86	86	3	1

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Achieving rapid door-to-needle treatment time in stroke Table 7. Nonrandomized Studies of Hospitals Achieving Rapid Door-to-Needle Times for IV Alteplase in Stroke Table 9. Nonrandomized Studies Comparing Efficacy of Multilevel Interventions to Increase Intravenous Alteplase Use									
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	Door to needle time, stroke	192	192	5	3
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	"Door-to-needle" time, stroke	188	188	5	3
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	DTN time, stroke	41	41	0	0
Cochrane Library	2/4/2017	no limit	Trials	Non-English	Door to needle time, stroke, variations	27	27	0	0
Google Scholar	2/4/2017	1/1/2011-2/4/2017	In-Title Search	Non-English	"door to needle time stroke"	106	106	5	3
Increasing alteplase treatment in stroke Table 72. Nonrandomized Studies of Hospital Stroke CapabilitiesTable 8. Randomized Controlled Trials Comparing Efficacy of Multilevel Interventions to Increase Intravenous Alteplase Use Table 9. Nonrandomized Studies Comparing Efficacy of Multilevel Interventions to Increase Intravenous Alteplase Use									
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	Quality Improvement, stroke	112	112	4	2
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	Community hospitals, stroke, time factors	55	55	5	3
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	Community hospitals, stroke, treatment,	26	26	5	3
Benefit of participation in QI registry Table 9. Nonrandomized Studies Comparing Efficacy of Multilevel Interventions to Increase Intravenous Alteplase Use Table 14. Nonrandomized Studies Assessing the Impact of Stroke System Quality Improvement Processes									
PubMed	2/4/2017	1/1/2011-2/4/2017	Clinical Studies, Clinical Trials	Non-English	quality improvement program, stroke	231	231	5	3
Telestroke and Teleradiology Table 10. Randomized Controlled Trials of Level of Agreement Between Central Read and Spoke Radiologists and Hub Neurologists in Interpreting Head Computed Tomography Scans of Stroke Patients Presenting to Telestroke Hospitals Table 11. Randomized Controlled Trials Comparing Synchronous Audio Video Telemedicine to Telephone-Only for Acute Ischemic Stroke Table 78. Nonrandomized Trials, Observational Studies, and/or Registries of Telestroke for Triaging Patients for Endovascular Therapy									
MEDLINE	1/12/2017	1/1/1999-3/1/2017	RCT, Since 1999, Human, Adults, English	None	[(Telemedicine or Remote Consultation) AND Stroke] OR Telestroke; Limited to Humans, Adults, and Randomized Controlled Trials	35	35	7	7

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Early mobility Table 58. Randomized Controlled Trials of Mobility Intervention									
PubMed	2/21/2017	1/1/2010-2/21/2017	RCT	pediatrics - late rehabilitation	(("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("early ambulation"[MeSH Terms] OR ("early"[All Fields] AND "ambulation"[All Fields]) OR "early ambulation"[All Fields]) AND ("treatment outcome"[MeSH Terms] OR ("treatment"[All Fields] AND "outcome"[All Fields]) OR "treatment outcome"	44	12	5	5
Nutrition Table 53. Randomized Controlled Trials of Nutrition									
PubMed	2/21/2017	1/1/2010-4/26/2017	RCT	Pediatrics	(("enteral nutrition"[MeSH Terms] OR ("enteral"[All Fields] AND "nutrition"[All Fields]) OR "enteral nutrition"[All Fields]) AND ("stroke"[MeSH Terms] OR "stroke"[All Fields])) AND Clinical Trial[ptyp]	18	10	4	4
Oral care Table 54. Nonrandomized Trials, Observational Studies, and/or Registries of Oral Hygiene Table 42. Randomized Controlled Trials of Oral Care									
PubMed	4/26/2017	1/1/2010-4/26/2017	Guidelines and up to data sources RCT	Pediatrics and late rehabilitation	oral care methods, stroke, stroke nursing,	48	7	3	1
PubMed	4/26/2017	1/1/2010-4/26/2017	Guidelines and up to date sources - NRCT, Systematic Reviews, observation, adults >=18	Pediatrics and late rehabilitation	("mouth"[MeSH Terms] OR "mouth"[All Fields] OR "oral"[All Fields]) AND care[All Fields] AND ("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND ("pneumonia"[MeSH Terms] OR "pneumonia"[All Fields])	29	10	7	4

Database searched or other source used	Date search conducted	Date range covered by literature search	Inclusion criteria	Exclusion criteria	Search terms	No. studies returned	No titles and abstracts screened	No. full-text articles reviewed	No. studies included based on authors' determination of quality and major impact
Stroke, DVT prophylaxis Table 56. Randomized Controlled Trials Comparing Deep Vein Thrombosis Prophylaxis									
PubMed	12/23/2016 (updated 1/20/2017)	1/1/2010-1/20/2017	RCTs only, English only, adults ≥18	Pediatrics	(("stroke"[MeSH Terms] OR "stroke"[All Fields]) AND dvt[All Fields] AND ("prevention and control"[Subheading] OR ("prevention"[All Fields] AND "control"[All Fields]) OR "prevention and control"[All Fields] OR "prophylaxis"[All Fields])) AND ((Clinical Trial[ptyp] OR Randomized Controlled Trial[ptyp]) AND hasabstract[text])	24	11	11	5