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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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Guidelines for the Early Management of Patients With Acute Ischemic Stroke

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

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

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

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American Heart Association | American Stroke Association

Background and Purpose—The authors present an overview of the current evidence and management recommendations for evaluation and treatment of adults with acute ischemic stroke. The intended audiences are prehospital care providers, physicians, allied health professionals, and hospital administrators responsible for the care of acute ischemic stroke patients within the first 48 hours from stroke onset. These guidelines supersede the prior 2007 guidelines and 2009 updates.

Methods—Members of the writing committee were appointed by the American Stroke Association Stroke Council's Scientific Statement Oversight Committee, representing various areas of medical expertise. Strict adherence to the American Heart Association conflict of interest policy was maintained throughout the consensus process. Panel members were assigned topics relevant to their areas of expertise, reviewed the stroke literature with emphasis on publications since the prior guidelines, and drafted recommendations in accordance with the American Heart Association Stroke Council's Level of Evidence grading algorithm.

Results—The goal of these guidelines is to limit the morbidity and mortality associated with stroke. The guidelines support the overarching concept of stroke systems of care and detail aspects of stroke care from patient recognition; emergency medical services activation, transport, and triage; through the initial hours in the emergency department and stroke unit. The guideline discusses early stroke evaluation and general medical care, as well as ischemic stroke, specific interventions such as reperfusion strategies, and general physiological optimization for cerebral resuscitation.

Stroke
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Conclusions—Because many of the recommendations are based on limited data, additional research on treatment of acute ischemic stroke remains urgently needed. **(*Stroke*. 2013;44:XXX-XXX.)**

Key Words: AHA Scientific Statements ■ acute cerebral infarction ■ emergency medical services ■ reperfusion ■ stroke ■ tissue plasminogen activator

Despite the increase in the global burden of stroke, advances are being made. In 2008, after years of being the third-leading cause of death in the United States, stroke dropped to fourth.[1] In part, this may reflect the results of a commitment made by the American Heart Association/American Stroke Association (AHA/ASA) more than a decade ago to reduce stroke, coronary heart disease, and cardiovascular risk by 25% by the year 2010 (a goal met a year early in 2009). The reason for the success was multifactorial and included improved prevention and improved care within the first hours of acute stroke. To continue these encouraging trends, the public and healthcare professionals must remain vigilant and committed to improving overall stroke care. This document addresses opportunities for optimal stroke care in the acute phase of the ischemic stroke.

The intended audience of these updated guidelines is healthcare professionals involved in the emergency identification, evaluation, transport, and management of patients with acute ischemic stroke. This includes prehospital care providers, emergency department (ED) physicians and nurses, stroke team members, inpatient nurses, hospitalists, general medicine physicians, hospital administrators, and ancillary healthcare personnel. These guidelines deal with the acute diagnosis, stabilization, and acute medical and surgical treatments of acute ischemic stroke, as well as early inpatient management, secondary prevention, and complication management. Over the past several years, several new guidelines, policy statements, and recommendations on implementation strategies for emergency medical services (EMS) within stroke systems of care, imaging in acute ischemic stroke, management of stroke in infants and children, nursing and interdisciplinary care in acute stroke, primary prevention of ischemic stroke, stroke systems of care, and management of transient ischemic attack (TIA) related to acute ischemic stroke have been published by the AHA/ASA. To minimize redundancy, the reader will be referred to these publications where appropriate.[2–10]

The Stroke Council of the AHA/ASA commissioned the assembled authors, representing the fields of cardiology, emergency medicine, neurosurgery, nursing, radiology, rehabilitation, neurocritical care, endovascular neurosurgical radiology, and vascular neurology, to completely revise and update the guidelines for the management of acute ischemic stroke.[11–13] In writing these guidelines, the panel applied the rules of evidence and the formulation of strength of recommendations used by other panels of the AHA/ASA (Tables 1 and 2). The data were collected through a systematic review of the literature. Because of the wide scope of the guidelines, individual members of the panel were assigned as primary and secondary authors for individual sections, then the panel assessed the complete guidelines. If the panel concluded that data supported or did not support the use of a specific intervention, appropriate recommendations were made. In some instances, supporting evidence based on clinical trial research was not available for a specific intervention, but the panel has made a specific recommendation on the basis of pathophysiological reasoning and expert practice experience. In cases in which strong trial, physiological, and practice experience data were not available, no specific recommendation was made. Recommendations that have been changed or added since the publication of the previous guideline are accompanied by explicit statements indicating the revised or new status.

This publication serves as a current comprehensive guideline statement on the management of patients with acute ischemic stroke. This publication supersedes prior guidelines and practice advisories published by the AHA/ASA relevant to acute ischemic stroke.[11–14] The reader is also encouraged to read complementary AHA/ASA articles, including statements on the development of stroke systems of care, EMS integration in stroke systems, telemedicine, and neuroimaging in acute stroke, which contain more detailed discussions of several aspects of acute stroke management.[2–5]

This document uses a framework based on the AHA stroke systems of care publication by Schwamm et al[4] to provide a framework of how to develop stroke care within a regional network of healthcare facilities that provide a range of stroke care capabilities. Similarly, for an individual patient, this document draws on the 2010 advanced cardiac life support stroke chain of survival[15] (Table 3), which describes the critical links to the process of moving a patient from stroke ictus through recognition, transport, triage, early diagnosis and treatment, and the final hospital disposition. Within regions and institutions, the exact composition of the system and chain may vary, but the principles remain constant: preparation, integration, and an emphasis on timeliness.

Public Stroke Education

The chain of events favoring good functional outcome from an acute ischemic stroke begins with the recognition of stroke when it occurs. Data show that the public's knowledge of stroke warning signs remains poor.[16] Fewer than half of 9-1-1 calls for stroke events were made within 1 hour of symptom onset, and fewer than half of those callers thought stroke was the cause of their symptoms.[17] Many studies have demonstrated that intense and ongoing public education about the signs and symptoms of stroke improves stroke recognition.[18] The California Acute Stroke Pilot Registry (CASPR) reported that the expected overall rate of fibrinolytic treatment within 3 hours could be increased from 4.3% to 28.6% if all patients arrived early after onset, which indicates a need to conduct campaigns that educate patients to seek treatment sooner.[19] Effective community education tools include printed material, audiovisual programs, lectures, and television and billboard

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Table 1. Applying Classification of Recommendations and Level of Evidence

ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	SIZE OF TREATMENT EFFECT: CLASS I *Benefit >>> Risk* Procedure/Treatment **SHOULD** be performed/ administered	CLASS IIa *Benefit >> Risk* *Additional studies with focused objectives needed* **IT IS REASONABLE** to perform procedure/administer treatment	CLASS IIb *Benefit ≥ Risk* *Additional studies with broad objectives needed; additional registry data would be helpful* Procedure/Treatment **MAY BE CONSIDERED**	CLASS III *No Benefit* or CLASS III *Harm* Procedure/ Test / Treatment COR III: No benefit: Not Helpful / No Proven Benefit COR III: Harm: Excess Cost w/o Benefit or Harmful / Harmful to Patients
LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	■ Recommendation that procedure or treatment is useful/effective ■ Sufficient evidence from multiple randomized trials or meta-analyses	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from multiple randomized trials or meta-analyses	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Sufficient evidence from multiple randomized trials or meta-analyses
LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is useful/effective ■ Evidence from single randomized trial or nonrandomized studies	■ Recommendation in favor of treatment or procedure being useful/effective ■ Some conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation's usefulness/efficacy less well established ■ Greater conflicting evidence from single randomized trial or nonrandomized studies	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Evidence from single randomized trial or nonrandomized studies
LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	■ Recommendation that procedure or treatment is useful/effective ■ Only expert opinion, case studies, or standard of care	■ Recommendation in favor of treatment or procedure being useful/effective ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation's usefulness/efficacy less well established ■ Only diverging expert opinion, case studies, or standard of care	■ Recommendation that procedure or treatment is not useful/effective and may be harmful ■ Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations	should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	COR III: No Benefit: is not recommended / is not indicated / should not be performed/ administered/ other / is not useful/ beneficial/ effective COR III: Harm: potentially harmful / causes harm / associated with excess morbidity/mortality / should not 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	treatment/strategy A is probably recommended/indicated in preference to treatment B it is reasonable to choose treatment A over treatment B		

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

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as sex, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use.

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

advertisements.[20] Stroke education should target not only prospective patients but also their family members and caregivers, empowering them to activate the emergency medical system. Stroke education campaigns have been successful among elementary and middle school students.[21,22]

Before 2008, the 5 "Suddens" of stroke warning signs (sudden weakness; sudden speech difficulty; sudden visual loss; sudden dizziness; sudden, severe headache) were used widely in public education campaigns. The FAST (face, arm, speech, time) message campaign, first promoted a decade ago, is being reintroduced in public education efforts. One or more of face weakness, arm weakness, and speech difficulty symptoms are present in 88% of all strokes and TIAs.[23] In one study, 100% of lay individuals remembered 3 months after education that facial droop and slurred speech are stroke warning signs, and 98% recalled arm weakness or numbness.[24] Regardless of the message, effective public education requires repetition for a sustained impact.

Another central public education point is the message to call 9-1-1 promptly when a stroke is suspected. Despite a decade of stressing the role of 9-1-1 and EMS in stroke, the recent National Hospital Ambulatory Medical Care Survey (NHAMCS) showed that only 53% of stroke patients used EMS.[25] Multiple studies have reported the benefits of 9-1-1 use and EMS involvement in acute stroke. Prehospital delays are shorter and initial computed tomography (CT) or magnetic

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Table 2. Definition of Classes and Levels of Evidence Used in AHA/ASA Recommendations

Class I	Conditions for which there is evidence for and/or general agreement that the procedure or treatment is useful and effective.
Class II	Conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment.
Class IIa	The weight of evidence or opinion is in favor of the procedure or treatment.
Class IIb	Usefulness/efficacy is less well established by evidence or opinion.
Class III	Conditions for which there is evidence and/or general agreement that the procedure or treatment is not useful/effective and in some cases may be harmful.
Therapeutic recommendations	
Level of Evidence A	Data derived from multiple randomized clinical trials or meta-analyses
Level of Evidence B	Data derived from a single randomized trial or nonrandomized studies
Level of Evidence C	Consensus opinion of experts, case studies, or standard of care
Diagnostic recommendations	
Level of Evidence A	Data derived from multiple prospective cohort studies using a reference standard applied by a masked evaluator
Level of Evidence B	Data derived from a single grade A study or 1 or more case-control studies, or studies using a reference standard applied by an unmasked evaluator
Level of Evidence C	Consensus opinion of experts

Table 3. Stroke Chain of Survival

Detection	Patient or bystander recognition of stroke signs and symptoms
Dispatch	Immediate activation of 9-1-1 and priority EMS dispatch
Delivery	Prompt triage and transport to most appropriate stroke hospital and prehospital notification
Door	Immediate ED triage to high-acuity area
Data	Prompt ED evaluation, stroke team activation, laboratory studies, and brain imaging
Decision	Diagnosis and determination of most appropriate therapy; discussion with patient and family
Drug	Administration of appropriate drugs or other interventions
Disposition	Timely admission to stroke unit, intensive care unit, or transfer

ED indicates emergency department; and EMS, emergency medical services.

resonance imaging (MRI) scans are obtained sooner if stroke patients are transported by ambulance.[25] Advance notification of stroke patient arrival by EMS also shortens the time to be seen for initial evaluation by an emergency physician, shortens the time to brain imaging, and increases the use of the intravenous recombinant tissue-type plasminogen activator (rtPA) alteplase.[26]

Prehospital Stroke Management

EMS Systems

After the 2007 publication of the "Guidelines for the Early Management of Adults With Ischemic Stroke,"[13] the AHA/ASA published a policy statement, "Implementation Strategies for Emergency Medical Services Within Stroke Systems of Care," from the Expert Panel on Emergency Medical Services Systems and the Stroke Council.[5] This statement serves as the blueprint that defines the critical roles of EMS and EMS systems (EMSS) in optimizing stroke care. EMS refers to the full scope of prehospital stroke care, including 9-1-1 activation and dispatch, emergency medical response, triage and stabilization in the field, and ground or air ambulance transport; EMSS refers to the system that involves the organization of public and private resources and includes the community, emergency healthcare personnel, public safety agencies, emergency facilities, and critical care units. Issues related to communication, transportation, access to care, patient transfer, mutual aid, and system review and evaluation are addressed in EMSS. To reach full potential, stroke systems of care must incorporate EMSS into the process.

The "Implementation Strategies for Emergency Medical Services Within Stroke Systems of Care" policy statement outlines specific parameters that measure the quality of an EMSS, including the following:

- Stroke patients are dispatched at the highest level of care available in the shortest time possible.
- The time between the receipt of the call and the dispatch of the response team is <90 seconds.
- EMSS response time is <8 minutes (time elapsed from the receipt of the call by the dispatch entity to the arrival on the scene of a properly equipped and staffed ambulance).
- Dispatch time is <1 minute.
- Turnout time (from when a call is received to the unit being en route) is <1 minute.
- The on-scene time is <15 minutes (barring extenuating circumstances such as extrication difficulties).
- Travel time is equivalent to trauma or acute myocardial infarction calls.[5]

With the use of electronic EMS data capture and storage, these performance measures are readily available for review and system improvement.

The call to the 9-1-1 dispatcher is the first link in the stroke chain of survival.[15] To facilitate the recognition of stroke and provide adequate prehospital stroke care by EMS, statewide standardization of telecommunication programs, stroke education modules, and care protocols is recommended.[27–29] The provision of ongoing education to dispatchers will improve their skills in recognizing the signs and symptoms of stroke.[30]

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In one study, 9-1-1 dispatchers correctly identified 80% of all stroke calls if the caller mentioned specific words such as stroke, facial droop, weakness/fall, or communication problems.[31] If there is diagnostic concordance of stroke between dispatchers and paramedics, the scene time and run times are shortened.[32] Once a stroke is suspected, it becomes a high-priority dispatch.

EMS Assessment and Management

As detailed in the recent update of the AHA's Emergency Cardiovascular Care Committee recommendations for acute stroke, the primary goals of EMS assessment and management are rapid evaluation, early stabilization, neurological evaluation, and rapid transport and triage to a stroke-ready hospital.[15] As in all scene responses, EMS personnel must assess and manage the patient's airway, breathing, and circulation (ABCs). Most patients with acute ischemic stroke do not require emergency airway management or acute interventions for respiratory and circulatory support.

Several prehospital interventions to improve the overall physiological state may be beneficial to patients with suspected acute stroke. Prehospital care has emerged from general principles of resuscitation. Although data from prehospital clinical trials are not always stroke-specific, they do provide guidance for making recommendations for potential stroke patients. Although the routine use of supplemental oxygen remains unproven, supplemental oxygen to maintain oxygen saturations >94% is recommended after cardiac arrest and is reasonable for patients with suspected stroke.[15,33] In potential stroke patients who are hypotensive, defined as blood pressure significantly lower than premorbid state or systolic blood pressure <120 mm Hg, placement of the head of the stretcher flat and administration of isotonic saline may improve their cerebral perfusion. In contrast, in patients who are hypertensive (systolic blood pressure ≥140 mm Hg), the benefit of routine prehospital blood pressure intervention is not proven; consultation with medical control may assist in making treatment decisions regarding patients with extreme hypertension (systolic blood pressure ≥220 mm Hg). The types of antihypertensive medications used in this setting are described in the inpatient section of hypertension management. Hypoglycemia is frequently found in patients with strokelike symptoms; thus, prehospital glucose testing is critical. If a patient is found to have blood glucose levels <60 mg/dL, intravenous administration of glucose may resolve the neurological deficits. For nonhypoglycemic patients, excessive dextrose-containing fluids have the potential to exacerbate cerebral injury; thus, normal saline is more appropriate if rehydration is required. Lastly, establishment of an intravenous line in the field not only facilitates the administration of prehospital medications and fluids but can also shorten treatment times in the ED. When possible, EMS may obtain blood samples for laboratory testing en route to the ED, where they can immediately be given to the laboratory on arrival. These steps may take place while stroke patients are being transported. There should be no delay in getting the stroke patient to the ED by establishing intravenous access, checking blood glucose level, or obtaining blood samples. Although all of these recommendations represent the ideal scenario, it is critical that interventions not delay transport of the patient to the hospital.

Once the initial patient assessment and stabilization are complete, EMS personnel may obtain a focused history from the patient or bystanders. The most important piece of information necessary for potential fibrinolytic treatment is the time of symptom onset, defined as the time the patient was last known normal. Often patients are aphasic or are unaware of their deficits and arrive without accompanying family who can provide necessary information. Thus, it is critical for EMS personnel to establish the time the patient was last known normal from those at the scene. Other important historical elements include any sign of seizure activity or trauma before onset of symptoms. Elements of the past medical history can assist in the prehospital diagnosis of stroke or a stroke mimic, such as history of seizures or hypoglycemia. A history of prior stroke, diabetes mellitus, hypertension, and atrial fibrillation all increase the likelihood that the patient's symptoms are caused by stroke. EMS personnel can identify current medications, especially any anticoagulants, and recent illnesses, surgery, or trauma. EMS personnel also can obtain phone numbers at which family members or witnesses can be reached by ED personnel to provide further history after arrival. When stroke patients are unable to provide information to hospital care providers, EMS personnel may consider transporting a family member along with the patient.

Once the primary survey is complete, EMS personnel should perform a more focused organ system assessment, but transport should not be delayed. Numerous prehospital neurological assessment tools have been developed to accurately identify stroke patients, which facilitates appropriate field treatment, prearrival notification, and routing to an appropriate hospital destination.[34,35] Given regional differences in stroke systems of care, local EMS personnel may use a regionally appropriate, validated prehospital neurological assessment tool. As with all prehospital evaluations, EMS personnel typically complete a secondary survey, reviewing the head and neck for signs of trauma, auscultating the heart and lungs, and observing the patient's extremities for any signs of trauma. To ensure optimal prehospital care, hospital stroke providers should provide feedback to EMS agencies as part of continuous quality improvement projects.

As is the case for patients with trauma or acute myocardial infarction, prehospital notification by EMS of a potential stroke is essential. Several studies have shown that prehospital notification leads to significant reductions in several stroke time benchmarks, including time from arrival to physician assessment, CT performance, and CT interpretation, and is associated with higher rates of intravenous rtPA administration.[26,36–38]

Air Medical Transport

Air transport service is particularly useful to facilitate stroke care in remote areas. As part of regional stroke systems of care, activation of air medical transport for stroke is reasonable when ground transport to the nearest stroke-capable hospital is >1 hour.[5] Local stroke hospitals may provide expertise to help create activation protocols and in-flight stroke management protocols to ensure safe and appropriate patient transports.[39,40]

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Interhospital Transport

With the development of primary stroke centers (PSCs) and comprehensive stroke centers (CSCs), which offer intra-arterial strategies, interhospital transfers of acute stroke patients are increasingly common. Some patients are transferred before fibrinolytic therapy, whereas others receive intravenous rtPA and then are transferred for higher-level care. Delaying intravenous rtPA therapy until after transport in otherwise eligible patients decreases the chance for a good outcome. In the "drip-and-ship" model, in which the patient begins to receive standard-dose intravenous rtPA before transfer, well-designed protocols that include strict adherence to blood pressure guidelines, assessment for clinical deterioration and bleeding, and aspiration precautions ensure safe interhospital transport. Transport personnel should be able to contact medical command or the receiving facility about any change in the patient's condition en route.

Conclusions and Recommendations

EMSS are essential elements in all stroke systems of care. Beginning with public education on recognizing signs and symptoms of stroke and the need for calling 9-1-1, these first elements in the stroke chain of survival are arguably the most important. Calling 9-1-1 and using EMS are the preferred ways of providing optimal prehospital stroke care and transport to stroke centers. Specific time frames have been established for the EMSS to follow on dispatch, response, and on-scene activities, and this should be monitored continuously. Notification of the receiving institution before arrival is critical because it facilitates the rapid diagnosis and management of stroke patients. All efforts must be made to avoid unnecessary delays during patient transport. Statewide, standardized EMS education and stroke care protocols for EMSS improve prehospital stroke recognition and management.

Recommendations

1. **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 *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
2. **Activation of the 9-1-1 system by patients or other members of the public is strongly recommended *(Class I; Level of Evidence B)*. 9-1-1 Dispatchers should make stroke a priority dispatch, and transport times should be minimized.** (Unchanged from the previous guideline[13])
3. **Prehospital care providers should use prehospital stroke assessment tools, such as the Los Angeles Prehospital Stroke Screen or Cincinnati Prehospital Stroke Scale *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
4. **EMS personnel should begin the initial management of stroke in the field, as outlined in** Table 4 ***(Class I; Level of Evidence B*). Development of a stroke protocol to be used by EMS personnel is strongly encouraged.** (Unchanged from the previous guideline[13])
5. **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 *(Class I; Level of Evidence A)*. In some instances, this may involve air medical transport and hospital bypass.** (Revised from the previous guideline[13])
6. **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 *(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])

Designation of Stroke Centers and Stroke Care Quality Improvement Process

Stroke Systems of Care

The ASA task force on the development of stroke systems has defined key components of a regional stroke system of care and recommended methods for the implementation of stroke systems.[4] Stroke systems of care integrate regional stroke facilities, including acute stroke-ready hospitals (ASRHs) that often have telemedicine and teleradiology capability, primary and comprehensive stroke centers, EMSS, and public and governmental agencies and resources. The goals of creating stroke systems of care include stroke prevention, community stroke

Table 4. Prehospital Evaluation and Management of Potential Stroke Patients

Recommended	Not Recommended
Assess and manage ABCs	Do not initiate interventions for hypertension unless directed by medical command
Initiate cardiac monitoring	
Provide supplemental oxygen to maintain O_2 saturation >94%	
Establish IV access per local protocol	Do not administer excessive IV fluids
Determine blood glucose and treat accordingly	Do not administer dextrose-containing fluids in nonhypoglycemic patients
	Do not administer medications by mouth (maintain NPO)
Determine time of symptom onset or last known normal, and obtain family contact information, preferably a cell phone	
Triage and rapidly transport patient to nearest most appropriate stroke hospital	Do not delay transport for prehospital interventions
Notify hospital of pending stroke patient arrival	

ABCs indicates airway, breathing, and circulation; IV, intravenous; and NPO, nothing by mouth.

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education, optimal use of EMS, effective acute and subacute stroke care, rehabilitation, and performance review of stroke care delivery. Essential to effective stroke systems of care are hospitals with the capacity and commitment to deliver acute stroke care, both in the ED and on the stroke unit. In regions with effective stroke systems, the majority of patients are now being transported to these stroke centers, which optimizes their chances for timely appropriate therapy and admission to stroke units, both of which decrease the morbidity and mortality associated with stroke.[41,42]

Hospital Stroke Capabilities

Primary Stroke Center

The definition of a PSC was first published in 2000.[43] This article defined the critical prehospital and hospital elements to deliver effective and efficient stroke care. Since The Joint Commission (TJC) began providing PSC certification in 2004, >800 certified PSCs have been established in the United States (as of January 2011).[44] Regardless of certifying agent (TJC or state health department), it is mandatory for all PSCs to closely track their performance on key quality stroke care measurements. In cluster controlled clinical trials comparing patient outcomes in PSCs with those in community hospitals without specialized stroke care, patients with ischemic stroke treated in centers with dedicated stroke resources had better clinical outcomes[45] and increased rates of intravenous rtPA administration.[20] In addition, numerous observational studies have demonstrated that PSC certification improves stroke care in many ways, for instance, by shortening door to physician contact time, door to CT time, and door to intravenous rtPA time, as well as by increasing rates of intravenous rtPA use.[46–48] Hospitals that have implemented organized stroke care have demonstrated sustained improvements in multiple measures of stroke care quality, including increased use of intravenous rtPA, increased lipid profile testing, and improved deep vein thrombosis (DVT) prophylaxis.[49,50]

Comprehensive Stroke Center

The recommendations to establish CSCs were published in 2005.[51] In 2011, the ASA published the scientific statement, "Metrics for Measuring Quality of Care in Comprehensive Stroke Centers," which delineates the set of metrics and related data that CSCs should track to ensure optimal stroke outcome and adherence to current recommendations.[10] According to these recommendations, a CSC should be able to offer 24/7 (24 hours per day, 7 days per week) state-of-the-art care on the full spectrum of cerebrovascular diseases. A few states, including New Jersey, Missouri, and Florida, have developed their own legislative efforts to certify PSCs and CSCs. In the fall of 2012, TJC began providing accreditation for CSCs using many of the metrics outlined in the ASA CSC publication.

The data highlighting the patient-centered benefits of integrating CSCs into regional stroke systems of care are emerging. Recently, Orange County, California, organized regional stroke care around CSCs in a hub-and-spoke model, serving just over 3 million people.[52] Among patients taken directly to the CSCs in this model, 25.1% received acute reperfusion therapies (intravenous rtPA, endovascular therapies, or both). A recent analysis of 134 441 stroke patients in New Jersey hospitals showed that CSCs had no gap in mortality rate between weekday and weekend admissions, whereas mortality was higher when patients were admitted on weekends at other stroke centers.[53] In Finland, where stroke systems of care are organized on a national level, a 7-year study of all stroke patients in the country demonstrated a clear association between the level of acute stroke care and patient outcomes, with the lowest rates of mortality and severe disability seen in CSCs.[41]

Neurocritical care units are essential elements of CSCs. The need for neurologically focused critical care has expanded rapidly in the past 2 decades in parallel with an increasing understanding of the nature of brain and spinal cord injury, especially the secondary injuries that commonly occur. Improvements in clinical outcome attributable to focused critical care have been documented,[54–56] as have a reduction in and an earlier recognition of complications[57] and reduced days of hospitalization.[54,56] In patients with acute ischemic stroke, admission to neurocritical care units should be considered for those with severe deficits, large-volume infarcts with the potential for significant cerebral edema, significant comorbidities, blood pressure that is difficult to control, or prior intravenous and intra-arterial recanalization interventions.

Acute Stroke-Ready Hospital

ASRHs, previously called *stroke-capable hospitals*, are hospitals that have made an institutional commitment to effectively and efficiently evaluate, diagnose, and treat most ED stroke patients but that do not have fully organized inpatient stroke systems of care. ASRHs have many of the same elements as a PSC:

- Written emergency stroke care protocols
- Written transfer agreement with a hospital with neurosurgical expertise
- Director of stroke care to oversee hospital stroke policies and procedures (this may be a clinical staff member or the designee of the hospital administrator)
- Ability to administer intravenous rtPA
- Ability to perform emergency brain imaging (eg, CT scan) at all times
- Ability to conduct emergency laboratory testing at all times
- Maintenance of a stroke patient log

Additionally, ASRHs have well-developed relationships with regional PSCs and CSCs for additional support. Stroke expertise and neuroimaging interpretation in ASRHs are often in the forms of telemedicine and teleradiology, which require close collaboration within the regional stroke system of care. Many ASRHs do not have sufficient resources to establish and maintain a stroke unit; thus, in some circumstances, once patients are diagnosed and initial treatments delivered, patients are transported to a PSC or CSC. ASRHs are also responsible for EMS stroke education and integration into the stroke system of care. The development of ASRHs has the potential to greatly extend the reach of stroke systems of care into underserved regions.

Telemedicine or "Telestroke"

With the rapid growth of telemedicine for stroke, more data are now available supporting the use of telemedicine

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to deliver stroke care in regions without local stroke expertise.[58,59] Telemedicine (also called *telestroke*) may help solve the shortage of neurologists and radiologists, allowing hospitals to become acute stroke ready.[2,3] Many uses of telemedicine for stroke involve a hub-and-spoke model, in which the hub hospital, often a tertiary stroke center, provides specialty services to spoke hospitals. Telemedicine is integrated audio and visual remote assessment. Telemedicine can provide 24/7 acute stroke expertise to hospitals without full-time neurological or radiological services at the spoke hospital.[60] Although the technological sophistication and prices of the systems can vary, it is essential that the system have the capability to provide 2-way real-time audiovisual conferencing and share the images. The benefits of telestroke are several: Telestroke optimizes the use of intravenous rtPA to treat patients in hospitals without an on-site neurologist,[61] decreases time to initiate intravenous rtPA, and provides treatment with similar safety as PSCs (symptomatic intracerebral hemorrhage [sICH] in 2%–7%, in-house mortality rate 3.5%).[62–65] Although the economic issues regarding the use of telestroke remain to be fully explored, the benefit of telestroke in extending timely stroke care to remote hospitals is clear. These benefits include immediate access to specialty consultations, reliable neurological examinations, and National Institutes of Health Stroke Scale (NIHSS) scores; high rates of intravenous fibrinolysis with low rates of hemorrhage; and mortality rates and functional outcomes of intravenous fibrinolysis comparable to those in randomized trials.[66–68] Therefore, when the physical presence of a stroke team physician at the bedside is not possible, telestroke should be established so that additional hospitals can potentially meet the criteria to become ASRHs and PSCs.[69,70]

Teleradiology

Teleradiology is a critical aspect of stroke telemedicine and is defined as the ability to obtain radiographic images at one location and transmit them to another for diagnostic and consultative purposes.[71] According to these standards of practice, the Centers for Medicare and Medicaid Services provide reimbursement for both intrastate and interstate teleradiology services,[72,73] and the TJC and other accrediting bodies play an important role in the performance, appraisal, and credentialing of teleradiology systems.[74] There are only a limited number of studies describing the use of teleradiology to read non–contrast-enhanced CT scans of the brain.[75–78] These studies have mainly focused on the feasibility of a teleradiology approach for stroke,[79] including some that used personal digital assistants[77,78] and smartphones.[80,81] One pilot study provided encouraging preliminary evidence that neurologists with stroke expertise can determine radiological intravenous rtPA eligibility via teleradiology.[82] Additional studies involving larger samples are necessary to validate these results.

Stroke Care Quality Improvement Process and Establishment of Data Repositories

There is now sufficient literature supporting the initiation of stroke care quality improvement processes. The success of such processes relies on the establishment of quality databases so that data on the performance of quality measurements can be captured. For all certified PSCs, there is an established database to capture the performances on the 8 TJC-mandated quality measures for stroke care. Although all certified PSCs submit their performance data to TJC quarterly, it is beneficial for all hospitals to establish a stroke care data repository. Hospitals can then routinely track their stroke care quality measurements, identify gaps and disparities in providing stroke care, and use these data to design programs to address the gaps or disparities. One such example is the Paul Coverdell National Acute Stroke Registry, which collects data from 8 participating states. Data from the first 4 prototype registries in Georgia, Massachusetts, Michigan, and Ohio showed that overall, 4.51% of ischemic stroke patients were receiving intravenous rtPA on admission.[83] By conducting process improvement programs, the Michigan Paul Coverdell National Acute Stroke Registry showed that documentation of the reasons for not giving intravenous rtPA increased by 13%.[84] Another example showed that hospitals participating in the Paul Coverdell National Acute Stroke Registry had significant improvements in 9 of the 10 performance measures from 2005 to 2009, with one being that the average annual use of intravenous rtPA increased by 11%.[85]

Get With The Guidelines (GWTG)-Stroke, provided by the AHA/ASA, is a patient management and data collection tool that ensures continuous quality improvement of acute stroke treatment and stroke prevention. It focuses on care team protocols to ensure that stroke patients are managed according to evidence-based medicine. Currently, there are >1500 hospitals in the United States using the GWTG-Stroke program.[86] From 2003 to 2007, a study of 322 847 hospitalized stroke patients in 790 US academic and community hospitals voluntarily participating in the GWTG-Stroke program showed significant improvement in stroke care by participating in the program. Improvements in receipt of guidelines-based care within the 5-year period were as follows: intravenous rtPA use within 2 hours, from 42.9% to 72.84%; antithrombotics within 48 hours of admission, from 91.46% to 97.04%; DVT prophylaxis, from 73.79% to 89.54%; discharged on antithrombotic medication, from 95.68% to 98.88%; anticoagulation for atrial fibrillation, from 95.3% to 98.39%; treatment of low-density lipoprotein cholesterol levels >100 mg/dL, from 73.63% to 88.29%; and smoking cessation efforts with either medication or counseling, from 65.21% to 93.61%.[87] A previous study of adherence to evidence-based interventions associated with the process improvement and internet-based data collection showed that the use of intravenous rtPA for patients with ischemic stroke presenting within 2 hours of onset improved from 23.5% to 40.8%. Eleven of 13 quality stroke care measurements showed statistically and clinically significant improvement.[88]

More recent analysis of the first 1 million patients from 1392 hospitals in GWTG-Stroke showed significant improvements over time from 2003 to 2009 in quality of care (all-or-none measure, 44.0% versus 84.3%; +40.3%, $P<0.0001$).[89] GWTG-Stroke also found disparities in stroke care between men and women. Women received less defect-free care than men (66.3% versus 71.1%; adjusted odds ratio [OR], 0.86; 95% confidence interval [CI], 0.85–0.87) and were less likely to be discharged home (41.0% versus 49.5%; adjusted OR, 0.84; 95% CI, 0.83–0.85).[90]

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Nevertheless, stroke care quality improvement should be an ongoing process for every hospital. One example of this process improvement is to shorten the door-to-needle time to <60 minutes. For every 15-minute reduction of door-to-needle time, there is a 5% lower odds of in-hospital mortality (adjusted OR, 0.95; 95% CI, 0.92–0.98; *P*=0.0007). However, from this set of GWTG-Stroke data, among 25 504 acute ischemic stroke patients treated with intravenous rtPA within 3 hours of symptom onset at 1082 hospital sites, only 26.6% of patients had a door-to-needle time of the recommended ≤60 minutes.[91]

Conclusions and Recommendations

All patients with stroke and at risk for stroke benefit from the development of stroke systems of care. States and regions should be encouraged to engage all regional stakeholders to build stroke systems, which in the end will improve patient outcomes through prevention and treatment of stroke, as well as poststroke rehabilitation.

Recommendations

1. **The creation of PSCs is recommended *(Class I; Level of Evidence B)*. The organization of such resources will depend on local resources. The stroke system design of regional ASRHs and PSCs that provide emergency care and that are closely associated with a CSC, which provides more extensive care, has considerable appeal.** (Unchanged from the previous guideline[13])
2. **Certification of stroke centers by an independent external body, such as TJC or state health department, is recommended *(Class I; Level of Evidence B)*. Additional medical centers should seek such certification.** (Revised from the previous guideline[13])
3. **Healthcare institutions should organize a multidisciplinary quality improvement committee to review and monitor stroke care quality benchmarks, indicators, evidence-based practices, and outcomes *(Class I; Level of Evidence B)*. 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.** (New recommendation)
4. **For patients with suspected stroke, EMS should bypass hospitals that do not have resources to treat stroke and go to the closest facility most capable of treating acute stroke *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
5. **For sites without in-house imaging interpretation expertise, teleradiology systems approved by the Food and Drug Administration (FDA) or equivalent organization are recommended for timely review of brain CT and MRI scans in patients with suspected acute stroke *(Class I; Level of Evidence B)*.** (New recommendation)
6. **When implemented within a telestroke network, teleradiology systems approved by the FDA (or equivalent organization) are useful in supporting rapid imaging interpretation in time for fibrinolysis decision making *(Class I; Level of Evidence B)*.** (New recommendation)
7. **The development of CSCs is recommended *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
8. **Implementation of telestroke consultation in conjunction with stroke education and training for healthcare providers can be useful in increasing the use of intravenous rtPA at community hospitals without access to adequate onsite stroke expertise *(Class IIa; Level of Evidence B)*.** (New recommendation)
9. **The creation of ASRHs can be useful *(Class IIa; Level of Evidence C)*. As with PSCs, the organization of such resources will depend on local resources. The stroke system design of regional ASRHs and PSCs that provide emergency care and that are closely associated with a CSC, which provides more extensive care, has considerable appeal.** (New recommendation)

Emergency Evaluation and Diagnosis of Acute Ischemic Stroke

Given the narrow therapeutic windows for treatment of acute ischemic stroke, timely ED evaluation and diagnosis of ischemic stroke are paramount.[92,93] Hospitals and EDs should create efficient processes and pathways to manage stroke patients in the ED and inpatient settings. This should include the ability to receive, identify, evaluate, treat, and/or refer patients with suspected stroke, as well as to obtain access to stroke expertise when necessary for diagnostic or treatment purposes.

A consensus panel convened by the National Institutes of Neurological Disorders and Stroke (NINDS) established goals for time frames in the evaluation of stroke patients in the ED.[94,95] At this same symposium, the "stroke chain of survival" was promoted as a template for identifying critical events in the ED identification, evaluation, and treatment of stroke patients (Table 5). By using this template and the time goals, hospitals and EDs can create effective systems for optimizing stroke patient care.[97]

Emergency Triage and Initial Evaluation

ED patients with suspected acute stroke should be triaged with the same priority as patients with acute myocardial infarction or serious trauma, regardless of the severity of neurological deficits. Although specific data on the efficacy of stroke screening tools and scoring systems are lacking for ED triage,

Table 5. ED-Based Care

Action	Time
Door to physician	≤10 minutes
Door to stroke team	≤15 minutes
Door to CT initiation	≤25 minutes
Door to CT interpretation	≤45 minutes
Door to drug (≥80% compliance)	≤60 minutes
Door to stroke unit admission	≤3 hours

CT indicates computed tomography; and ED, emergency department.
Source: Bock.[96]

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Table 6. Features of Clinical Situations Mimicking Stroke

Psychogenic	Lack of objective cranial nerve findings, neurological findings in a nonvascular distribution, inconsistent examination
Seizures	History of seizures, witnessed seizure activity, postictal period
Hypoglycemia	History of diabetes, low serum glucose, decreased level of consciousness
Migraine with aura (complicated migraine)	History of similar events, preceding aura, headache
Hypertensive encephalopathy	Headache, delirium, significant hypertension, cortical blindness, cerebral edema, seizure
Wernicke's encephalopathy	History of alcohol abuse, ataxia, ophthalmoplegia, confusion
CNS abscess	History of drug abuse, endocarditis, medical device implant with fever
CNS tumor	Gradual progression of symptoms, other primary malignancy, seizure at onset
Drug toxicity	Lithium, phenytoin, carbamazepine

CNS indicates central nervous system.

the demonstrated utility of such tools in the prehospital environment supports their use in this setting.[32,34,98,99] Once in the ED, validated tools for identification of stroke patients within the ED are available.[100]

The initial evaluation of a potential stroke patient is similar to that of other critically ill patients: immediate stabilization of the airway, breathing, and circulation (ABCs). This is quickly followed by an assessment of neurological deficits and possible comorbidities. The overall goal is not only to identify patients with possible stroke but also to exclude stroke mimics (conditions with strokelike symptoms), identify other conditions that require immediate intervention, and determine potential causes of the stroke for early secondary prevention. Importantly, early implementation of stroke pathways and/or stroke team notification should occur at this point.

Patient History

The single most important piece of historical information is the time of symptom onset. This is defined as when the patient was at his or her previous baseline or symptom-free state. For patients unable to provide this information or who awaken with stroke symptoms, the time of onset is defined as when the patient was last awake and symptom-free or known to be "normal."

Establishing onset time may require confirming the patient's, bystander's, or EMS personnel's initial assessment. Creative questioning to establish time anchors potentially allows treatment of patients initially identified as "onset time unknown." These include inquiring about prestroke or poststroke cellular phone use (and identifying the corresponding call time stamp) or use of television programming times to determine onset time. Patients with "wake-up" strokes may identify a time point when they were ambulatory to the bathroom or kitchen.

Often a patient's current symptoms were preceded by similar symptoms that subsequently resolved. For patients who had neurological symptoms that completely resolved, the therapeutic clock is reset, and the time of symptom onset begins anew. However, the longer the transient neurological deficits last, the greater the chance of detecting neuroanatomically relevant focal abnormalities on diffusion-weighted and apparent diffusion coefficient imaging.[75] Whether this represents an increased risk of hemorrhage with fibrinolysis remains to be determined.

Additional historical items include circumstances surrounding the development of the neurological symptoms and features that may point to other potential causes of the symptoms. Although not absolutely accurate, some early historical data and clinical findings may direct the physician toward an alternate diagnosis of another cause for the patient's symptoms (Table 6). It is important to ask about risk factors for arteriosclerosis and cardiac disease, as well as any history of drug abuse, migraine, seizure, infection, trauma, or pregnancy. Historical data related to eligibility for therapeutic interventions in acute ischemic stroke are equally important. Bystanders or family witnesses should be asked for information about onset time and historical issues as well, and EMS personnel should be encouraged to identify witnesses and bring them with the patient. This is of particular importance when patients are unable to provide a history.

Physical Examination

After the airway, breathing, and circulation have been assessed and specific vital signs determined, such as blood pressure, heart rate, oxygen saturation, and temperature, a more deliberate and detailed physical examination is performed. The detailed physical examination may be conducted by the emergency physician, the stroke expert, or both. The general examination is important to identify other potential causes of the patients' symptoms, potential causes of an ischemic stroke, coexisting comorbidities, or issues that may impact the management of an ischemic stroke. Examination of the head and face may reveal signs of trauma or seizure activity. Auscultation of the neck may reveal carotid bruits; palpation, auscultation, and observation may reveal signs of congestive heart failure. Auscultation of the chest similarly may reveal cardiac murmurs, arrhythmias, and rales. A general examination of the skin may reveal stigmata of coagulopathies, platelet disorders, signs of trauma, or embolic lesions (Janeway lesions, Osler nodes). A thorough examination to identify acute comorbidities and conditions that may impact treatment selection is important.

Neurological Examination and Stroke Scale/Scores

The initial neurological examination should be brief but thorough. At this point, if the initial history and brief examination are suggestive of a stroke, stroke code activation should occur. The use of a standardized neurological examination ensures that the major components of a neurological examination are performed in a timely and uniform fashion. Formal stroke scores or scales, such as the NIHSS or Canadian

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Neurological Scale, may be performed rapidly, have demonstrated utility, and may be administered by a broad spectrum of healthcare providers (Table 7).[101,102] Use of a standardized assessment and stroke scale helps quantify the degree of neurological deficits, facilitate communication, identify the location of vessel occlusion, provide early prognosis, help select patients for various interventions, and identify the potential for complications.[103–105]

Although strokes are the most common cause of new focal neurological deficits, other causes must be considered as well in the acute setting. Stroke mimics were identified in ≈3% of patients in 2 series of patients treated with fibrinolytics, with seizures and conversion disorder identified most frequently.[106,107] No evidence of increased fibrinolytic treatment risk, however, was identified for these patients. More recently, Chernyshev et al[108] reported from their registry of 512 patients treated with intravenous rtPA for presumed ischemic stroke within 3 hours from symptom onset that 21% were later determined to be stroke mimics. In this cohort composed largely of patients with seizures, complicated migraines, and conversion disorders, none experienced a symptomatic hemorrhage, and 87% were functionally independent at discharge. Important conditions mimicking stroke and their clinical features are listed in Table 6. Despite the lack of apparent harm of intravenous rtPA in stroke mimics, an accompanying editorial suggested stroke mimic treatment rates at experienced centers should be <3% using noncontrast CT alone.[109] Means for striking a balance between speed to treatment and diagnostic accuracy will continue to evolve.

Table 7. National Institutes of Health Stroke Scale

Tested Item	Title	Responses and Scores
IA	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) a. Left b. Right	0—No drift 1—Drift before 5 seconds 2—Falls before 10 seconds 3—No effort against gravity 4—No movement
6	Motor function (leg) a. Left b. Right	0—No drift 1—Drift before 5 seconds 2—Falls before 5 seconds 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)

Access to Neurological Expertise

Patients in many hospital settings have limited access to specialists with stroke expertise. Although evidence supporting the utility of acute "code stroke" teams and telestroke systems is plentiful, their availability is dependent on local resources. The evidence on the safety of fibrinolytic delivery without a neurologist stroke specialist present in person or by telemedicine is less robust.

Although emergency physicians exhibit high sensitivity and positive predictive value in identifying patients with stroke,[110,111] only 6 studies[112–117] have identified instances of fibrinolytic delivery in the setting of acute stroke by an emergency or primary care physician (either alone or in telephone consultation with a neurologist). The number of patients treated by nonneurologists in these studies was small, ranging from 6 to 53. Two additional studies reported cautionary findings for "community models" of acute stroke care, in which care is delivered outside an acute stroke team. One study noted an increase in sICH in a series of 70 patients treated by community neurologists,[118] and both found increased in-hospital mortality among intravenous rtPA–treated stroke patients.[118,119] In the case of the Cleveland, OH, experience, these poor outcomes led to quality improvement initiatives that decreased overall rates of symptomatic hemorrhage from 15.7% to 6.4%.[120]

Larger, more recent studies, however, found no evidence of increased risk for mortality, intracerebral hemorrhage (ICH), or reduced functional recovery with a variety of acute response arrangements in a US series of 273 consecutive stroke patients treated with fibrinolytics. These patients were treated by 95 emergency physicians from 4 hospitals without an acute fibrinolytic stroke team over a 9-year period.[121] One third of the cases were treated without a neurological consultation, with a telephone consultation only, or with an in-person consultation, respectively. An ongoing National Institutes of Health–supported study (Increasing Stroke Treatment Through Interventional Behavior Change Tactics [INSTINCT]) is expected to accrue >500 intravenous rtPA–treated patients in a randomly selected cohort of 24 Michigan hospitals and will

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provide a comprehensive assessment of the safety of intravenous rtPA use in the community ED setting.[122]

Thus, current data support multiple approaches to obtaining specialist consultation when needed in the setting of acute stroke. These range from using committed local physicians to using telephones and telemedicine (integrated audio and visual remote assessment) to access local or regional specialists or activating an acute stroke team. Development of local stroke processes to maximize available local and regional resources and to clearly identify access to neurological expertise optimizes opportunities for acute treatment.

Diagnostic Tests

Several tests should be routinely emergently performed as indicated in patients with suspected ischemic stroke, primarily to exclude important alternative diagnoses (especially ICH), assess for serious comorbid diseases, aid in treatment selection, and search for acute medical or neurological complications of stroke (Table 8). Laboratory tests to consider in all patients include blood glucose, electrolytes with renal function studies, complete blood count with platelet count, cardiac markers, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Hypoglycemia may cause focal signs and symptoms that mimic stroke, and hyperglycemia is associated with unfavorable outcomes. Determination of the platelet count and, in patients taking warfarin or with liver dysfunction, the PT/INR is important. Cardiac markers are frequently elevated in acute ischemic stroke, with elevations occurring in 5% to 34% of patients, and these elevations have prognostic significance.[123] Elevation of cardiac troponin T is associated with increased stroke severity and mortality risk, as well as worse clinical outcomes.[124–127]

Table 8. Immediate Diagnostic Studies: Evaluation of a Patient With Suspected Acute Ischemic Stroke

All patients
Noncontrast brain CT or brain MRI
Blood glucose
Oxygen saturation
Serum electrolytes/renal function tests*
Complete blood count, including platelet count*
Markers of cardiac ischemia*
Prothrombin time/INR*
Activated partial thromboplastin time*
ECG*
Selected patients
TT and/or ECT if it is suspected the patient is taking direct thrombin inhibitors or direct factor Xa inhibitors
Hepatic function tests
Toxicology screen
Blood alcohol level
Pregnancy test
Arterial blood gas tests (if hypoxia is suspected)
Chest radiography (if lung disease is suspected)
Lumbar puncture (if subarachnoid hemorrhage is suspected and CT scan is negative for blood
Electroencephalogram (if seizures are suspected)

CT indicates computed tomography; ECG, electrocardiogram; ECT, ecarin clotting time; INR, international normalized ratio; MRI, magnetic resonance imaging; and TT, thrombin time.

*Although it is desirable to know the results of these tests before giving intravenous recombinant tissue-type plasminogen activator, fibrinolytic therapy should not be delayed while awaiting the results unless (1) there is clinical suspicion of a bleeding abnormality or thrombocytopenia, (2) the patient has received heparin or warfarin, or (3) the patient has received other anticoagulants (direct thrombin inhibitors or direct factor Xa inhibitors).

Certain laboratory tests should be considered in select patients. As the use of direct thrombin inhibitors, such as dabigatran, and direct factor Xa inhibitors, such as rivaroxaban and apixaban, becomes more prevalent, it is important to understand what studies may assist in determining qualitatively whether an anticoagulant effect is present. The PT/INR is not helpful in determining whether an anticoagulant effect from dabigatran is present. A patient may have significant concentrations without alterations in PT/INR. A thrombin time (TT) is a sensitive indicator to the presence of dabigatran activity, and a normal TT excludes the presence of significant activity; however, it may be influenced by the use of other anticoagulants. The ecarin clotting time (ECT) demonstrates a linear relationship with direct thrombin inhibitor levels, and a normal ECT generally excludes a significant direct thrombin inhibitor effect and is not influenced by other anticoagulants; however, this test may not be available at all hospitals.[128] As newer anticoagulation agents become available, for instance, direct factor Xa inhibitors, specific assays of activity may be required.

Beyond new anticoagulants, specific laboratory tests may be helpful when there is a suspicion of drug abuse, particularly in cases of stroke in young adults. In this instance, toxicological screens for sympathomimetic use (cocaine, methamphetamine, etc) may identify the underlying cause of the stroke.[129] Although uncommon, women of childbearing age with acute stroke may be pregnant, and results from pregnancy testing may impact the patient's overall management. Examination of the cerebrospinal fluid has a limited role in the acute evaluation of patients with suspected stroke, unless there is a strong suspicion for subarachnoid hemorrhage or acute central nervous system infections.

Because time is critical, fibrinolytic therapy should not be delayed while awaiting the results of the PT, aPTT, or platelet count unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking warfarin and heparin, or anticoagulation use is uncertain. Retrospective reviews of patients who received intravenous fibrinolysis demonstrated very low rates of unsuspected coagulopathies and thrombocytopenia that would have constituted a contraindication to fibrinolysis.[130,131] The only laboratory result required in all patients before fibrinolytic therapy is initiated is a glucose determination; use of finger-stick measurement devices is acceptable.

Chest radiography is often performed in patients with acute stroke; however, only limited observational data are available to guide decision making regarding its utility. One study that evaluated chest radiographs obtained 12 to 24 hours after admission for stroke found clinical management was altered

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in 3.8% of cases.[132] A different study found 3.8% of routine chest radiographs obtained during a code stroke activation (within 6 hours of symptom onset) had a potentially relevant abnormality, with 1 film showing a possibly wide mediastinum (subsequently determined to be normal) and 1.8% having confirmed pulmonary opacities. Thus, the utility of routine chest radiography is debatable in the absence of clinical suspicion of underlying pulmonary, cardiac, or vascular disease.[133] As with diagnostic laboratory tests, chest radiography should not delay administration of intravenous rtPA unless there are specific concerns about intrathoracic issues, such as aortic dissection.

All acute stroke patients should undergo cardiovascular evaluation, both for determination of the cause of the stroke and to optimize immediate and long-term management. This cardiac assessment should not delay reperfusion strategies. Atrial fibrillation may be seen on an admission electrocardiogram; however, its absence does not exclude the possibility of atrial fibrillation as the cause of the event. Thus, ongoing monitoring of cardiac rhythm on telemetry or by Holter monitoring may detect atrial fibrillation or other serious arrhythmias.[134,135] Acute stroke and acute myocardial infarction can present contemporaneously, with one precipitating the other. Ischemic stroke can also cause electrocardiogram abnormalities and, occasionally, cardiac decompensation (cardiomyopathy) via neurohormonal pathways.[136–139]

Because of the close association between stroke and cardiac abnormalities, it is important to assess the cardiovascular status of patients presenting with acute stroke. Baseline electrocardiogram and cardiac biomarkers may identify concurrent myocardial ischemia or cardiac arrhythmias. Troponin is preferred because of its increased sensitivity and specificity over creatine phosphokinase or creatine phosphokinase–MB. Repeat electrocardiogram and serial cardiac enzymes may identify developing silent ischemia or paroxysmal arrhythmias not detected on initial studies.

Conclusions and Recommendations

The evaluation and initial treatment of patients with stroke should be performed expeditiously. Organized protocols and the availability of a stroke team speed the clinical assessment, the performance of diagnostic studies, and decisions for early management. The clinical assessment (history, general examination, and neurological examination) remains the cornerstone of the evaluation. Stroke scales, such as the NIHSS, provide important information about the severity of stroke and prognostic information and influence decisions about acute treatment.

Because time is critical, a limited number of essential diagnostic tests are recommended. Additional diagnostic studies, including cardiac and vascular imaging, often are time consuming and may delay emergency treatment. Stroke protocols and pathways should clearly define which tests must be performed before acute treatment decisions and which may be performed subsequent to acute stroke therapies.

Recommendations

1. **An organized protocol for the emergency evaluation of patients with suspected stroke is recommended *(Class I; Level of Evidence B)*. The goal is to complete an evaluation and to begin fibrinolytic treatment within 60 minutes of the patient's arrival in an ED. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is encouraged. Patients with stroke should have a careful clinical assessment, including neurological examination.** (Unchanged from the previous guideline)
2. **The use of a stroke rating scale, preferably the NIHSS, is recommended *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
3. **A limited number of hematologic, coagulation, and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of intravenous rtPA** (Table 8) ***(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])
4. **Baseline electrocardiogram assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA *(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])
5. **Baseline troponin assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
6. **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 *(Class IIb; Level of Evidence B)*.** (Revised from the previous guideline[13])

Early Diagnosis: Brain and Vascular Imaging

Timely brain imaging and interpretation remains critical to the rapid evaluation and diagnosis of patients with potential ischemic strokes. Newer strategies are playing an increasingly important role in the initial evaluation of patients with acute stroke. Brain imaging findings, including the size, location, and vascular distribution of the infarction, the presence of bleeding, severity of ischemic stroke, and/or presence of large-vessel occlusion, affect immediate and long-term treatment decisions. Information about the possible degree of reversibility of ischemic injury, intracranial vessel status (including the location and size of occlusion), and cerebral hemodynamic status can be obtained by modern imaging studies.[140,141] Although these modalities are increasingly available emergently, non–contrast-enhanced computed tomography (NECT) remains sufficient for identification of contraindications to fibrinolysis and allows patients with ischemic stroke to receive timely intravenous fibrinolytic therapy. NECT should be obtained within 25 minutes of the patient's arrival in the ED.

Parenchymal Brain Imaging

NECT and Contrast-Enhanced CT Scans of the Brain

NECT definitively excludes parenchymal hemorrhage and can assess other exclusion criteria for intravenous rtPA, such as widespread hypoattenuation.[142–145] NECT scanning of the

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brain accurately identifies most cases of intracranial hemorrhage and helps discriminate nonvascular causes of neurological symptoms (eg, brain tumor). NECT may demonstrate subtle visible parenchymal damage within 3 hours.[146–148] NECT is relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa.[75] Despite these limitations, its widespread immediate availability, relative ease of interpretation, and acquisition speed make NECT the most common modality used in acute ischemic stroke imaging.

With the advent of intravenous rtPA treatment, interest has grown in using NECT to identify subtle, early signs of ischemic brain injury (early infarct signs) or arterial occlusion (hyperdense vessel sign) that might affect decisions about treatment. A sign of cerebral ischemia within the first few hours after symptom onset on NECT is loss of gray-white differentiation.[76–78,149,150] This sign may manifest as loss of distinction among the nuclei of the basal ganglia (lenticular obscuration) or as a blending of the densities of the cortex and underlying white matter in the insula (insular ribbon sign)[150] and over the convexities (cortical ribbon sign). Another sign of cerebral ischemia is swelling of the gyri that produces sulcal effacement. The more rapidly these signs become evident, the more profound the degree of ischemia. However, the ability of observers to detect these early infarct signs on NECT is quite variable and occurs in ≤67% of cases imaged within 3 hours. Detection is influenced by the size of the infarct, severity of ischemia, and the time between symptom onset and imaging.[151,152] Detection may increase with the use of a structured scoring system such as the Alberta Stroke Program Early CT Score (ASPECTS) or the CT Summit Criteria,[151–155] as well as with the use of better CT "windowing and leveling" to differentiate between normal and abnormal tissues.[156]

Another useful CT sign is that of increased density within the occluded artery, such as the hyperdense middle cerebral artery (MCA) sign, indicative of large-vessel occlusion.[157] Large-vessel occlusion typically causes severe stroke, independently predicts poor neurological outcome,[157–159] and is a stronger predictor of "neurological deterioration" (91% positive predictive value) than even early CT evidence of >50% MCA involvement (75% positive predictive value).[159,160] The hyperdense MCA sign, however, is seen in only one third to one half of cases of angiographically proven thromboses[160,161]; hence, it is an appropriate indicator of thrombus when present. Another NECT sign is the hyperdense MCA "dot" sign.[162] The MCA dot sign represents a clot within a branch of the MCA and is thus typically smaller than the thrombus volume in the MCA and possibly a better target for intravenous rtPA. Barber et al[162] found that patients with the MCA dot sign alone had better outcomes than patients with a hyperdense MCA sign. Validation for the MCA dot sign has been performed with angiography, with the conclusion that the sensitivity is low (38%) but the specificity is 100%.[163] The hyperdense basilar artery sign has been described with similar implications as the hyperdense MCA sign.[164,165]

The presence, clarity, and extent of early ischemia and infarction on NECT are correlated with a higher risk of hemorrhagic transformation after treatment with fibrinolytic agents. In combined data from 2 trials of intravenous rtPA administered within 3 hours of symptom onset, NECT evidence of early clear hypodensity or mass effect was accompanied by an 8-fold increase in the risk of symptomatic hemorrhage.[166] In a second analysis, more subtle early infarct signs involving more than one third of the territory of the MCA were not independently associated with increased risk of adverse outcome after intravenous rtPA treatment, and as a group, these patients still benefited from therapy.[148] In a European trial in which fibrinolytic therapy was administered within 6 hours of symptom onset, patients estimated to have involvement of more than one third of the territory of the MCA had an increased risk of ICH, whereas those with less involvement benefited the most from fibrinolytic treatment.[144,167] Because of this increased hemorrhage risk, patients with involvement of more than one third of the territory of the MCA by early ischemic signs were excluded from entry in the pivotal trial confirming the benefit of intravenous fibrinolytic therapy in the 3- to 4.5-hour window and the major trials of intra-arterial fibrinolysis up to 6 hours after onset.[168–170]

MRI of the Brain

Standard MRI sequences (T1 weighted, T2 weighted, fluid-attenuated inversion recovery [FLAIR]) are relatively insensitive to the changes of acute ischemia.[171] Diffusion-weighted imaging (DWI) has emerged as the most sensitive and specific imaging technique for acute infarct, far better than NECT or any other MRI sequence. DWI has a high sensitivity (88% to 100%) and specificity (95% to 100%) for detecting infarcted regions, even at very early time points,[172–174] within minutes of symptom onset.[172,175–181] DWI allows identification of the lesion size, site, and age. DWI can detect relatively small cortical lesions and small deep or subcortical lesions, including those in the brain stem or cerebellum, areas often poorly or not visualized with standard MRI sequences and NECT scan techniques.[182–185] DWI can identify subclinical satellite ischemic lesions that provide information on stroke mechanism.[173,176,179,186–197] There are a few articles describing negative DWI studies when cerebral perfusion is decreased enough to produce infarction[198,199] and the reversal, partial or complete, of DWI abnormalities with restoration of perfusion.[200] Thus, early after ischemia onset, the visible diffusion lesion will include both regions of irreversible infarction with more severe apparent diffusion coefficient changes and regions of salvageable penumbra with less severe apparent diffusion coefficient changes.

The *artery susceptibility sign* is the magnetic resonance (MR) correlate of the hyperdense MCA seen on NECT. A direct comparison of NECT and MRI in patients with occlusion of the proximal MCA found that 54% of patients demonstrated this sign on NECT, whereas 82% of the same patients had clot demonstrated on MRI using a gradient echo sequence.[161] Vascular hyperintensities on fluid-attenuated inversion recovery sequences can indicate slow-flowing blood passing through leptomeningeal collaterals.[201] Conventional MRI is more sensitive than standard NECT in identifying both new and preexisting ischemic lesions in patients with 24-hour time-defined TIAs.[202–220] Multiple series show convergent results regarding the frequency of DWI positivity among time-defined TIA patients; among 19 studies that included

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1117 patients with TIA, the aggregate rate of DWI positivity was 39%, with frequency by site ranging from 25% to 67%. DWI-positive lesions tend to be smaller and multiple in TIA patients.[75] There does not appear to be a predilection for cortical or subcortical regions or particular vascular territories. Recently, several studies have demonstrated that DWI positivity in TIA patients is associated with a higher risk of recurrent ischemic events.[221–223]

The appearance of hemorrhage on MRI is dependent on both the age of the blood and the pulsing sequences used.[224–231] Magnetic susceptibility imaging is based on the ability of a T2*-weighted MR sequence to detect very small amounts of deoxyhemoglobin, in addition to other compounds such as those containing iron or calcium. Two prospective studies demonstrated that MRI was as accurate as NECT in detecting hyperacute intraparenchymal hemorrhage in patients presenting with stroke symptoms within 6 hours of onset when gradient echo sequences were used.[228,232] Accordingly, MRI may be used as the sole initial imaging modality to evaluate acute stroke patients, including candidates for fibrinolytic treatment. Gradient echo sequences also have the ability to detect clinically silent prior microbleeds not visualized on NECT. Some data suggest that microbleeds represent markers of bleeding-prone angiopathy and increased risk of hemorrhagic transformation after antithrombotic and fibrinolytic therapy.[233–235] However, other studies have not found an increased risk in patients with small numbers of microbleeds.[236] The importance of the presence of large numbers of microbleeds on MRI in fibrinolytic decision making remains uncertain.

Compared with CT, advantages of MRI for parenchymal imaging include the ability to distinguish acute, small cortical, small deep, and posterior fossa infarcts; the ability to distinguish acute from chronic ischemia; identification of subclinical satellite ischemic lesions that provide information on stroke mechanism; the avoidance of exposure to ionizing radiation; and greater spatial resolution. Limitations of MRI in the acute setting include cost, relatively limited availability of the test, relatively long duration of the test, increased vulnerability to motion artifact, and patient contraindications such as claustrophobia, cardiac pacemakers, patient confusion, or metal implants. Additionally, in ≈10% of patients, an inability to remain motionless may obviate the ability to obtain a quality MRI.

Intracranial Vascular Imaging

An important aspect of the workup of patients with stroke, TIA, or suspected cerebrovascular disease is imaging of intracranial vasculature. The majority of large strokes are caused by occlusion in ≥1 large vessel. Large-vessel occlusion is a devastating condition.[158,159,237–249] Detection of large-vessel occlusion by means of noninvasive intracranial vascular imaging greatly improves the ability to make appropriate clinical decisions.[168,170,237,239,241,250] It is also essential to establish as soon as possible the mechanism of ischemia to prevent subsequent episodes. Large-vessel occlusion can be identified by NECT as described above (hyperdense MCA sign, etc). The length of a clot within the MCA has been directly related to the success of recanalization with intravenous rtPA.[251]

CT Angiography

Helical CT angiography (CTA) provides a means to rapidly and noninvasively evaluate the intracranial and extracranial vasculature in acute, subacute, and chronic stroke settings and thus to provide potentially important information about the presence of vessel occlusions or stenoses.[242,252] The accuracy of CTA for evaluation of large-vessel intracranial stenoses and occlusions is very high,[253–256] and in some cases its overall accuracy approaches or exceeds that of digital subtraction angiography (DSA).[253,257] The sensitivity and specificity of CTA for the detection of intracranial occlusions ranges between 92% and 100% and between 82% and 100%, respectively, with a positive predictive value of 91% to 100%.[242,258–260] Because CTA provides a static image of vascular anatomy, it is inferior to DSA for the demonstration of flow rates and direction.

Direct comparisons of CTA source images (CTA-SI) and MRI/DWI have demonstrated very similar sensitivity of these 2 techniques for detecting ischemic regions, with DWI being better at demonstrating smaller abnormalities (reversible or irreversible) and those in the brainstem and posterior fossa.[261,262] In one study, CTA-SI was superior in stroke identification for readers with all levels of experience.[263] Improved stroke detection explains the greater predictive value for final infarct size by use of CTA-SI.[248] For early strokes (<3 hours), CTA-SI ASPECTS has a greater sensitivity to ischemic changes and more accurately identifies the volume of tissue that will ultimately become infarcted than NECT alone.[159,248] CTA-SI is more an estimate of cerebral blood volume than the expression of cytotoxic edema seen on NECT.

MR Angiography

Intracranial MR angiography (MRA) is performed in combination with brain MRI in the setting of acute stroke to guide therapeutic decision making.[264] There are several different MRA techniques that are used for imaging intracranial vessels. They include 2-dimensional time of flight (TOF), 3-dimensional TOF, multiple overlapping thin-slab acquisition, and contrast-enhanced MRA.[265] Intracranial MRA with nonenhanced TOF techniques has a sensitivity ranging from 60% to 85% for stenoses and from 80% to 90% for occlusions compared with CTA or DSA.[253,258] Typically, TOF MRA is useful in identifying acute proximal large-vessel occlusions but cannot reliably identify distal or branch occlusions.[266]

Doppler Ultrasound

Transcranial Doppler (TCD) ultrasonography has been used to detect intracranial vessel abnormalities.[267,268] TCD has been used to evaluate occlusions and stenoses in intracranial vessels. TCD accuracy is less than that of CTA and MRA for steno-occlusive disease, with a sensitivity and specificity of TCD ranging from 55% to 90% and from 90% to 95%, respectively.[269–276] TCD can detect microembolic signals, which are seen with extracranial or cardiac sources of embolism.[277–279]

In an attempt to better define the accuracy rate of TCD for intracranial stenoses (a common cause of stroke), the Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Trial was designed to evaluate the controlled patient population in the Warfarin-Aspirin Symptomatic Intracranial

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Disease Study (WASID).[276] SONIA enrolled 407 patients at 46 sites. For 50% to 99% stenoses that were angiographically confirmed (the "gold standard"), TCD was able to positively predict 55% of these lesions but was able to rule out 83% of vessels that had <80% stenosis (a low hurdle). This multi-institutional study suggested less than optimal TCD accuracy.[276] TCD is more accurate for proximal M1 than distal M1 or M2 disease.[256]

TCD has been shown to predict, as well as enhance, intravenous rtPA outcomes.[280] Large-vessel occlusions and more proximal occlusions identified by TCD have been predictive of poor revascularization results with intravenous rtPA and worse clinical outcomes.[281,282] In the presence of an appropriate bone window and for vessels capable of visualization by sonography, TCD has been used to monitor the response of cerebral vessels to fibrinolytic therapy over time, as well as to augment such therapy using ultrasonic energy to enhance clot lysis[280,283–286]; TCD provides continuous, real-time imaging and can thus determine the timing of recanalization and the occurrence of reocclusion of vessels capable of visualization by sonography.[282,284,285,287–290] CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic rtPA) indicated recanalization improvement with continuous TCD but was underpowered to detect a significant final clinical improvement. Although higher-frequency ultrasound appeared safe as a lytic enhancer in CLOTBUST, the Transcranial Low-Frequency Ultrasound-Mediated Thrombolysis in Brain Ischemia study (TRUMBI)[291] indicated an increased risk of hemorrhage with low-frequency ultrasound. However, the usefulness of TCD is limited in patients with poor bony windows, and its overall accuracy is dependent on the experience of the technician, the interpreter, and the patient's vascular anatomy. For posterior circulation stroke, Doppler ultrasound is not helpful; CTA, MRA, or a conventional angiogram is required.

Conventional Angiography

DSA remains the "gold standard" for the detection of many types of cerebrovascular lesions and diseases.[292–294] For most types of cerebrovascular disease, the resolution, sensitivity, and specificity of DSA equal or exceed those of the noninvasive techniques, including for arterial stenoses.[292,294–298] However, if noninvasive imaging provides firm diagnostic findings, cerebral angiography may not be required.

DSA is an invasive test and can cause serious complications such as stroke and death, although recent advances in high-resolution rapid-sequence digital subtraction imaging, digital image reconstruction with 3-dimensional techniques, catheter technology, and nonionic contrast media have made cervicocerebral angiography easier and safer over the past 2 decades. Most large series have reported rates of stroke or death in <1% of DSA procedures.[299–301] The largest series of cases to date reported a rate of stroke or death of <0.2%.[299–301] Cerebral angiography need not be the initial imaging modality for emergency intracerebral evaluation of large-vessel occlusion in stroke because of the time necessary to perform the examination; a CTA or MRA can be performed in an additional 2 to 4 minutes during initial stroke evaluation (in a multimodal evaluation in process) and can obviate the need for catheter angiography.[292,294]

Extracranial Vascular Imaging

It is important to evaluate the extracranial vasculature after the onset of acute cerebral ischemia (stroke or TIA) to aid in the determination of the mechanism of the stroke and thus potentially to prevent a recurrence.[6,302] In addition, carotid endarterectomy (CEA) or angioplasty/stenting is occasionally performed acutely, which requires appropriate imaging. The major extracranial cerebral vessels can be imaged by several noninvasive techniques, such as ultrasound, CTA, TOF and contrast-enhanced MRA, and DSA.[303–305] Although each technique has certain advantages in specific clinical situations, the noninvasive techniques show general agreement to DSA in 85% to 90% of cases. For evaluation of the degree of stenosis and for determination of patient eligibility for CEA or carotid angioplasty and stenting, DSA is the "gold standard" imaging modality. The use of 2 concordant noninvasive techniques (among ultrasound, CTA, and MRA) to assess treatment candidacy has the advantage of avoiding catheterization risks.[306,307] CTA (in the absence of heavy calcifications) and multimodal MRI (including MRA and fat-saturation axial T1 imaging) are highly accurate for detecting dissection; for subtle dissections, DSA and multimodal MRI are complementary, and there have been reports of dissections detected by one modality but not the other.[308,309] A very high-grade stenosis ("string sign") is most accurately detected by DSA, followed closely by CTA and contrast-enhanced MRA.[310]

Carotid Doppler Ultrasound

Carotid ultrasound is a safe and inexpensive screening technique for imaging the carotid bifurcation and measuring blood velocities.[303,311,312] Doppler measures that have been correlated with angiographic stenosis include internal carotid artery peak systolic velocity and end-diastolic velocity, as well as ratios of internal carotid artery and common carotid artery peak systolic velocity.[313] Doppler test results and diagnostic criteria are influenced by several factors, such as the equipment, the specific laboratory, and the technologist performing the test.[314,315] For these reasons, it is recommended that each laboratory validate its own Doppler criteria for clinically relevant stenosis.[316,317] Sensitivity and specificity of carotid ultrasound for detecting lesions >70% are less than for other modalities, in the range of 83% to 86% for sensitivity and 87% to 99% for specificity.[318–320] Carotid ultrasound has limited ability to image the extracranial vasculature proximal or distal to the bifurcation.

CT Angiography

CTA is a sensitive, specific, and accurate technique for imaging the extracranial vasculature. CTA is clearly superior to carotid ultrasound for differentiating a carotid occlusion from a very high-grade stenosis[321] and has been reported to have an excellent (100%) negative predictive value for excluding >70% stenosis compared with catheter angiography, thereby functioning well as a screening test.[322] A large meta-analysis found it to have a sensitivity >90% and specificity >95% for detecting significant lesions compared with DSA.[255,319,323–326]

MR Angiography

Two-dimensional and 3-dimensional TOF MRA used for the detection of extracranial carotid disease (threshold stenosis

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typically 70%) showed a mean sensitivity of 93% and a mean specificity of 88%.[265] Contrast-enhanced MRA is more accurate than nonenhanced TOF techniques, with specificities and sensitivities of 86% to 97% and 62% to 91%, respectively, compared with DSA.[320,327–332] Craniocervical arterial dissections of the carotid and vertebral arteries can often be detected with MRA.[333–336] Contrast-enhanced MRA may improve the detection of arterial dissections,[337] although there are few large, prospective studies to prove its accuracy versus catheter angiography. Nonenhanced T1-weighted MRI with fat-saturation techniques can frequently depict a subacute hematoma within the wall of an artery, which is highly suggestive of a recent dissection.[338,339] However, an acute intramural hematoma may not be well visualized on fat-saturated T1-weighted MRI until the blood is metabolized to methemoglobin, which may require a few days after ictus. MRA is also helpful for detecting other less common causes of ischemic stroke or TIAs such as arterial dissection, fibromuscular dysplasia, venous thrombosis, and some cases of vasculitis.[337]

Conventional Angiography

DSA remains the most informative technique for imaging the cervical carotid and vertebral arteries, particularly when making decisions about invasive therapies. In addition to providing specific information about a vascular lesion, DSA can provide valuable information about collateral flow, perfusion status, and other occult vascular lesions that may affect patient management.[292–298] As mentioned above, DSA is associated with a risk, albeit small (<1%), of serious complications such as stroke or death.[299–301] Catheter angiography can be particularly useful in cases of carotid dissection, both to image the dissection and to delineate the collateral supply to the brain.

Perfusion CT and MRI

In recent years, it has become apparent that information about the nature and severity of the ischemic insult may be just as important as the "time" of the ischemic event for predicting outcome and making therapeutic judgments. There is a growing body of literature positing that ischemic, potentially salvageable "penumbral" tissue is an ideal target for reperfusion and neuroprotective strategies but requires proper patient selection.[159,247,262,282,340–344] However, in the acute stroke setting, there is a trade-off between the increased information provided by perfusion imaging and the increased time needed to acquire additional imaging sequences. The performance of these additional imaging sequences should not unduly delay treatment with intravenous rtPA in the ≤4.5-hour window in appropriate patients.[283,286,292,297–301]

Brain perfusion imaging provides information about regional cerebral hemodynamics in the form of such parameters as cerebral blood flow, cerebral blood volume, and mean transit time. Perfusion CT and perfusion-weighted MRI have been widely incorporated into acute multimodal imaging protocols. Combined with parenchymal imaging, perfusion-weighted MRI or perfusion CT imaging permits delineation of the ischemic penumbra.[213,215,216,218,345–349] Perfusion imaging can also indicate areas that are severely and probably irretrievably infarcted. A current technical challenge is that methods for processing of perfusion data to derive perfusion parameters vary, and the most biologically salient perfusion parameters and thresholds for acute decision making have not been fully defined.[218] On MRI, the ischemic penumbra is roughly indexed as the area of perfusion-weighted imaging–DWI mismatch.[176,203,205,214] On perfusion CT imaging, the penumbra is indexed as the area of mean transit time–cerebral blood volume mismatch.[202,210,212,219] "Core" ischemia can be defined accurately by perfusion CT depending on equipment and programming. Various studies have used different hemodynamic parameters, such as mean transit time, cerebral blood volume, and cerebral blood flow,[252–258,260,264–275,350] different thresholds for determining hemodynamic abnormality (eg, degree of reduction in cerebral blood volume and absolute versus relative threshold), and different thresholds for the amount of penumbral tissue that warrants treatment (eg, 20%, 100%, or 200% the size of the infarct core).[206,207,213,215–217,347–349] The International Stroke Imaging Repository (STIR) consortium is currently addressing these issues and is attempting to standardize imaging methodology, processing, and interpretation.[218]

Advantages of the multimodal CT approach over MRI include wider availability of emergency CT imaging, more rapid imaging, and fewer contraindications to CT versus MRI.[351–353] Perfusion CT parameters of cerebral blood volume, cerebral blood flow, and mean transit time can be more easily quantified than their perfusion-weighted MRI counterparts, owing in part to the linear relationship between iodinated CT contrast concentration and resulting CT image density, a relationship that does not hold for gadolinium concentration versus MRI signal intensity. Because of its availability and greater degree of quantification, perfusion CT has the potential to increase patient access to new treatments and imaging-based clinical trials.

Disadvantages of the CT approach over MRI include the use of ionizing radiation and iodinated contrast, which carries a small risk of nephrotoxicity. Use of low-osmolar or iso-osmolar contrast minimizes the risk of contrast-induced nephropathy.[354,355] A recent study of CTA in patients with acute ischemic and hemorrhagic stroke demonstrated a very low rate of contrast-induced nephropathy (3%), and no patients required dialysis.[356] Another disadvantage of perfusion CT is limited brain coverage, typically a 4-cm-thick slab per contrast bolus.[242,259,357,358] Developments such as the toggling-table technique allow doubling of the perfusion CT coverage (typically up to 8 cm).[359] Finally, the latest generations of the 256- and 320-slice CT scanners afford whole-brain coverage but are limited in availability.

The major advantages of perfusion MRI over perfusion CT include its inclusion in a package of imaging sequences that effectively evaluate many aspects of the parenchyma, including the presence of infarction with DWI, and the avoidance of ionizing radiation. Of note, the whole-brain coverage offered by perfusion MRI comes at the cost of a limited spatial resolution (matrix size or interslice gap) or temporal resolution. Disadvantages of perfusion MRI include limited availability in emergency settings, duration of the study, and patient contraindications such as claustrophobia, cardiac pacemakers, patient confusion and/or motion, or metal

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implants. Gadolinium reactions are uncommon but can be dangerous.[353,360] Nephrogenic systemic fibrosis/nephrogenic fibrosing dermopathy is caused by gadolinium-based contrast agents used for MRI.[360] Gadolinium-based MR contrast media generally should be avoided in the presence of advanced renal failure with estimated glomerular filtration rate <30 mL·mi $n^{-1.73}$·m^{-2}.[360,361] Arterial spin labeling is an MRI method that assesses brain perfusion without the need to inject gadolinium contrast material, but it is not widely available.[277]

Several recent trials have studied MRI perfusion/diffusion mismatch. EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) was designed to answer the question of whether intravenous rtPA given 3 to 6 hours after stroke onset promotes reperfusion and attenuates infarct growth in patients who have a "mismatch" between perfusion-weighted and diffusion-weighted MRI. Intravenous rtPA was nonsignificantly associated with lower infarct growth but significantly associated with increased reperfusion in patients who had mismatch.[29,255,286] In the Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) study, a target mismatch pattern of small core and large penumbra was associated with greater clinical response to reperfusion.[345,346,362,363] DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke)[347] appeared to show intravenous desmoteplase to be safe and led to 2 pivotal studies, Desmoteplase in Acute Ischemic Stroke (DIAS) 1 and 2, that tested the concept of using advanced MR or CT for intravenous fibrinolysis triage in the 3- to 9-hour time window.[349,364] Unfortunately, there was no clinical benefit demonstrated, although favorable trends were seen in the MR-selected patients.[364] Newer studies are under way that incorporate lessons from these experiences.

Stroke
Journal of the American Heart Association

Conclusions and Recommendations

Brain and vascular imaging remains a required component of the emergency assessment of patients with suspected stroke and TIA. Either CT or MRI may be used as the initial imaging test. MRI is more sensitive to the presence of ischemia, but at most institutions, CT remains the most practical initial brain imaging test. A physician skilled in assessing CT or MRI studies should be available to promptly examine the initial scan. In particular, the scan should be evaluated for evidence of early signs of infarction, vessel thrombosis, or bleed. For ischemic stroke patients, both CT and MRI platforms offer powerful multimodal imaging capabilities. Generally, an institution may adopt one platform as its primary imaging strategy and optimize systems operations to attain rapid and reliable scan performance. For patients with rapidly transient symptoms, diffusion MRI provides unique insight into whether a stroke has occurred and is the preferred modality if available. Information about multimodal CT and MRI of the brain suggests that these diagnostic studies provide important information about the diagnosis, prognosis, and appropriate treatment of patients with acute stroke. Emergency imaging of the intracranial vasculature is particularly useful in those institutions that provide endovascular recanalization therapies.

Recommendations for Patients With Acute Cerebral Ischemic Symptoms That Have Not Yet Resolved

1. **Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke *(Class I; Level of Evidence A)*. In most instances, NECT will provide the necessary information to make decisions about emergency management.** (Unchanged from the previous guideline[13])
2. **Either NECT or MRI is recommended before intravenous rtPA administration to exclude ICH (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present *(Class I; Level of Evidence A)*.** (Revised from the 2009 imaging scientific statement[9])
3. **Intravenous fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodensity) on CT, regardless of their extent *(Class I; Level of Evidence A)*.** (Revised from the 2009 imaging scientific statement[9])
4. **A noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either intra-arterial fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay intravenous rtPA if indicated *(Class I; Level of Evidence A)*.** (Revised from the 2009 imaging scientific statement[9])
5. **In intravenous fibrinolysis candidates, the brain imaging study should be interpreted within 45 minutes of patient arrival in the ED by a physician with expertise in reading CT and MRI studies of the brain parenchyma *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
6. **CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for intravenous fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making *(Class IIb; Level of Evidence B)*.** (Revised from the 2009 imaging scientific statement[9])
7. **Frank hypodensity on NECT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one third of the MCA territory, intravenous rtPA treatment should be withheld *(Class III; Level of Evidence A)*.** (Revised from the 2009 imaging scientific statement[9])

Recommendations for Patients With Cerebral Ischemic Symptoms That Have Resolved

1. **Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIAs *(Class I; Level of Evidence A)*.** (Unchanged from the 2009 TIA scientific statement[6])
2. **Noninvasive imaging by means of CTA or MRA of the intracranial vasculature is recommended to exclude the presence of proximal intracranial stenosis and/or**

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occlusion *(Class I; Level of Evidence A)* and should be obtained when knowledge of intracranial stenoocclusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with noninvasive testing. (Revised from the 2009 TIA scientific statement[6])

3. **Patients with transient ischemic neurological symptoms should undergo neuroimaging evaluation within 24 hours of symptom onset or as soon as possible in patients with delayed presentations. MRI, including DWI, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed *(Class I; Level of Evidence B)*.** (Unchanged from the 2009 TIA scientific statement[6])

General Supportive Care and Treatment of Acute Complications

Airway, Ventilatory Support, and Supplemental Oxygen

Stroke is a primary failure of focal tissue oxygenation and energy supply. Thus, it is intuitive that systemic hypoxemia and hypotension be avoided and, if present, corrected to limit further cellular damage. Initial assessment of the airway, breathing, and circulation occurs in the prehospital setting and again on arrival in the ED. Constant reassessment of the airway, breathing, and circulation is required to identify oxygen desaturation, respiratory compromise, and hypotension.

Hypoxia

Hypoxia appears frequently after stroke. In one small study of hemiparetic patients, 63% developed hypoxia (defined as oxygen saturation <96% for a period >5 minutes) within 48 hours of stroke onset. In those with a history of cardiac or pulmonary disease, all were noted to develop hypoxemia.[365] In another study assessing nocturnal hypoxia in stroke patients, 50% (120 of 238) of potentially eligible subjects were excluded because of oxygen requirements. Of the enrolled patients, one third had a mean nocturnal oxygen saturation <93%, and 6% had a saturation <90%.[366]

Common causes of hypoxia include partial airway obstruction, hypoventilation, aspiration, atelectasis, and pneumonia. Patients with decreased consciousness or brain stem dysfunction are at increased risk of airway compromise because of impaired oropharyngeal mobility and loss of protective reflexes.[367,368] Central periodic breathing (Cheyne-Stokes respirations) is a frequent complication of stroke and is associated with decreases in oxygen saturation.[369,370] Given the frequency of hypoxia, careful observation and prevention are essential.

Patient Positioning and Monitoring

Data indicate patient positioning can influence oxygen saturation,[371] cerebral perfusion pressure, MCA mean flow velocity,[372,373] and intracranial pressure (ICP).[373] The ideal position of a stroke patient to optimize these parameters, however, is unknown, and the clinician must balance often competing interests, as well as patient tolerance.

Available evidence suggests that in stroke patients without hypoxia or significant respiratory or pulmonary comorbidities, the supine or side position has minimal effect on oxygen saturation.[371,374–377] Limited data suggest stroke patients with hypoxia or significant pulmonary comorbidities have lower oxygen saturation in the supine position than in upright positions.[371,377] In patients who are able to maintain oxygenation while lying flat, the supine position may offer advantages in cerebral perfusion.[372,373]

Thus, in nonhypoxic patients able to tolerate lying flat, a supine position is recommended. Patients at risk for airway obstruction or aspiration and those with suspected elevated ICP[378] should have the head of the bed elevated 15° to 30°. When patient position is altered, close monitoring of the airway, oxygenation, and neurological status is recommended, and adjustment to changing clinical parameters may be required.

Supplemental Oxygen

Although provision of supplemental oxygen may seem intuitive, only limited data exist regarding its benefit. A pilot study found that high-flow, normobaric oxygen, started within 12 hours of stroke onset, may be associated with a transient improvement in neurological impairments[379] and improvements in MRI spectroscopy and diffusion/perfusion imaging.[380] Another feasibility study, however, found no significant differences in patients with MCA territory infarctions treated with 40% oxygen via Venturi mask compared with oxygen 2 L/min delivered via nasal cannula.[381] The results of a large, quasi-randomized controlled trial in stroke found no statistical difference in 1-year mortality or neurological disability between patients who received 3 L of oxygen per minute via nasal cannula for 24 hours after admission and those who received no treatment.[382]

On the basis of these data, it is not apparent that routine supplemental oxygen is required acutely in nonhypoxic patients with mild or moderate strokes. Supplemental oxygen may be beneficial in patients with severe strokes, although the present data are inconclusive, and further research in this area is recommended.[382] On the basis of data from reviews largely focusing on resuscitated post–cardiac arrest patients, recent AHA guidelines for emergency cardiovascular care for stroke and resuscitated cardiac arrest patients recommend administration of oxygen to hypoxemic patients to maintain oxygen saturation >94%.[15] When oxygen therapy is indicated, it is reasonable to use the least invasive method possible to achieve normoxia. Available methods include nasal cannula, Venturi mask, nonrebreather mask, bilevel positive airway pressure, continuous positive airway pressure, or endotracheal intubation with mechanical ventilation.

No clinical trial has tested the utility of endotracheal intubation in the management of critically ill patients with stroke. It is generally agreed that endotracheal intubation and mechanical ventilation should be performed if the airway is threatened. Evidence suggests that prevention of early aspiration reduces the incidence of pneumonia,[383] and protection of the airway may be an important approach in certain patients. Endotracheal intubation and mechanical ventilation may also assist in the management of elevated ICP or malignant brain edema after stroke.[378,384] The need for intubation has prognostic implications. Although a small percentage of patients may

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have a satisfactory outcome after intubation,[385] the overall prognosis of intubated stroke patients is poor, with up to 50% mortality within 30 days after stroke.[386–388]

Temperature

Hyperthermia

Approximately one third of patients admitted with stroke will be hyperthermic (temperature >37.6°C) within the first hours after stroke onset.[389,390] In the setting of acute ischemic stroke, hyperthermia is associated with poor neurological outcome, possibly secondary to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production.[389,391–398]

The physician should determine the source of hyperthermia. Hyperthermia may be secondary to a cause of stroke, such as infective endocarditis, or may represent a complication, such as pneumonia, urinary tract infection (UTI), or sepsis. Because of the negative effects of hyperthermia, maintenance of normothermia or lowering of an acutely elevated body temperature has been hypothesized to improve the prognosis of patients with stroke.[399] Measures to achieve normothermia or prevent hyperthermia include both pharmacological and mechanical interventions.

Sulter et al[400] found that either aspirin or acetaminophen was modestly successful in achieving normothermia, but those patients with a temperature >38°C were relatively unresponsive to this treatment. In a small, randomized trial, Kasner et al[401] administered 3900 mg of acetaminophen daily to afebrile patients with stroke. They concluded that the medication might prevent hyperthermia or modestly promote hypothermia but that the effects were not likely to have a robust clinical impact. Dippel et al[402] tested 2 different doses of acetaminophen in a small clinical trial and concluded a daily dosage of 6000 mg might have a potential beneficial effect in lowering body temperature. In a subsequent study, Dippel et al[403] compared the effects of placebo, ibuprofen, or acetaminophen on body temperature and demonstrated that no differences in mean body temperature were observed after 24 hours of treatment.

A large, 2500-patient, randomized, double-blind, placebo-controlled trial evaluating whether early treatment with acetaminophen improved functional outcome by reducing body temperature and fever prevention found no statistical difference between groups; however, the trial was terminated prematurely (after 1400 patients) because of lack of funding.[404] Post hoc analysis identified a beneficial effect in patients with a baseline body temperature of 37°C to 39°C; however, this was not a prespecified analysis. Treated patients had a mean body temperature 0.26°C (95% CI, 0.18°C–0.31°C) lower than the control group 24 hours after starting therapy.[404] More recently, an updated meta-analysis of the relationship of hyperthermia and stroke mortality in patients with acute stroke demonstrated a 2-fold increase in short-term mortality in patients with hyperthermia within the first 24 hours of hospitalization.[398]

Hypothermia

Although strong experimental and clinical evidence indicates that induced hypothermia can protect the brain in the presence of global hypoxia or ischemia, including after cardiac arrest, data about the utility of induced hypothermia for treatment of patients with stroke are not yet available. Hypothermia is discussed in more detail in the "Neuroprotective Agents" section of this statement.

Cardiac Monitoring

Cardiac monitoring begins in the prehospital setting and continues throughout the initial assessment and management of acute stroke. As mentioned before, continuous cardiac monitoring is indicated for at least the first 24 hours after stroke.[136,405,406] Recent studies have suggested Holter monitoring is more effective in identifying atrial fibrillation or other serious arrhythmias after stroke.[134] Outpatient event monitoring may be indicated in patients with cryptogenic stroke and suspected paroxysmal arrhythmias, especially in those patients with short hospitalizations in which monitoring was brief. The utility of prophylactic administration of medications to prevent cardiac arrhythmias among patients with stroke is not known.

Blood Pressure

Arterial Hypertension

Arterial blood pressure is a dynamic parameter that can fluctuate significantly, with clinical consequences. Elevated blood pressure is common during acute ischemic stroke. In one observational study, the systolic blood pressure was >139 mm Hg in 77% and >184 mm Hg in 15% of patients on arrival at the ED.[407] The blood pressure is often higher in acute stroke patients with a history of hypertension than in those without premorbid hypertension. Blood pressure typically decreases spontaneously during the acute phase of ischemic stroke, starting within 90 minutes after onset of stroke symptoms.[408–414] Extreme arterial hypertension is clearly detrimental, because it leads to encephalopathy, cardiac complications, and renal insufficiency. Theoretically, moderate arterial hypertension during acute ischemic stroke might be advantageous by improving cerebral perfusion of the ischemic tissue, or it might be detrimental by exacerbating edema and hemorrhagic transformation of the ischemic tissue. Extreme arterial hypotension is clearly detrimental, because it decreases perfusion to multiple organs, especially the ischemic brain, exacerbating the ischemic injury. Thus, an arterial blood pressure range likely exists that is optimal during acute ischemic stroke on an individual basis. Unfortunately, such an ideal blood pressure range has not yet been scientifically determined. It is likely that an ideal blood pressure range during acute ischemic stroke will depend on the stroke subtype and other patient-specific comorbidities.

Multiple studies investigated various blood pressure parameters during the admission for acute ischemic stroke and clinical outcomes. Some studies found a U-shaped relation between the admission blood pressure and favorable clinical outcomes, with an optimal systolic blood pressure ranging from 121 to 200 mm Hg and diastolic blood pressure ranging from 81 to 110 mm Hg[415–418] among these studies. However, elevated in-hospital blood pressure during acute ischemic stroke has been associated with worse clinical outcomes in a more linear fashion.[419–427]

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Studies analyzing the extent of in-hospital blood pressure fluctuations during acute ischemic stroke found inconsistent associations with clinical outcomes.[415,421,422,424,428,429] Three studies found that decreases in blood pressure were associated with poor clinical outcomes.[415,421,428] Two studies found no association between blood pressure fluctuations and clinical outcomes.[424,429] One study found that decreases in blood pressure were associated with favorable clinical outcome.[422] Although these observational studies analyzed data controlling for confounding factors, the blood pressure treatments were not controlled, and it is impossible to ascertain the role of the blood pressure in relation to the outcomes.

One acute ischemic stroke treatment trial, the Intravenous Nimodipine West European Stroke Trial (INWEST),[430] set out to test the calcium channel blocker nimodipine as cytoprotective therapy within 24 hours after ischemic stroke onset and found complications related to blood pressure lowering.[408] A decrease in blood pressure was associated with intravenous nimodipine therapy and worse clinical outcome at 21 days. Also, a decrease in diastolic blood pressure >10 mm Hg, but not in the systolic pressure, was significantly associated with worse outcome.

A few preliminary randomized trials of blood pressure lowering in acute ischemic stroke have been published.[411,413,431] A placebo-controlled randomized trial tested oral nimodipine starting within 48 hours after ischemic stroke onset in 350 patients.[413] The systolic and diastolic blood pressures were both significantly lower in the nimodipine group. Functional outcome at 3 months was similar in the 2 treatment groups, but mortality was significantly higher in the nimodipine group. A placebo-controlled randomized trial of therapy with the angiotensin receptor blocker candesartan cilexetil, starting an average of 30 hours after ischemic stroke onset in 342 patients with elevated blood pressure,[431] was stopped early. Although blood pressure and the Barthel index score at 3 months were similar in the 2 study groups, patients who received the active drug had significantly lower mortality and fewer vascular events at 12 months. However, a larger efficacy trial (n=2004) of candesartan therapy with a similar study design showed a mean blood pressure reduction of 7/5 mm Hg at day 7 and no improvement in functional outcome.[432] Favorable outcomes at 6 months, however, were less likely with candesartan than with placebo (modified Rankin Scale [mRS] score 0–2 in 75% versus 77%; significant by shift analysis [P=0.048]).

A 3-armed randomized trial tested labetalol or lisinopril compared with placebo starting within 36 hours after stroke onset in 179 patients.[411] Inclusion of patients with ICH in this trial (14% of the trial patients) obscures the interpretation of results in relation to acute ischemic stroke patients. Over the initial 24 hours, the systolic blood pressure dropped significantly more in the 2 active treatment groups than in the placebo group (21 mm Hg [≈12%] versus 11 mm Hg). Systolic blood pressure over the initial 24 hours compared with placebo dropped significantly more in the lisinopril group (by 14 mm Hg) than in the labetalol group (by 7 mm Hg). The greater blood pressure drops in the active treatment groups were not associated with complications. The primary outcome of death or dependency at 2 weeks was similar in the 2 active treatment groups overall and among patients with ischemic stroke. However, mortality at 3 months was significantly lower in the 2 active treatment groups (9.7%) than with placebo (20.3%, P=0.05).

The Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS) compared the continuation of antihypertensive therapy to stopping preexisting antihypertensive drugs during acute hospitalization for ischemic stroke.[433] Patients were enrolled within 48 hours of stroke onset and the last dose of antihypertensive medication and were maintained in the 2 treatment arms for 2 weeks. The study was terminated prematurely; however, continuation of antihypertensive medications did not reduce 2-week mortality or morbidity and was not associated with 6-month mortality or cardiovascular event rates.

Adding to the complexity and uncertainty of arterial blood pressure management during acute ischemic stroke, small pilot trials have carefully raised the blood pressure in acute ischemic stroke patients without apparent complications. It remains unclear what the risk-benefit ratio is for lowering or raising the blood pressure during acute ischemic stroke. Larger trials with well-defined criteria are needed. At this time, the previous recommendation not to lower the blood pressure during the initial 24 hours of acute ischemic stroke unless the blood pressure is >220/120 mm Hg or there is a concomitant specific medical condition that would benefit from blood pressure lowering remains reasonable.

Some conditions, such as myocardial ischemia, aortic dissection, and heart failure, may accompany acute ischemic stroke and may be exacerbated by arterial hypertension. When blood pressure management is indicated for a specific medical condition in the setting of concurrent acute cerebral ischemia, an optimal approach has not been determined, and at present, blood pressure targets are based on best clinical judgment. A reasonable estimate might be to initially lower the systolic blood pressure by 15% and monitor for neurological deterioration related to the pressure lowering.

Specific blood pressure management recommendations have been established for acute ischemic stroke patients being considered for fibrinolytic therapy (Table 9). These recommendations include a gentle approach to bringing the pressure below 185/110 mm Hg to qualify for fibrinolytic therapy with intravenous rtPA. Once intravenous rtPA is given, the blood pressure must be maintained below 180/105 mm Hg to limit the risk of ICH. A recently published observational study of 11 080 patients with acute ischemic stroke treated with intravenous rtPA further supports the association between elevated blood pressure and adverse outcomes in this setting.[434] Higher blood pressures during the initial 24 hours were associated with greater risk of sICH in a linear fashion. However, a U-shaped relation was found between blood pressure during the initial 24 hours and death or dependency at 3 months, with best outcomes associated with systolic blood pressures of 141 to 150 mm Hg.

Because arterial blood pressure is a dynamic parameter, it is important to monitor it frequently, especially during the first day of stroke, to identify trends and extreme fluctuations that would require intervention. When lowering the blood pressure during acute ischemic stroke is indicated, risk would be minimized by lowering the pressure in a well-controlled manner.

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Table 9. Potential Approaches to Arterial Hypertension in Acute Ischemic Stroke Patients Who Are Candidates for Acute Reperfusion Therapy

Patient otherwise eligible for acute reperfusion therapy except that BP is >185/110 mm Hg:
Labetalol 10–20 mg IV over 1–2 minutes, may repeat 1 time; or
Nicardipine 5 mg/h IV, titrate up by 2.5 mg/h every 5–15 minutes, maximum 15 mg/h; when desired BP reached, adjust to maintain proper BP limits; or
Other agents (hydralazine, enalaprilat, etc) may be considered when appropriate
If BP is not maintained at or below 185/110 mm Hg, do not administer rtPA
Management of BP during and after rtPA or other acute reperfusion therapy to maintain BP at or below 180/105 mm Hg:
Monitor BP every 15 minutes for 2 hours from the start of rtPA therapy, then every 30 minutes for 6 hours, and then every hour for 16 hours
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 minutes, maximum 15 mg/h
If BP not controlled or diastolic BP >140 mm Hg, consider IV sodium nitroprusside

BP indicates blood pressure; IV, intravenously; and rtPA, recombinant tissue-type plasminogen activator.

Controlled blood pressure lowering during acute stroke can best be achieved with intravenous antihypertensive therapies. A single optimal medication to lower the blood pressure in all patients with acute stroke has not been determined, and an individualized approach is best.

It is reasonable to temporarily discontinue or reduce (to prevent the rare occurrence of antihypertensive withdrawal syndrome, primarily seen in β-blocker discontinuation) premorbid antihypertensive medications at the onset of acute ischemic stroke, because swallowing is often impaired, and responses to the medications may be less predictable during the acute stress.[435] The optimal time after the onset of acute ischemic stroke to restart or start long-term antihypertensive therapy has not been established. The optimal time may depend on various patient and stroke characteristics. Nonetheless, it is reasonable to initiate long-term antihypertensive therapy after the initial 24 hours from stroke onset in most patients.[411] An optimal long-term antihypertensive therapy for patients after stroke has not been definitively established, and it might be best to individualize such therapy based on relevant comorbidities, ability to swallow, and likelihood to continue with the prescribed therapy.

Arterial Hypotension

Arterial hypotension is rare during acute ischemic stroke and suggests another cause, such as cardiac arrhythmia or ischemia, aortic dissection, or shock. In a study of 930 patients with acute ischemic stroke, the admission systolic blood pressure was <100 mm Hg in only 2.5% of the patients, and this was associated with ischemic heart disease.[412] In a study of 11 080 patients treated with intravenous rtPA for acute ischemic stroke, the admission systolic blood pressure was <100 mm Hg in only 64 (0.6%) of the patients.[434] The brain is especially vulnerable to arterial hypotension during acute ischemic stroke because of impaired cerebral autoregulation. Arterial hypotension on admission in acute ischemic stroke patients has been associated with poor outcomes in multiple studies.[412,415–417,434] The exact definition of arterial hypotension needs to be individualized. In a given patient, a blood pressure that is lower during acute ischemic stroke than the premorbid pressure could be considered hypotension. Urgent evaluation, diagnosis, and correction of the cause of arterial hypotension are needed to minimize the extent of brain damage. If the arterial hypotension cannot be corrected rapidly by other means, use of vasopressor agents is reasonable. Relatively small trials have evaluated the use of drug-induced hypertension and intravascular volume expansion in acute ischemic stroke, and these are summarized in the "Volume Expansion, Vasodilators, and Induced Hypertension" section of this guideline.

Intravenous Fluids

Patients presenting with acute ischemic stroke are predominantly either euvolemic or hypovolemic. Hypovolemia may predispose to hypoperfusion and exacerbate the ischemic brain injury, cause renal impairment, and potentiate thrombosis. Hypervolemia may exacerbate ischemic brain edema and increase stress on the myocardium. Thus, euvolemia is desirable. One observational study found an association between elevated osmolality (>296 mOsm/kg) during the initial 7 days of acute stroke (90% ischemic) and mortality within 3 months after adjustment for potential confounding factors.[436] In that study, serum sodium and urea measurements were associated with the measured plasma osmolality and thus might be useful in monitoring hydration status. However, the cause-and-effect relationship between hydration during acute ischemic stroke and outcome remains unclear.

For patients who are euvolemic at presentation, clinicians should initiate maintenance intravenous fluids. Apart from unusual losses, daily fluid maintenance for adults can be estimated as 30 mL per kilogram of body weight.[437] For patients who are hypovolemic at presentation, rapid replacement of the depleted intravascular volume followed by maintenance intravenous fluids is reasonable. Although plasma osmolality was similar in acute stroke patients hydrated orally or intravenously,[436] some stroke patients have impaired swallowing. Extra precaution is needed in patients who are especially vulnerable to intravascular volume overload, such as those with renal or heart failure. Treatment of patients with specific conditions, such as syndrome of inappropriate antidiuretic hormone secretion or fever, requires modifications to standard hydration protocols.

A substantial proportion of hypotonic solutions, such as 5% dextrose (after the glucose is metabolized) or 0.45% saline, is distributed into the intracellular spaces and may exacerbate ischemic brain edema. Isotonic solutions such as 0.9% saline are more evenly distributed into the extracellular spaces (interstitial and intravascular) and may be better for patients with acute ischemic stroke.

Blood Glucose

Hypoglycemia

Hypoglycemia during acute ischemic stroke is rare and likely related to antidiabetic medications. If severe enough,

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hypoglycemia is known to cause autonomic and neurological symptoms, including stroke mimics and seizures. Such symptoms are readily reversible if the hypoglycemia is rapidly corrected. However, if untreated, severe or prolonged hypoglycemia can result in permanent brain damage. Thus, blood glucose should be measured as soon as possible in patients with acute ischemic stroke; low levels (<60 mg/dL) should be corrected urgently.

The combination of symptoms attributable to hypoglycemia and the threshold for such symptoms vary considerably between individuals. In healthy people, autonomic symptoms (such as sweating, trembling, or anxiety) usually begin to appear when the blood glucose level drops below 57 mg/dL, and manifestations of brain dysfunction (such as disorientation, dizziness, or slowing of speech) usually begin to appear when the glucose level drops below 47 mg/dL.[438,439] However, in patients with poorly controlled diabetes mellitus, these thresholds are shifted to higher blood glucose levels.[438] Occasionally, brain dysfunction occurs before the autonomic symptoms. Hypoglycemia (blood glucose level <60 mg/dL) can be corrected rapidly in most patients with a slow intravenous push of 25 mL of 50% dextrose. Oral glucose–containing solutions are also reasonable treatment options but take longer to raise the blood glucose level and may not be feasible in patients with dysphagia.

Hyperglycemia

Hyperglycemia is common during acute ischemic stroke. Several studies have shown admission blood glucose is elevated in >40% of patients with acute ischemic stroke, most commonly among patients with a history of diabetes mellitus.[440,441] Blood glucose elevations during acute stroke are related in part to a nonfasting state and in part to a stress reaction with impaired glucose metabolism. Multiple observational studies have found an association between admission and in-hospital hyperglycemia and worse clinical outcomes than with normoglycemia.[442,443] Among stroke patients treated with intravenous rtPA, hyperglycemia has been associated with sICH and worse clinical outcomes.[444–447] Also, multiple studies found an association between acute ischemic stroke hyperglycemia and worse outcomes defined by MRI infarct volume.[448–451] Although multiple observational studies consistently found an association between acute stroke hyperglycemia and worse outcomes, it cannot be determined whether this is a cause-and-effect relationship on the basis of such studies.

So far, only 1 randomized efficacy trial of hyperglycemia treatment in acute stroke has been reported (the Glucose-Insulin-Stroke Trial–UK [GIST-UK]).[452] Patients (n=933) with acute ischemic stroke within 24 hours of symptom onset, not previously treated with insulin, were randomized to unblinded intravenous treatment with insulin, potassium, and glucose versus saline. Protocol treatment continued for 24 hours. Although the results of this trial were neutral (no difference in clinical outcomes between the 2 treatment groups), the design was such that key questions remain unanswered. First, the GIST-UK trial was stopped early, because 2355 subjects were originally planned, and it was thus underpowered to detect a possible treatment effect. Second, the mean glucose level in the insulin-treated group was only 10 mg/dL lower than in the saline control group, and the control group was only mildly hyperglycemic (≈122 mg/dL between hours 8–24). This was likely because of the inclusion of predominantly nondiabetic patients (84%). Larger decreases in glucose levels may be needed to detect a therapeutic effect. Third, the median time to initiation of protocol treatment was 13 hours. Although the optimal time to correct hyperglycemia during acute ischemic stroke has not been established, earlier treatment may have been therapeutic. Pilot clinical trials have demonstrated the feasibility and safety of rapid reductions in glucose levels with intravenous insulin during acute ischemic stroke.[453–456] Thus, the definitive efficacy and safety of earlier and greater reductions in glucose levels during acute ischemic stroke remain to be studied.

There is currently no clinical evidence that targeting the blood glucose to a particular level during acute ischemic stroke will improve outcomes. The main risk from aggressive hyperglycemia correction in acute stroke appears to be possible hypoglycemia. Avoidance of hypoglycemia requires frequent glucose monitoring, and in many hospitals this necessitates admission to an intensive care unit, which may otherwise not be needed.

Further clinical trials should establish the efficacy and the risk-benefit ratio of rapid hyperglycemia correction during acute stroke. Also, if lowering hyperglycemia during acute ischemic stroke proves beneficial, it would be useful to know whether this is a linear effect and what glucose levels can be considered dangerously low. In the meantime, it is prudent to treat hyperglycemia during acute stroke in a manner that avoids excessive resources, labor, and risk. It is reasonable to follow the current American Diabetes Association recommendation to maintain the blood glucose in a range of 140 to 180 mg/dL in all hospitalized patients.[457] There are multiple subcutaneous and intravenous insulin protocols that use insulin to lower hyperglycemia during hospitalization, and these have not been compared with each other in acute stroke patients. The subcutaneous insulin protocols can safely lower and maintain blood glucose levels below 180 mg/dL in acute stroke patients without excessive use of healthcare resources.[453,454,458] However, some hospitals may be prepared to safely administer intravenous insulin to patients with acute stroke and hyperglycemia and maintain the glucose levels considerably below 200 mg/dL.

Recommendations

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 *(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])
2. **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 *(Class I; Level of Evidence B)* before fibrinolytic therapy is initiated. If medications are given to lower blood pressure, the clinician should be**

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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. (Unchanged from the previous guideline[13])

3. **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 *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
4. **Supplemental oxygen should be provided to maintain oxygen saturation >94% *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
5. **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 *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
6. **Until other data become available, consensus exists that the previously described blood pressure recommendations should be followed in patients undergoing other acute interventions to recanalize occluded vessels, including intra-arterial fibrinolysis *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
7. **In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
8. **Hypovolemia should be corrected with intravenous normal saline, and cardiac arrhythmias that might be reducing cardiac output should be corrected *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
9. **Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with acute ischemic stroke *(Class I; Level of Evidence C)*. The goal is to achieve normoglycemia.** (Revised from the previous guideline[13])
10. **Evidence from one clinical trial indicates that initiation of antihypertensive therapy within 24 hours of stroke is relatively safe. Restarting antihypertensive medications is reasonable after the first 24 hours for patients who have preexisting hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known *(Class IIa; Level of Evidence B)*.** (Revised from the previous guideline[13])
11. **No data are available to guide selection of medications for the lowering of blood pressure in the setting of acute ischemic stroke. The antihypertensive medications and doses included in** Table 9 **are reasonable choices based on general consensus *(Class IIa; Level of Evidence C)*.** (Revised from the previous guideline[13])
12. **Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke 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 acute ischemic stroke *(Class IIa; Level of Evidence C)*.** (Revised from the previous guideline[13])
13. **The management of arterial hypertension in patients not undergoing reperfusion strategies remains challenging. Data to guide recommendations for treatment are inconclusive or conflicting. Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke. Until more definitive data are available, the benefit of treating arterial hypertension in the setting of acute ischemic stroke is not well established *(Class IIb; Level of Evidence C)*. Patients who have malignant hypertension or other medical indications for aggressive treatment of blood pressure should be treated accordingly.** (Revised from the previous guideline[13])
14. **Supplemental oxygen is not recommended in nonhypoxic patients with acute ischemic stroke *(Class III; Level of Evidence B)*.** (Unchanged from the previous guideline[13])

Intravenous Fibrinolysis

Intravenous rtPA

Intravenous fibrinolytic therapy for acute stroke is now widely accepted.[459–467] The US FDA approved the use of intravenous rtPA in 1996, in part on the basis of the results of the 2-part NINDS rtPA Stroke Trial, in which 624 patients with ischemic stroke were treated with placebo or intravenous rtPA (0.9 mg/kg IV, maximum 90 mg) within 3 hours of symptom onset, with approximately one half treated within 90 minutes.[166] In the first trial (Part I), the primary end point was neurological improvement at 24 hours, as indicated by complete neurological recovery or an improvement of 4 points on the NIHSS. In the second trial (Part II), the pivotal efficacy trial, the primary end point was a global OR for a favorable outcome, defined as complete or nearly complete neurological recovery 3 months after stroke. Treatment with intravenous rtPA was associated with an increase in the odds of a favorable outcome (OR, 1.9; 95% CI, 1.2–2.9). Excellent outcomes on individual functional measures were more frequent with intravenous rtPA for global disability (40% versus 28%), global outcome (43% versus 32%), activities of daily living (53% versus 38%), and neurological deficits (34% versus 20%). The benefit was similar 1 year after stroke.[468]

The major risk of intravenous rtPA treatment remains sICH. In the NINDS rtPA Stroke Trial, early minimal neurological symptoms or neurological deterioration temporally associated with any intracranial hemorrhage occurred in 6.4% of patients treated with intravenous rtPA and 0.6% of patients given placebo. However, mortality in the 2 treatment groups was similar at 3 months (17% versus 20%) and 1 year (24% versus 28%).[166,469] Although the presence of edema or mass effect on baseline CT scan was associated with higher risk of sICH, patients with these findings were more likely to have an excellent outcome if they received fibrinolytic therapy.[470]

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The presence of early ischemic changes on CT scan was not associated with adverse outcome.[148] The likelihood of a favorable outcome also was associated with the severity of deficits and the patient's age. Patients with mild to moderate strokes (NIHSS score <20) and people <75 years of age had the greatest potential for an excellent outcome with treatment.[103] The chances of a complete or nearly complete recovery among patients with severe stroke (NIHSS score of >20) improved with treatment, but such recovery occurred less often in this group of critically ill patients.[103] Four subsequent trials, the European Cooperative Acute Stroke Study (ECASS I and ECASS II) and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS A and ATLANTIS B), enrolled subsets of patients in the ≤3-hour time period and found largely similar effects in this time window to those observed in the 2 NINDS rtPA trials.[92,167,462,471–473]

Debate about time of initiation of intravenous rtPA treatment merits attention. The NINDS investigators reported a time-to-treatment interaction in a subgroup analysis of the NINDS rtPA Stroke Trial.[93] Treatment with intravenous rtPA initiated within 90 minutes of symptom onset was associated with an OR of 2.11 (95% CI, 1.33–3.55) for favorable outcome at 3 months compared with placebo. In comparison, the OR for good outcome at 3 months for treatment with intravenous rtPA initiated within 90 to 180 minutes was 1.69 (95% CI, 1.09–2.62). The investigators concluded that the earlier that treatment is initiated, the better the result. A subsequent pooled analysis of all large, multicenter, placebo-controlled trials of intravenous rtPA for acute stroke confirmed a time effect.[468] Investigation of the early time epoch in the NINDS trials revealed a potential confounder in the original data: 19% of the patients treated with intravenous rtPA between 91 and 180 minutes after stroke onset had an NIHSS score of <5 compared with 4% of the placebo patients. On the basis of this observation, it has been suggested that the relative preponderance of mild strokes with a likely good outcome in the intravenous rtPA treatment group may explain the entire benefit reported for patients treated between 91 and 180 minutes. Subsequent reanalysis showed that the imbalance in patients with minor stroke did not explain the difference between treatment and placebo.[474] The adjusted OR for 3-month favorable outcome (ORs for treatment compared with placebo) for the subgroup of patients from the 2 NINDS intravenous rtPA stroke trials with NIHSS score of <5 at baseline and time from stroke onset to treatment of 91 to 180 minutes was statistically significant in favor of treatment. Indeed, when all possible subgroups were examined separately, no effect of the severity imbalance could be shown to influence the overall result that intravenous rtPA therapy positively influenced outcome. In separate analyses by independent groups, an identical finding was reached: Baseline imbalances in the numbers of patients with mild stroke did not explain the overall study result.[475–477]

Subsequent to the approval of intravenous rtPA for treatment of patients with acute ischemic stroke, numerous groups reported on the utility of the treatment in a community setting.[117,120,122,478–483] Some groups reported rates of intracranial hemorrhage and favorable outcomes that were similar to those found in the NINDS trials, but others did not. It is now clear that the risk of hemorrhage is proportional to the degree to which the NINDS protocol is not followed.[120,483,484] In addition to the risk of sICH, other potential adverse experiences include systemic bleeding, myocardial rupture if fibrinolytics are given within a few days of acute myocardial infarction, and reactions such as anaphylaxis or angioedema, although these events are rare.[460]

Orolingual angioedema reactions (swelling of tongue, lips, or oropharynx) are typically mild, transient, and contralateral to the ischemic hemisphere.[485] Angioedema is estimated to occur in 1.3% to 5.1% of all patients who receive intravenous rtPA treatment for ischemic stroke.[464,485,486] Risk of angioedema is associated with angiotensin-converting enzyme inhibitor use and with infarctions that involve the insular and frontal cortex. Empiric monitoring recommendations include inspection of tongue, lips, and oropharynx after intravenous rtPA administration. Empiric treatment recommendations include intravenous ranitidine, diphenhydramine, and methylprednisolone.[486]

The largest community experience, the SITS-ISTR Registry (Safe Implementation of Thrombolysis in Stroke–International Stroke Thrombolysis Register, which incorporates the SITS-MOST [Safe Implementation of Thrombolysis in Stroke–Monitoring Study] Registry), resulted when, in 2002, the European Medicines Evaluation Agency granted license for the use of intravenous rtPA for the treatment of ischemic stroke patients within 3 hours of symptom onset. The approval was conditional on the completion of a prospective registry of patient treatment experience with intravenous rtPA within the 3-hour window from stroke onset. SITS-ISTR reported on 11 865 patients treated within 3 hours of onset at 478 centers in 31 countries worldwide.[468] The frequency of early neurological deterioration temporally associated with substantial parenchymal hematoma after intravenous rtPA was 1.6% (95% CI, 1.4%–1.8%). The frequency of favorable outcome (combined mRS scores of 0, 1, and 2) at 90 days was 56.3% (CI, 55.3%–57.2%) in the intravenous rtPA patients, comparable to the favorable outcome rate among patients treated within 3 hours in the pooled analysis of the 6 randomized trials.[468] These findings appear to confirm the safety of intravenous rtPA within the 3-hour window at sites that have an institutional commitment to acute stroke care.

With >15 years of fibrinolytic experience in acute ischemic stroke, multiple groups have reported their outcomes in treating patients with "off-label" fibrinolysis.[487–493] These groups report the use of fibrinolysis in patients with conditions including extreme age (>80 years), prior stroke and diabetes mellitus, minor stroke, rapidly improving stroke symptoms, recent myocardial infarction, major surgery or trauma within the preceding 3 months, and oral anticoagulation use. Overall, the outcomes in the treated patients with these contraindications were better than nontreated "controls" from registry data. Rates of sICH were not increased in these reports. Because stroke patients continue to present with conditions not specifically stated in the original indications for and usage of intravenous rtPA, further experience may allow consideration for fibrinolysis in these situations.

Extended Window for Intravenous rtPA

Subsequent to the NINDS trials, 5 clinical trials have tested the use of intravenous rtPA up to 6 hours after stroke onset

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without specialized imaging for patient selection. The first 4 trials, ECASS I, ECASS II, ATLANTIS A, and ATLANTIS B,[167,471,473,494] collectively enrolled 1847 patients in the 3- to 6-hour time period. None of these 4 trials was individually positive on its prespecified primary end point. In a pooled individual patient-level analysis of these 4 trials, a benefit of therapy in the 3- to 4.5-hour window was suggested, both in increasing the rate of excellent outcomes (adjusted OR, 1.40; 95% CI, 1.05–1.85) and in improving outcomes along the entire range of poststroke disability.[92,495] Fibrinolytic therapy in the 4.5- to 6-hour window produced a statistically nonsignificant increase in the rate of excellent outcomes (adjusted OR, 1.15; 95% CI, 0.90–1.47).[92,495] In the 3- to 4.5-hour window, across all trials, rates of radiological parenchymal hematoma were higher with fibrinolytic therapy, 5.9% versus 1.7%, but mortality was not increased at 13% versus 12%. In the 4.5- to 6-hour window, fibrinolytic therapy increased rates of both radiological parenchymal hematoma (6.9% versus 1.0%) and mortality (15% versus 10%). When data from all time windows in the first 6 large intravenous rtPA trials were pooled, a time-to-treatment interaction was shown.[92] Treatment with intravenous rtPA initiated within 1.5 hours of symptom onset was associated with an OR of 2.81 (95% CI, 1.75–4.50) for favorable outcome at 3 months compared with placebo. The OR for good outcome at 3 months for treatment with intravenous rtPA initiated within 1.5 to 3 hours was 1.55 (95% CI, 1.12–2.15) compared with 1.40 (95% CI, 1.05–1.85) within 3 to 4.5 hours and 1.15 (0.90–1.47) within 4.5 to 6 hours.

The ECASS III trial was undertaken to prove or disprove the benefit of intravenous rtPA in the 3- to 4.5-hour window suggested by the pooled analysis of the 4 prior trials. In ECASS III, patients between 3.0 and 4.5 hours from symptom onset were randomized to either intravenous rtPA (n=418) or placebo (n=403).[169] The dosing regimen was 0.9 mg/kg (maximum of 90 mg), with 10% given as an initial bolus and the remainder infused over 1 hour.[13] The inclusion and exclusion criteria for the trial were similar to those in the existing AHA Stroke Council guidelines for treatment of patients within 3 hours of stroke onset,[13] except for the time window and that the trial additionally excluded people >80 years old, those with a baseline NIHSS score >25, those taking oral anticoagulants (even if their INR was <1.7), and those who had the combination of a previous stroke and diabetes mellitus. Patients were permitted to receive low-dose parenteral anticoagulants for prophylaxis of DVT within 24 hours after treatment with intravenous rtPA.

Early neurological deterioration likely caused by intracranial hemorrhage was identified in 10 subjects treated with intravenous rtPA (2.4%) and 1 subject administered placebo (0.2%; OR, 9.85; 95% CI, 1.26–77.32; P=0.008).[169] However, mortality in the 2 treatment groups did not differ significantly and was nominally higher among the subjects treated with placebo.[169] The primary efficacy outcome in ECASS III was excellent 90-day outcome on the mRS global disability scale (mRS score 0–1). This outcome was more frequent with intravenous rtPA (52.4%) than placebo (45.2%; OR, 1.34; 95% CI, 1.02–1.76; risk ratio, 1.16; 95% CI, 1.01–1.34; P=0.04). The ECASS III findings align with preclinical and clinical data that suggest a time dependency for benefit from treatment with intravenous rtPA. The point estimate for the degree of benefit seen in ECASS III (OR for global favorable outcome, 1.28; 95% CI, 1.00–1.65) was less than the point estimate of that found in the pool of patients enrolled from 0 to 3 hours in the NINDS study (OR, 1.9; 95% CI, 1.2–2.9)[166,169] and was similar to the pooled analysis of the results of subjects enrolled in the 3- to 4.5-hour window in previous trials of intravenous rtPA (OR, 1.4).[92,166,167,471,473,494] Overall, the ECASS III results were consistent with the results of previous trials,[92,496,497] which indicates that intravenous rtPA can be given safely to, and can improve outcomes for, carefully selected patients treated 3 to 4.5 hours after stroke.

In June 2012, the results from the Third International Stroke Trial (IST-3), the largest randomized, placebo-controlled trial to date of intravenous rtPA, were published.[498] The trial enrolled 3035 patients who were randomized to treatment within 6 hours from symptom onset with 0.9 mL/kg in the active arm. Eligibility criteria were similar to other intravenous rtPA trials with several exceptions, including no upper limit to age and broader blood pressure eligibility (systolic blood pressure 90–220 mm Hg and diastolic blood pressure 40–130 mm Hg). The primary outcome measure, an Oxford Handicap Score of 0 to 2 (alive and independent) at 6 months, was achieved in 37% of patients in the intravenous rtPA group versus 35% in the control group (OR, 1.13; 95% CI, 0.95–1.35; P=0.181). Using an ordinal analysis, there was a significant shift in overall Oxford Handicap Score (OR, 1.27; 95% CI, 1.10–1.47; P=0.001). Within 7 days, fatal or nonfatal sICH occurred in 7% versus 1% in the treatment versus placebo arms, respectively. More deaths occurred within 7 days in the intravenous rtPA group (11%) than in the control group (7%; adjusted OR, 1.60; 95% CI, 1.22–2.08; P=0.001), but by 6 months, 27% of patients had died in both groups.

Also in June 2012, Sandercock and colleagues[498] published a meta-analysis of 12 intravenous rtPA trials that had enrolled 7012 patients up to 6 hours from symptom onset. The results confirmed the benefits of intravenous rtPA administered within 6 hours from symptom onset, with final follow-up mRS score of 0 to 2 in 46.3% of intravenous rtPA–treated patients compared with 42.1% of patients in the placebo arms (OR, 1.17; 95% CI, 1.06–1.29; P=0.001). The data also reinforced the importance of timely treatment, because the benefit of intravenous rtPA was greatest in patients treated within 3 hours from symptom onset (mRS score 0–2, 40.7% versus 31.7%; OR, 1.53, 95% CI, 1.26–1.86; P<0.0001). As noted in the IST-3 trial, sICH events were more common in the intravenous rtPA group (7.7% versus 1.8%; OR, 3.72, 95% CI, 2.98–4.64; P<0.0001), and death within 7 days was increased in intravenous rtPA patients (8.9%) compared with the placebo arms (6.4%; OR, 1.44, 95% CI, 1.18–1.76; P=0.0003), but by final follow-up, the number of deaths was similar (19.1% versus 18.5%; OR, 1.06, 95% CI, 0.94–1.20; P=0.33). Importantly, the authors found patients of all ages received benefit from intravenous rtPA treatment compared with placebo.

Drug regulatory authorities have recently taken contradictory actions with regard to later administration of intravenous rtPA, with the European Medicines Agency expanding approval of intravenous rtPA to the 3- to 4.5-hour window and the US FDA declining to do so. The basis of these decisions

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currently remains confidential as part of the regulatory process. To inform this update of the guidelines, the AHA/ASA Writing Committee leadership requested and was granted by the US manufacturer (Genentech) partial access to the FDA decision correspondence. The degree of evidence that AHA/ASA requires for a Grade B recommendation is less than for a Grade A recommendation, and the latter generally more closely approximates the level of evidence that the FDA requires for label approval. On the basis of the review, it is the opinion of the writing committee leadership that the existing Grade B recommendation remains reasonable. The sponsor indicated it planned to work with academic investigators to independently replicate the types of analyses undertaken as part of the FDA review process and make the resultant findings public, and this approach was supported by the writing committee.

Although the maximum time window in which fibrinolytic therapy may be given in many patients has been expanded to 4.5 hours, preclinical, cerebrovascular imaging, and clinical trial evidence indicate the fundamental importance of minimizing total ischemic time and restoring blood flow to threatened but not yet infarcted tissue as soon as feasible. Experience with acute myocardial infarction and acute ischemic stroke systems of care have demonstrated that health system responsiveness is improved by the establishment and monitoring of a time interval within which most patients should be treated after first presentation to the hospital.[499,500] Health systems should set a goal of increasing their percentage of stroke patients treated within 60 minutes of presentation to hospital (door-to-needle time of 60 minutes) to at least 80%.[43,501,502]

Patients With Minor and Isolated or Rapidly Improving Neurological Signs

Minor and isolated symptoms are those that are not presently potentially disabling. Although most patients with potentially disabling symptoms will have NIHSS scores ≥4, certain patients, such as those with gait disturbance, isolated aphasia, or isolated hemianopia, may have potentially disabling symptoms although their NIHSS score is just 2.

Several studies have now reported that approximately one third of patients who are not treated with intravenous rtPA because of mild or rapidly improving stroke symptoms on hospital arrival have a poor final stroke outcome.[503–507] A persistent large-artery occlusion on imaging, despite minor symptoms or clinical improvement, may identify patients at increased risk of subsequent deterioration.[508] In light of these observations, the practice of withholding intravenous fibrinolytic therapy because of mild or rapidly improving symptoms has been questioned, which justifies further study.

Patients Taking Direct Thrombin Inhibitors and Direct Factor Xa Inhibitors

New classes of anticoagulants are rapidly changing the way physicians treat and prevent disorders of thrombosis. Although most potential agents are in clinical development, the direct thrombin inhibitor dabigatran and the direct factor Xa inhibitor rivaroxaban have been approved for use in the United States. Other factor Xa inhibitors are on the horizon: Apixiban has recently been approved by the FDA, and edoxaban is in the late stages of clinical development. These classes of oral anticoagulants do not require therapeutic monitoring, have fewer side effects (especially lower rates of major hemorrhage), and have fewer drug and food interactions than warfarin.[509–512] The challenge for physicians evaluating and considering treatment options for patients with acute ischemic stroke is determining the anticoagulant effect of these agents and estimating the potential increased risk of hemorrhage after reperfusion strategies are initiated.

Specific to dabigatran, drug concentrations peak ≈2 to 3 hours after an oral dose. The active moiety has a half-life of 12 to 17 hours and is cleared primarily by renal elimination. In patients with impaired renal function, the half-life may extend to 20 to 30 hours. The challenge for the physician treating acute stroke patients with this agent is estimating the impact of the drug on the coagulation system. Traditional coagulation tests are not reliable for measuring the anticoagulant effect of dabigatran. The effects of dabigatran on the INR are not predictable. Similarly, the effects of dabigatran on aPTT are not predictable. Although there is correlation between dabigatran plasma concentrations and aPTT results, the correlation is nonlinear. TT and ECT both show a good linear correlation with direct thrombin inhibitors, including dabigatran, and are very sensitive. If the TT or ECT is normal, it is reasonable to assume that plasma concentrations of dabigatran are minimal. Regrettably, these tests are not performed routinely in the ED, and results may take hours to become available.

Specific to the direct factor Xa inhibitors, rivaroxaban has a half-life of 5 to 9 hours and is cleared by renal, fecal, and hepatic mechanisms, whereas apixaban has a half-life of 8 to 15 hours and is cleared by the cytochrome P450 system. The direct factor Xa inhibitors may cause prolongation of the PT and aPTT, but these indexes are not reliable for measuring the pharmacodynamics effects of these agents. Direct factor Xa activity assays may be able to indicate treatment effects but are not routinely performed in the ED, and results may take hours to become available.

Until a simple, fast, and reliable method is determined to measure the clinical impact of the direct thrombin inhibitors and direct factor Xa inhibitors, and more data are collected on use of fibrinolytics and reperfusion strategies in patients taking these classes of drugs, a good medical history will be critical. In patients known to have taken one of these agents in the past, but for whom history or a readily available assay suggests no current substantial anticoagulant effects of the agent, cautious treatment may be pursued. In patients with historical or assay suggestion of at least modest anticoagulant effects of dabigatran, fibrinolytic therapy is likely to be of greater risk and ordinarily would not be undertaken. As other classes of anticoagulants become available for clinical use, similar considerations will be necessary.

For instance, as this guideline was undergoing revisions, the results of 2 large phase III trials of oral direct factor Xa inhibitors for the treatment of patients with atrial fibrillation were published.[513,514] These medications, rivaroxaban (FDA approved) and apixaban (recently approved), are pharmacologically different from dabigatran. The recommendations made for dabigatran may not be applicable in all cases for these newer agents because of differences in metabolism. We urge caution in applying these recommendations to these new oral direct factor Xa inhibitor agents.

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Other Fibrinolytic Agents

Clinical trials of streptokinase (administered at the treatment dose for acute myocardial ischemia, 1.5 million units) were halted prematurely because of unacceptably high rates of hemorrhage, and this agent should not be used.[515–518] Other intravenously administered fibrinolytic agents, including reteplase, urokinase, anistreplase, and staphylokinase, have not been tested extensively. Tenecteplase is a modified tissue plasminogen activator with a longer half-life and higher fibrin specificity than alteplase and appears promising as an effective fibrinolytic, with greater reperfusion and major vessel recanalization with fewer bleeding complications than alteplase in pilot studies. Recently, a US phase IIb study of intravenous tenecteplase in acute stroke was terminated prematurely for nonsafety issues, but an Australian phase IIb trial comparing tenecteplase with alteplase showed significantly improved rates of reperfusion and clinical outcomes by use of imaging-based patient selection.[519–521]

Desmoteplase is a fibrinolytic agent isolated from vampire bat saliva. Two phase II trials of desmoteplase provided encouraging safety and potential efficacy data in penumbral imaging–selected patients 9 hours after stroke onset.[347,349] However, a larger trial revealed no benefit of either of 2 doses of desmoteplase over placebo, possibly because of a higher than projected good outcome rate in the placebo group. Phase III studies are ongoing.

Defibrogenating Enzymes

Extracts derived from pit viper venom have been demonstrated to cleave fibrinogen rather than fibrin, reducing plasma fibrinogen, which leads to reduced blood viscosity, increased blood flow, and the prevention of clot formation and/or clot extension. Ancrod, a defibrinogenating agent, has been investigated in patients with acute ischemic stroke.[522–526] A systematic meta-analysis of defibrinogenating agents in acute ischemic stroke analyzed 6 trials involving 4148 subjects. The review authors identified a trend toward benefit in reducing death or dependency at the end of the follow-up period (43.7% versus 46.7%, for an absolute risk reduction of 3.0% [95% CI, –0.1% to 5.9%]). The meta-analysis also found that treatment increased early minimal neurological symptoms or neurological deterioration temporally associated with any intracranial hemorrhage (4.9% versus 1.0%, for an absolute risk increase of 3.8% [95% CI, 2.3% to 5.4%]). However, more recently, 2 phase III ancrod trials investigating a refined dosing regimen were stopped after a planned interim analysis found no clinically meaningful difference in outcome between the 2 treatment groups in averting disability.[527]

Transcranial Ultrasound Fibrinolysis Augmentation

Ultrasound enhancement of fibrinolysis was demonstrated in preclinical models and studied in pilot human stroke trials. Ultrasound can be delivered to an acute cerebral arterial occlusion in several ways, including (1) by a sonographic operator actively positioning a diagnostic Doppler or B-mode/color flow duplex imaging probe[285,528,529]; (2) by unfocused, low-frequency ultrasound that sonicates both the vessels and brain without imaging guidance[291]; and (3) intra-arterial or intraclot delivery via catheter, such as with the EKOS technology.[532]

In the CLOTBUST trial,[280] 83% of patients achieved any recanalization (46% complete, 27% partial) with intravenous rtPA and TCD versus 50% (17% complete, 33% partial) with intravenous rtPA alone within 2 hours of treatment (P=0.001). The sICH rate was 3.8% in both groups (P=NS).

Because application in humans of frequencies below the diagnostic range resulted in increased symptomatic bleeding rates,[291] mechanisms by which megahertz and kilohertz frequencies interact with the clot–residual flow interface and endothelium are currently under renewed investigations, while trials of diagnostic ultrasound enhancement of fibrinolysis are ongoing.[531]

Combination Intravenous Therapies

Combinations of fibrinolytic(s) plus anticoagulant and/or antiplatelet agents may offer considerable potential to achieve and maintain arterial patency. Multiple exploratory pilot trials have been encouraging, but definitive phase III efficacy trials have yet to be performed.[532]

Consent Issues

As with any medical therapy that carries more than minimal risk, explicit informed patient consent for fibrinolytic therapy is indicated. For the incompetent patient, consent may be provided by a legally authorized representative who can provide proxy consent. A physician's note documenting explicit discussion in a consent conversation is acceptable. In some institutions, the patient or representative must sign a written consent form conveying the risks and benefits of therapy. In an emergency, when the patient is not competent and there is no available legally authorized representative to provide proxy consent, it is both ethically and legally permissible to proceed with fibrinolysis.[533] Generally accepted legal and ethical doctrines recognize an exception to the obligation to obtain explicit informed consent in emergency situations in which immediate treatment is required to prevent more serious harm, the patient lacks decision-making capacity, and no substitute decision maker (surrogate) is available.[533–535] Regulatory precedents set by FDA and the Department of Health and Human Services in the United States and by the World Medical Association internationally support the use of intravenous rtPA in patients lacking capacity when an alternative form of consent cannot be obtained within the treatment window.[534]

Conclusions and Recommendations

Intravenous administration of rtPA remains the only FDA-approved pharmacological therapy for treatment of patients with acute ischemic stroke.[11] Its use is associated with improved outcomes for a broad spectrum of patients who can be treated within 3 hours of the last known well time before symptom onset and a mildly more selective spectrum of patients who can be treated between 3 and 4.5 hours of the last known well time. Most importantly, earlier treatment is more likely to result in a favorable outcome. Patients within 3 hours of onset with major strokes (NIHSS score >22) have a very poor prognosis, but some positive treatment effect with intravenous rtPA remains.[536] Treatment with intravenous rtPA is associated with increased rates of intracranial hemorrhage, which may be fatal.

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Recommendations for the management of intracranial hemorrhage after treatment with intravenous rtPA are provided in the AHA Stroke Council's updated guideline statement on management of ICH.[536a] The best methods for preventing bleeding complications are careful selection of patients and scrupulous ancillary care, especially close observation, as well as monitoring of the patient with early treatment of arterial hypertension. Factors that affect decisions about administration of intravenous rtPA are outlined in Tables 10 and 11, and the treatment regimen for administration of intravenous rtPA is included in Table 12. Case series have suggested that fibrinolysis may be used in patients with seizures at the time of presentation when evidence suggests that residual deficits are attributable to ischemia rather than the postictal state.[537,538] Additional refinement of relative and absolute contraindications to fibrinolysis needs to be considered. Benefit of therapy has been demonstrated only in trials that avoided concomitant treatment with anticoagulants and antiplatelet agents during the first 24 hours after treatment. Although other fibrinolytic agents, including defibrinogenating drugs, have been tested, none has been established as effective or as a replacement for intravenous rtPA.

Recommendations

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 *(Class I; Level of Evidence A)*. 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. A recommended regimen for observation and treatment of patients who receive intravenous rtPA is described in** Table 12. (Unchanged from the previous guideline[13])
2. **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 *(Class I; Level of Evidence A)*.** (New recommendation)
3. **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 *(Class I; Level of Evidence B)*. 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.** (Revised from the 2009 intravenous rtPA Science Advisory[14])
4. **Intravenous rtPA is reasonable in patients whose blood pressure can be lowered safely (to below 185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous rtPA *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])

Table 10. Inclusion and Exclusion Characteristics of Patients With Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms <3 hours before beginning treatment
Aged ≥18 years
Exclusion criteria
Significant head trauma or prior stroke in previous 3 months
Symptoms suggest subarachnoid hemorrhage
Arterial puncture at noncompressible site in previous 7 days
History of previous intracranial hemorrhage
Intracranial neoplasm, arteriovenous malformation, or aneurysm
Recent intracranial or intraspinal surgery
Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
Active internal bleeding
Acute bleeding diathesis, including but not limited to
Platelet count <100 000/mm^3
Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
Current use of anticoagulant with INR >1.7 or PT >15 seconds
Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT, INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)
Blood glucose concentration <50 mg/dL (2.7 mmol/L)
CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative exclusion criteria
Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rtPA administration carefully if any of these relative contraindications are present:
Only minor or rapidly improving stroke symptoms (clearing spontaneously)
Pregnancy
Seizure at onset with postictal residual neurological impairments
Major surgery or serious trauma within previous 14 days
Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
Recent acute myocardial infarction (within previous 3 months)

The checklist includes some FDA-approved indications and contraindications for administration of IV rtPA for acute ischemic stroke. Recent guideline revisions have modified the original FDA-approved indications. A physician with expertise in acute stroke care may modify this list.

Onset time is defined as either the witnessed onset of symptoms or the time last known normal if symptom onset was not witnessed.

In patients without recent use of oral anticoagulants or heparin, treatment with IV rtPA 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.

In patients without history of thrombocytopenia, treatment with IV rtPA can be initiated before availability of platelet count but should be discontinued if platelet count is <100 000/mm^3.

aPTT indicates activated partial thromboplastin time; CT, computed tomography; ECT, ecarin clotting time;FDA, Food and Drug Administration; INR, international normalized ratio; IV, intravenous; PT, partial thromboplastin time; rtPA, recombinant tissue plasminogen activator; and TT, thrombin time.

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Table 11. Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset

Inclusion criteria
Diagnosis of ischemic stroke causing measurable neurological deficit
Onset of symptoms within 3 to 4.5 hours before beginning treatment
Relative exclusion criteria
Aged >80 years
Severe stroke (NIHSS>25)
Taking an oral anticoagulant regardless of INR
History of both diabetes and prior ischemic stroke

INR indicates international normalized ratio; IV, intravenous; NIHSS, National Institutes of Health Stroke Scale; and rtPA, recombinant tissue plasminogen activator.

Table 12. Treatment of Acute Ischemic Stroke: Intravenous Administration of rtPA

Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 minutes, with 10% of the dose given as a bolus over 1 minute.
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 rtPA is being administered) and obtain emergent CT scan.
Measure blood pressure and perform neurological assessments every 15 minutes during and after IV rtPA infusion for 2 hours, then every 30 minutes for 6 hours, then hourly until 24 hours after IV rtPA treatment.
Increase the frequency of blood pressure measurements if systolic blood pressure is >180 mm Hg or if diastolic blood pressure is >105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels (Table 8).
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 hours after IV rtPA before starting anticoagulants or antiplatelet agents.

CT indicates computed tomography; IV, intravenous; MRI, magnetic resonance imaging; and rtPA, recombinant tissue plasminogen activator.

5. **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 *(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])
6. **Intravenous rtPA is reasonable in patients with a seizure at the time of onset of stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon *(Class IIa; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
7. **The effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established *(Class IIb; Level of Evidence B)*.** (New recommendation)
8. **The usefulness of intravenous administration of tenecteplase, reteplase, desmoteplase, urokinase, or other fibrinolytic agents and the intravenous administration of ancrod or other defibrinogenating agents is not well established, and they should only be used in the setting of a clinical trial *(Class IIb; Level of Evidence B)*.** (Revised from the previous guideline[13])
9. **The effectiveness of intravenous treatment with rtPA is not well established *(Class IIb; Level of Evidence C)* and requires further study for patients who can be treated in the time period of 3 to 4.5 hours after stroke but have 1 or more of the following exclusion criteria: (1) patients >80 years old, (2) those taking oral anticoagulants, even with INR ≤1.7, (3) those with a baseline NIHSS score >25, or (4) those with a history of both stroke and diabetes mellitus.** (Revised from the 2009 intravenous rtPA Science Advisory[14])
10. **Use of intravenous fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered, and potential increased risk should be weighed against the anticipated benefits *(Class IIb; Level of Evidence C)*. These circumstances require further study.** (New recommendation)
11. **The intravenous administration of streptokinase for treatment of stroke is not recommended *(Class III; Level of Evidence A)*.** (Revised from the previous guideline[13])
12. **The use of intravenous rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as aPTT, INR, platelet count, and ECT, TT, or appropriate direct factor Xa activity assays are normal, or the patient has not received a dose of these agents for >2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rtPA *(Class III; Level of Evidence C)*.** (New recommendation) **Further study is required.**

Endovascular Interventions

The number of options for endovascular treatment of ischemic stroke has increased substantially over the past decade to include intra-arterial fibrinolysis, mechanical clot retrieval with the Mechanical Embolus Removal in Cerebral Ischemia (Merci) Retrieval System (Concentric Medical, Inc, Mountain View, CA), mechanical clot aspiration with the Penumbra System (Penumbra, Inc, Alameda, CA), and acute angioplasty and stenting. Intra-arterial fibrinolysis with recombinant prourokinase (r-pro-UK) was studied in the first randomized trial of an endovascular therapy, and this study was published in 1999.[168] The Prolyse in Acute Cerebral Thromboembolism (PROACT) II trial of r-pro-UK was positive; however, 2 trials are necessary for any new drug to receive FDA approval. A second trial has not been undertaken, and thus, r-pro-UK has not received FDA approval. Subsequently, the Merci Retrieval System (2004), the Penumbra System (2007), the Solitaire Flow Restoration Device (ev3 Endovascular, Inc, Plymouth, MN; 2012), and the Trevo Retriever (Stryker Neurovascular, Fremont, CA; 2012) were introduced as mechanical means of recanalization based on pivotal studies without noninterventional control groups. None of these devices have an FDA clinical indication because of the need for randomized comparison with medical therapy strategies. However, they were cleared for use by the FDA as mechanical methods for restoring blood flow to occluded arteries based on their

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comparability to predicate devices; drugs do not have a comparable mechanistic approval pathway. On the basis of FDA clearance of the Merci and Penumbra devices, the Centers for Medicare and Medicaid Services now provides hospital reimbursement for these procedures. There is no approved drug, including alteplase, for intra-arterial use, and therefore, it is not differentially reimbursed compared with intravenous rtPA. It is in this complex regulatory and financial environment that clinical treatment decisions must be made and randomized clinical trials must be conducted.

Intra-arterial Fibrinolysis

Evidence for intra-arterial fibrinolysis comes primarily from 2 randomized trials, the randomized PROACT II study and the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT).[168,170] PROACT II was a prospective, phase III randomized trial designed to test the effectiveness of intra-arterial fibrinolysis using r-pro-UK to treat MCA (M1 or M2) occlusions within 6 hours of stroke symptom onset.[168] Selection criteria included NIHSS score ≥4 (except isolated aphasia or hemianopia) and age 18 to 85 years. Among the 180 randomized patients, there was an excess of diabetic patients in the control arm (31% versus 13%) and an excess of baseline CT scan protocol violations in the r-pro-UK arm (10% versus 4%). In the primary intention-to-treat analysis, 40% of the 121 patients treated with r-pro-UK and 25% of the 59 control patients had an mRS score of 0 to 2 at 90 days (P=0.04). MCA recanalization was achieved in 66% of the r-pro-UK arm and 18% of the control group (P=0.001). sICH occurred in 10% of patients treated with r-pro-UK and in 2% of the control group (P=0.06). Mortality in the 2 groups was similar.

MELT compared medical management with intra-arterial urokinase within 6 hours and was stopped prematurely because of Japan's regulatory approval of intravenous rtPA for ischemic strokes within 3 hours.[170,539] At stoppage, rates of the primary end point (mRS score 0–2) were numerically higher in the urokinase-treated group than the control group, but this did not reach statistical significance (49.1% versus 36.8%; P=0.35). The preplanned secondary end point (mRS score 0–1) was achieved in 42.1% of urokinase-treated cases and 22.8% of control cases (P=0.045). sICH occurred in 9% of urokinase-treated cases. Both the treatment effect size and sICH rates were consistent with the results of the PROACT II trial, and meta-analysis (combined with PROACT II) showed cumulative evidence in favor of the intra-arterial fibrinolytic approach.[540,541]

Extrapolation of the randomized trial data to other currently available fibrinolytic agents, including alteplase, is based primarily on consensus and case series data.[542–544] The use of intra-arterial fibrinolysis for occlusions in additional locations, such as the basilar artery and intracranial carotid artery, is based primarily on consensus and case series data as well.[164,246,545–548] Macleod et al[539] randomized 16 patients with angiographic evidence of posterior circulation occlusions who presented within 24 hours of symptom onset to either intra-arterial urokinase or conservative management; both arms underwent anticoagulation with heparin, followed by warfarin. In this small study, good clinical outcomes (defined by a combined mRS and Barthel index end point) were observed in 50% of the intra-arterial urokinase arm compared with 12.5% of the nonurokinase arm (P=0.28).

The intra-arterial approach is thought to be more efficacious for recanalization of proximal arterial occlusions than intravenous fibrinolysis, but the evidence for this is limited. Supportive evidence comes primarily from a cohort study by Mattle et al.[245] They compared stroke outcomes at 2 stroke units, each of which treated exclusively with either intravenous rtPA or intra-arterial urokinase. Favorable outcomes (mRS score 0–2) were seen in 29 (53%) of 55 intra-arterial cases and 13 (23%) of 57 intravenous cases (P=0.001). In addition, a small feasibility study by Sen et al[549] randomized consecutive patients with proximal arterial occlusions on CTA scan within 3 hours of stroke symptom onset to standard intravenous rtPA (0.9 mg/kg) versus intra-arterial rtPA (up to 22 mg over 2 hours). Median NIHSS scores were 17 and 16 and mean ages were 71 and 66 years for the intravenous and intra-arterial arms, respectively. Fibrinolysis was initiated at a mean of 95 minutes for the intravenous arm and 120 minutes for the intra-arterial arm (P=0.4). The intravenous group had 1 sICH, and the intra-arterial group had 1 asymptomatic ICH. All intra-arterial cases had recanalization, and none of the intravenous cases had recanalization (P=0.03). Neurological improvement (a 4-point decrease in NIHSS score at 90 days) was seen in 3 of 4 patients treated with intravenous rtPA and 2 of 3 treated with intra-arterial rtPA.

On the basis of the premise that intra-arterial therapy may be more effective for recanalization of larger thrombi, severe neurological deficits (NIHSS score ≥10) that suggest a proximal arterial occlusion and radiographic evidence of occlusion of a major intracranial vessel have been considered potential indications for the use of intra-arterial therapy. However, this clinical benefit may be counterbalanced by delay to treatment initiation with the intra-arterial approach and consequent late reperfusion, potential risks of periprocedural sedation, and treatment-related complications. Definitive data from randomized controlled trials delineating the relative efficacy of intra-arterial therapy versus intravenous rtPA treatment are lacking at this time.

Intra-arterial fibrinolysis is a consideration for patients ineligible for intravenous rtPA. For example, the PROACT II trial may be applicable to patients eligible for treatment within 6 hours; more definitive data for patients in the extended time window from randomized controlled trials are needed.[550] Recent history of a major surgical procedure poses systemic bleeding risk in the setting of intravenous rtPA and may represent another group for consideration of intra-arterial fibrinolysis. Several small case series of postoperative cardiac surgery cases suggest reasonable safety of intra-arterial fibrinolysis.[551–553] In addition, a retrospective case series of 36 ischemic stroke patients from 6 academic centers treated with intra-arterial fibrinolysis after surgical procedures, including open heart surgery (n=18), CEA (n=6), and urologic-gynecologic surgery (n=4), suggested that intra-arterial rtPA is reasonably safe in the postoperative setting, with the exception of neurosurgical procedures (n=3).[554] Major systemic bleeding occurred in 4 cases, including 3 postcraniotomy ICHs and 1 post–coronary artery bypass graft hemopericardium.

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Rates of good clinical outcome after intra-arterial fibrinolysis are likely to be highly time dependent, as is the case with intravenous rtPA treatment.[92,93,555] If intra-arterial fibrinolysis treatment is planned, an emphasis should be placed on rapid triage, patient transport, and clinical team mobilization.

Combination Intravenous and Intra-arterial Fibrinolysis

Initial studies of fibrinolytic therapy in acute ischemic stroke involved a single pharmacological agent, alteplase, given either intravenously or intra-arterially. It was subsequently proposed that combined intravenous and intra-arterial fibrinolysis may be a more efficient way to rapidly recanalize major intracranial arterial occlusions. This would allow for immediate initiation of intravenous fibrinolysis in an ED, followed by rapid mobilization of the neuroangiographic team and transport of the patient to the angiographic suite for further titrated intra-arterial fibrinolytic therapy, if necessary. This approach could address the concern that delays to intra-arterial therapy may negate the potential benefits of more efficacious recanalization. Proximal intracranial arterial occlusions (distal internal carotid artery, MCA, or basilar artery) may benefit most from this approach because of larger clot burdens that would be more likely to fail treatment with intravenous rtPA alone.

A series of pilot trials have evaluated the combined intravenous/intra-arterial fibrinolytic approach using low-dose rtPA.[556–558] The Emergency Management of Stroke Bridging trial was a retrospective analysis of 20 patients with severe stroke who received intravenous and intra-arterial rtPA within 3 hours from symptom onset.[558] Despite a median baseline NIHSS score of 21, 50% of patients recovered to an mRS score of 0 to 1 on follow-up. The feasibility and suggestion of efficacy led to the creation of the Interventional Management of Stroke (IMS) study. The IMS study enrolled 80 patients 18 to 80 years old with an initial NIHSS score ≥10 who presented within 3 hours of stroke onset.[556] Patients received intravenous rtPA (0.6 mg/kg, 60 mg maximum over 30 minutes) started within 3 hours of stroke symptom onset, followed by additional intra-arterial rtPA (up to 22 mg) at the site of the thrombus if there was a persistent occlusion. The median baseline NIHSS score was 18. The rate of sICH (6.3%) was similar to that of comparable intravenous rtPA–treated subjects (6.6%) in the NINDS rtPA Stroke Trial. The 3-month mortality rate (16%) was similar to the placebo (24%) and intravenous rtPA (21%) arms of the NINDS rtPA Stroke Trial. Reperfusion, as quantified by the Thrombolysis in Cerebral Infarction (TICI) score, which attempts to standardized flow restoration reporting in clinical trials[559] (TICI score 2–3 indicates good reperfusion), was seen in 56% of cases. Good clinical outcomes (mRS score 0–2) were seen in 43% of cases. The subsequent IMS II study enrolled 81 additional patients and, together with combined intravenous/intra-arterial rtPA, delivered low-energy ultrasound by use of the EKOS system whenever possible. The sICH rate (9.9%) and mortality rate (16%) were again comparable to the NINDS rtPA trial. Reperfusion (TICI score 2–3) was seen in 61% of cases. Good clinical outcomes (mRS score 0–2) were seen in 46% of cases. Both studies showed better outcomes than comparable NINDS placebo cases, and IMS II showed statistically better outcomes in secondary outcome analyses. The phase III IMS III trial, with a planned enrollment of 900 patients with an NIHSS score ≥10 treated within 3 hours of stroke symptom onset, was recently stopped for reported futility; further results from the study are pending.[560]

Shaltoni et al[561] evaluated the combined approach using full-dose (0.9 mg/kg) rtPA followed by intra-arterial fibrinolysis (with reteplase, alteplase, or urokinase) in a prospective cohort of ischemic stroke patients at a single center who presented within 3 hours of symptom onset. These patients were routinely offered intra-arterial therapy if they had a persisting disabling neurological deficit or a persistent or reoccluding thrombus by TCD after they completed the 60-minute intravenous rtPA infusion. The sICH rate was 5.8% (4/69) and the mortality rate was 17.4% (12/69). Partial or complete reperfusion (TICI score 2–3) was seen in 72.5% of cases, and favorable outcome (discharge to acute rehabilitation or home) was seen in 55% of cases.

As with intravenous fibrinolysis, reducing the time to reperfusion with endovascular therapies is likely pivotal in achieving the best clinical outcomes. This is supported by a post hoc pooled analysis of the IMS I and II pilot trials that showed that time to reperfusion, as estimated by the time from symptom onset to completion of the intra-arterial procedure, was an independent predictor of the probability of good clinical outcome. When the time to reperfusion was increased by 30 minutes, from 280 to 310 minutes, the probability of a favorable outcome (mRS score 0–2) was 10.6% less likely.[555]

Mechanical Clot Disruption/Extraction

Mechanical thrombectomy is a consideration as both a primary reperfusion strategy and in conjunction with pharmacological fibrinolysis for achieving recanalization in patients with acute ischemic stroke.[562] Recanalization by this means may occur because of a combination of thrombus fragmentation, thrombus retrieval, and enhancement of fibrinolytic penetration. There are currently 4 devices cleared by the FDA for recanalization of arterial occlusion in patients with ischemic stroke. The Merci Retrieval System received FDA clearance in 2004 and consists of the Merci Retriever, the Merci Balloon Guide Catheter, and the Merci Microcatheter. The Merci Retriever uses a memory-shaped nitinol wire with helical loops of decreasing diameter at its distal end to engage the clot. It is advanced through the microcatheter in its compressed form distal to the occlusion. Subsequent withdrawal of the microcatheter deploys the device in its preimposed helical shape. Since initial FDA clearance, the retriever design has been updated, with the newest V series retriever having a series of loops to engage and capture the clot. The Penumbra System received FDA clearance in 2007 and consists of the aspiration pump, reperfusion catheters, and separators. It is designed to aspirate thrombus from large intracranial vessels by placing a reperfusion catheter at the proximal end of the thrombus and connecting it to a vacuum source. A continuous aspiration-debulking process is facilitated by advancing and withdrawing the separator through the Penumbra reperfusion catheter. Since initial FDA clearance, the reperfusion catheter has been modified with a larger, tapered lumen and new polymer composition at the distal end to increase accessibility and aspiration efficiency. A further update consisting

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of a 3-dimensional separator is under investigational study. Most recently, the Solitaire Flow Restoration Device and the Trevo Retriever received FDA clearance in 2012. These are both retrievable stents that are deployed within the thrombus to displace it radially, incorporate it within the stent's struts, and then extract it.

The Merci Retriever was evaluated in patients ineligible for intravenous rtPA and with arterial occlusions who presented within 8 hours of stroke symptom onset in the pivotal single-arm, prospective, multicenter MERCI trial.[563] Recanalization was achieved in 46% (n=69) of the 151 patients on intention-to-treat analysis and in 48% (n=68) of the 141 patients in whom the device was deployed. Clinically significant procedural complications and sICH occurred in 7% and 8% of the patients, respectively. Good neurological outcomes (mRS score 0–2) at 90 days were observed more frequently in patients with successful recanalization than in those with unsuccessful recanalization (46% versus 10%, $P<0.0001$). The Multi MERCI trial[564] studied thrombectomy in patients with ischemic stroke and large-vessel occlusion treated within 8 hours of symptom onset with newer-generation retriever devices. Patients with persistent occlusion after intravenous rtPA treatment were included. One hundred sixty-four patients were treated with thrombectomy, and 131 were treated initially with the new-generation retrievers. Treatment with the new-generation retriever resulted in successful recanalization in 57% of treated arteries and in 70% after adjunctive therapy (intra-arterial fibrinolysis or other mechanical devices). Overall, favorable clinical outcomes (mRS score 0–2) were seen in 36% of the patients, and 34% of the patients died. Clinically significant procedural complications and sICH occurred in 6% and 10% of the patients, respectively.

A subgroup analysis of Multi MERCI trial compared outcomes between patients who did or did not receive intravenous rtPA before thrombectomy.[565] Thirty patients (27%) received intravenous rtPA before thrombectomy. The sICH rate was 7% and 10% in patients pretreated and not pretreated with intravenous rtPA, respectively. Two subgroup analyses compared outcomes in patients with arterial occlusion located at particular sites in the MERCI and Multi MERCI trials. Of the 80 patients with intracranial internal carotid artery occlusion,[566] 53% and 63% had recanalization with the retriever alone and with the retriever and additional endovascular treatment, respectively. Good clinical outcome (mRS score 0–2) at 90 days occurred in 39% of patients with recanalization and in 3% of patients without recanalization. Recanalization remained a significant predictor of a good 90-day outcome in multivariate analysis. In another analysis of 27 patients with vertebrobasilar arterial occlusions, recanalization occurred in 78% of patients after retriever use in the MERCI and Multi MERCI trials.[567] Good clinical outcome (mRS score 0–3) at 90 days occurred in 41% of patients, and 44% died. Another analysis of patients recruited in the MERCI and Multi MERCI trials compared outcomes between patients with abnormal INR >1.7, PTT >45 seconds, or platelet count <100 000/μL and those with normal hemostasis.[568] Rates of partial or complete recanalization, mortality, or major sICH were not significantly different; however, the rate of favorable outcomes was substantially lower among those with abnormal hemostasis (9% versus 35%, $P=0.002$). Another subgroup analysis compared outcomes in similar patients from the MERCI and Multi MERCI cohorts with historical comparators from the active and control arms of the PROACT II trial. Mechanical thrombectomy produced rates of good clinical outcomes (mRS score 0–2; 39.9%) similar to PROACT II patients treated with intra-arterial pro-UK (39.5%) compared with PROACT II control patients (25.4%).[569]

The pivotal Penumbra trial was a prospective, multicenter, single-arm study[570] of 125 patients with NIHSS scores ≥8 who presented within 8 hours of symptom onset and were treated with the Penumbra System.[570] Patients who presented within 3 hours from symptom onset were either ineligible for intravenous rtPA or refractory to intravenous rtPA. Partial or complete recanalization was reported in 82% of the treated vessels, although the operational method for characterizing recanalization was not specified. Procedural complications and sICH occurred in 13% and 11% of the patients, respectively. Overall, favorable clinical outcomes (mRS score 0–2) were seen in 25% of the patients, and 33% of the patients died. Subsequently, Tarr and colleagues[571] conducted a post–FDA approval multicenter retrospective case review of 157 consecutive patients treated with the Penumbra system. Partial or complete target-vessel recanalization was achieved in 87% of patients (54% with Thrombolysis in Myocardial Infarction [TIMI] grade 2 and 33% with TIMI grade 3). Procedural events occurred in 9 patients and device malfunctions in 3. sICH, defined by any evidence of ICH on CT within 24 hours after the procedure and a deterioration of the NIHSS score by >4 points, occurred in 6.4% of patients. At 90 days after stroke, 41% of patients had achieved an mRS score of 0 to 2, and all-cause mortality was 20%.

The pivotal studies of the Solitaire and Trevo devices were published most recently.[572,573] The SWIFT study (Solitaire FR With the Intention for Thrombectomy) compared the recanalization efficacy of Solitaire with the Merci Retrieval System in a randomized, prospective noninferiority trial of 113 subjects with moderate or severe strokes. Eligible subjects were within 8 hours of symptom onset and were either ineligible for or refractory to intravenous rtPA. After a prespecified interim analysis led to early halting of the trial, successful revascularization (TIMI 2–3 recanalization) without symptomatic intracranial hemorrhage was reported in 61% of Solitaire cases versus 24% of the MERCI group ($P<0.001$) based on a blinded assessment. This corresponded to 90-day good neurological outcome rates (mRS score 0–2) of 58% versus 33% ($P=0.001$), respectively, and 90-day mortality rates of 17% versus 38% ($P=0.001$), respectively. The TREVO 2 study (Thrombectomy REvascularization of large Vessel Occlusions) was a similar design with the exception of the primary outcome definition. In this case, the Trevo Retriever was compared with the Merci Retriever in a randomized noninferiority study of 178 subjects. The primary outcome was TICI 2 to 3 angiographic reperfusion assessed in an unblinded manner. The study reported revascularization rates of 86% in the Trevo group versus 60% in the MERCI group ($P<0.0001$). Correspondingly, 90-day good clinical outcomes (mRS score 0–2) were seen in 40% versus 22%, respectively ($P=0.01$), and 90-day mortality was seen in 33% versus 24%, respectively

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(P=0.18). Both studies supported superiority of their devices compared with the predicate Merci device and concluded that prospective randomized studies compared with medical treatment alone were needed.

The IMS III trial studied intravenous rtPA alone compared with combined intravenous rtPA and endovascular therapies including mechanical devices (largely Merci and Penumbra) as an option for the combined intravenous/intra-arterial approach being tested, with the hope of providing additional safety and efficacy data for this approach. It was halted early on the basis of a prespecified interim analysis that demonstrated futility, and detailed results are pending.[574]

Acute Angioplasty and Stenting

Intracranial Acute Angioplasty and Stenting

Increasingly, urgent angioplasty with adjunctive stent deployment is being used to restore antegrade flow, with or without fibrinolysis or clot extraction. The nonrandomized, single-center Stent-Assisted Recanalization in Acute Ischemic Stroke (SARIS) study suggested that direct stenting of the occluded culprit vessel, at least for intracranial locations, is technically effective in restoring flow promptly.[575] Among 20 patients ineligible for or not responsive to intravenous rtPA, partial or complete recanalization was achieved in all patients, sICH occurred in 5%, and fair or better functional outcomes (mRS score 0–3) at 1 month were seen in 60%. The SARIS study provides evidence that additional patients with acute stroke might benefit from expeditious reperfusion with stents, but this approach requires additional study.

Retrievable stents are the newest approach to endovascular recanalization. Examples include the Solitaire FR and Trevo devices. These stent retrievers are deployed within symptomatic intracranial thrombi to reperfuse tissue immediately and then used to engage and retrieve the clot. Removal of the stent eliminates the need for acute double-antiplatelet therapy, as is needed for permanent stent placement. Current data, which are limited to case series, suggest high (80%–90%) recanalization rates and reasonable safety.[576,577] Registries and additional randomized controlled studies are also under way.

Extracranial Acute Angioplasty and Stenting

Angioplasty and stenting of extracranial carotid (or extracranial vertebral arteries) is predominantly performed for stroke prevention rather than acute stroke treatment. However, this therapy has been used on an emergency basis in the setting of acute stroke for 2 situations in particular: when the primary cause of the stroke is attenuation or cessation of flow in the extracranial carotid or vertebral artery, such as with total or near-total occlusion caused by severe atherosclerosis or dissection, and when catheter access to a culprit intracranial thrombus is impeded by severe stenosis of the extracranial carotid, and angioplasty/stenting of the carotid is required before treatment of a more distal intracranial occlusion.

Although there are no completed prospective, randomized controlled trials demonstrating relative efficacy and safety of angioplasty and stenting of the extracranial carotid in acute ischemic stroke, small retrospective case series have reported promising results.[578–585] Nedeltchev et al[582] described angioplasty and stenting of the internal carotid artery in conjunction with intra-arterial fibrinolysis in 25 patients who had acute carotid artery occlusion that caused MCA territory ischemic stroke and compared them with a group of 31 medically treated patients. Favorable outcomes were more frequent (56% versus 26%) among patients who received endovascular treatment. Jovin et al[581] showed that emergency revascularization of internal carotid occlusion with a carotid stent had a high success rate (23 of 25 patients) with low rates of adverse events. Similarly, Nikas et al[578] showed a high rate of procedural success (83%) in 14 patients with atheromatous obstruction and 4 patients with dissection of the internal carotid artery. Imai et al[580] demonstrated that an emergency carotid stent can improve 7-day neurological outcome and may improve midterm clinical outcomes compared with historical controls. In selected patients with acute vertebrobasilar ischemic stroke, angioplasty and stenting of the vertebral artery has been combined with emergency administration of fibrinolytic agents.[585]

The relative role of endovascular versus surgical revascularization of the extracranial carotid artery emergently in acute stroke remains to be determined. No studies have yet been performed to compare the utility of these alternative approaches for revascularization of the extracranial internal carotid artery in acute stroke. Additional studies must be undertaken to define the role of angioplasty and stenting of the extracranial carotid arteries in the early management of acute stroke.

Revascularization Quantification

More emphasis has been placed on deriving information from the initial and postrevascularization angiograms, with emphasis on the site of occlusion, identification of collateral supply to the affected region, and precise definitions of revascularization. There are new data that suggest that this information may be incorporated into a scheme to stratify patients with regard to expected rate of recanalization and short-term outcome after intra-arterial fibrinolysis. The angiographic results of cerebral reperfusion procedures were initially characterized with the TIMI grading system, a 4-point scale from 0 (complete occlusion) to 3 (complete reperfusion) that was originally developed to assess arterial occlusion and perfusion in patients with myocardial infarction.[586] However, the TIMI grading system has several limitations. It does not account for occlusion location or collateral circulation. Even as a measure of anterograde reperfusion, the cardiac TIMI scale cannot be applied to the more complex cerebral vasculature without the creation of additional operational rules. Under the rubric "TIMI scale," recent stroke clinical trials have actually used very different brain-adapted versions of the TIMI, which hampers comparisons and understanding of trial findings.[587] The Qureshi grading system is a scale from 0 (best possible score) to 5 (worst possible score) that angiographically classifies location of arterial occlusions before and after recanalization.[588–590] Other studies have placed emphasis on 2 scales developed specifically for the cerebral circulation to measure recanalization of the primary arterial occlusive lesion and global reperfusion of the distal vascular bed.[530,591] The Arterial Occlusive Lesion (AOL) score is defined on a scale of 0 to 3, ranging from no recanalization to complete recanalization of the primary occlusion. The TICI score was developed in

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2003 in an effort to standardize reporting of revascularization efforts. The TICI score is defined from 0 to 3, ranging from no perfusion to full perfusion with filling of all distal branches.[559] TICI is currently being used in the IMS trial[560] and an ongoing stroke registry.[592]

Additional studies have examined reocclusion and distal fragmentation after a combination of pharmacological fibrinolysis and mechanical thrombectomy. In an analysis of data from 4 prospective acute stroke protocols,[593] distal embolization was defined qualitatively as appearance of an occlusion on a downstream vessel, and arterial reocclusion was defined as subsequent reocclusion of the target vessel after initial recanalization had been achieved. Arterial reocclusion occurred in 18% of these patients, whereas distal embolization occurred in 16% of the 91 patients treated in these protocols. Arterial reocclusion, but not distal embolization, was associated with a lower likelihood of favorable outcome at 1 to 3 months after adjustment for potential confounders. Another analysis of 56 patients[594] who underwent cerebral angiography at 24 hours to determine the status of occlusion after endovascular treatment (compared with immediate postprocedure angiogram) observed subacute recanalization in 16 patients (29%), including additional recanalization in 8 patients with early recanalization. Subacute reocclusion was observed in 5 patients (9%). Subacute recanalization was associated with a trend toward a higher rate of favorable outcome after adjustment for other covariates.

Conclusions and Recommendations

A number of techniques and devices are under study in several trials. Although several devices have resulted in recanalization with acceptable safety, direct comparative data between the devices are not available. The combination of pharmacological fibrinolysis and mechanical thrombectomy appears to have the highest rate of recanalization without any difference in rate of intracranial hemorrhage. As the rate of recanalization has increased, new challenges such as reocclusion, distal fragmentation, and lack of clinical benefit despite complete recanalization have been identified. Consistently, recanalization rates in trials exceed rates of the best clinical outcomes, which suggests the importance of patient selection independent of the technical effectiveness of thrombectomy devices. As with the intra-arterial administration of fibrinolytics, the use of these devices will be limited to those CSCs that have the resources and physician expertise to perform these procedures safely.[595] Lastly, as with intravenous fibrinolysis, *time is brain* for all forms of endovascular reperfusion, and all efforts must be made to reduce time to reperfusion, because the likelihood of favorable outcome is directly linked to the time to reperfusion.[555]

Recommendations

1. **Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered *(Class I; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
2. **Intra-arterial fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the MCA who are not otherwise candidates for intravenous rtPA *(Class I; Level of Evidence B)*. The optimal dose of intra-arterial rtPA is not well established, and rtPA does not have FDA approval for intra-arterial use**. (Revised from the previous guideline[13])
3. **As with intravenous fibrinolytic therapy, reduced time from symptom onset to reperfusion with intra-arterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy *(Class I; Level of Evidence B)*.** (New recommendation)
4. **Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
5. **When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci *(Class I; Level of Evidence A)*. The relative effectiveness of the Penumbra System versus stent retrievers is not yet characterized.** (New recommendation)
6. **The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients *(Class IIa; Level of Evidence B)*. Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in randomized controlled trials to determine the efficacy of such treatments in improving patient outcomes.** (Revised from the previous guideline[13])
7. **Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis *(Class IIa; Level of Evidence C)*.** (Revised from the previous guideline[13])
8. **Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have not responded to intravenous fibrinolysis. Additional randomized trial data are needed *(Class IIb; Level of Evidence B)*.** (New recommendation)
9. **The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established *(Class IIb; Level of Evidence C)*. These devices should be used in the setting of clinical trials.** (Revised from the previous guideline[13])
10. **The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials *(Class IIb; Level of Evidence C)*.** (New recommendation)
11. **The usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients is not well established *(Class IIb;***

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***Level of Evidence C*)**. **Use of these techniques may be considered in certain circumstances, such as in the treatment of acute ischemic stroke resulting from cervical atherosclerosis or dissection *(Class IIb; Level of Evidence C)*. Additional randomized trial data are needed.** (New recommendation)

Anticoagulants

For >50 years, physicians have prescribed intravenously administered anticoagulants for treatment of patients with acute ischemic stroke, but these medications are now used less often.[596,597] The cited reasons for emergency use of these medications to treat stroke include (1) to halt neurological worsening, (2) to prevent early recurrent embolization, and (3) to improve neurological outcomes. Past panels of the AHA concluded that the data about the safety and efficacy of heparin or other emergently administered anticoagulants were either negative or inconclusive.[11,13,598,599] Other groups also have concluded that the data from clinical trials have not established the utility of emergency anticoagulation in treatment of patients with recent ischemic stroke.[143,600,601]

Anticoagulants often were prescribed to patients with recent stroke in an effort to prevent early recurrent cardioembolic stroke, including those with atrial fibrillation. The Cerebral Embolism Study Group estimated that the risk of early recurrent embolism was ≈12% among untreated patients with embolic stroke.[602,603] Subsequently, a trial found that the risk of recurrent stroke within 1 week was ≈8% among patients with atrial fibrillation.[604] Other trials testing anticoagulants administered immediately after stroke have reported much lower rates (≈0.3%–0.5% per day).[605–607] These relatively low rates mean that detection of a therapeutic effect from anticoagulants for prevention of early recurrent embolism will be difficult to achieve.

Unfractionated Heparin

The International Stroke Trial (IST) tested subcutaneously administered unfractionated heparin (UFH) in doses of 5000 or 25 000 U/d started within 48 hours of stroke.[606] Dual randomization meant that approximately half of the patients receiving heparin were also prescribed aspirin. Neither monitoring of the level of anticoagulation nor adjustment of dosages in response to levels of anticoagulation was performed. In addition, some patients did not have a brain imaging study before entry into the trial, and thus, some patients with hemorrhagic stroke may have been enrolled. Although heparin was effective in lowering the risk of early recurrent stroke, an increased rate of bleeding complications negated this benefit. A subgroup analysis did not find a benefit from heparin in lowering the risk of recurrent stroke among those patients with atrial fibrillation.[608]

Other studies of anticoagulation similarly failed to show definitive benefit. A Swedish study failed to demonstrate a benefit from heparin for treatment of patients with progressing stroke.[609] A single-center Italian trial enrolled patients within 3 hours after onset of stroke and treated patients with an infusion of intravenous heparin starting with a bolus dose, with adjustments in dosage in response to aPTT.[610] Thirteen of 208 heparin-treated patients had symptomatic hemorrhagic complications (6.2%; 7 fatal), whereas 3 of 210 control patients (1.4%) had sICH. Favorable outcomes at 90 days were reported in 81 patients treated with heparin (38.9%) and 60 control patients (28.6%). Given the results of this trial, the authors concluded that additional study of very early administration of heparin in patients with cardioembolic stroke was reasonable.[611] A multicenter European trial administered heparin to 32 patients and aspirin to 35 patients before it was halted prematurely.[612] The investigators reported no significant differences in outcomes, rates of recurrent ischemic stroke, symptomatic hemorrhage, or death between the 2 treatment groups. Sandercock et al[613] performed a systemic review of anticoagulants in treatment of acute ischemic stroke and concluded that treatment with immediate anticoagulant therapy was not associated with any net short- or long-term benefit.

A meta-analysis of anticoagulants in patients with presumed cardioembolic stroke found that the agents were associated with a nonsignificant reduction in the rate of early recurrent stroke, an increased risk of ICH, and no reduction in either death or disability.[614] The safety and efficacy of heparin, given as an interim therapy for those patients with atrial fibrillation who were beginning to receive oral anticoagulants, was evaluated in an observational study.[615] Heparin did not reduce the risk of thromboembolic events or increase the risk of bleeding complications, but the heparin bridging did prolong hospitalization. Besides an associated risk of bleeding, the administration of heparin to patients with acute ischemic stroke may be complicated by the development of heparin-induced thrombocytopenia.[616]

Lower-Molecular-Weight Heparins and Danaparoid

The utility of several different low-molecular-weight heparins (LMWHs) or danaparoid in treating patients with acute ischemic stroke has been evaluated in clinical trials. Most trials tested subcutaneous administration of these anticoagulants. Some trials compared these medications to UFH or aspirin, whereas others have compared these medications to control or placebo. Generally, the results of these trials were negative.

Early increased hemorrhage risk was found in most early LMWH trials, outweighing early prevention benefits. Kay et al[617] tested 2 doses of nadroparin given over a 10-day period after stroke. Although a benefit was not found at 3 months, those who received the larger dose of nadroparin had a significantly lower mortality at 6 months than the control group. Another trial of nadroparin did not find improvement in favorable outcomes but found an increased risk of bleeding with the higher of the 2 doses of the medication.[618] In a Norwegian trial, dalteparin was not more effective than aspirin in preventing recurrent events, and more bleeding was seen with the LMWH.[604] A subsequent subgroup analysis did not demonstrate any group of patients who would have benefited from dalteparin.[619] Similar trials of certoparin and tinzaparin demonstrated no differences in the rates of favorable outcomes.[620,621]

Intravenous administration of danaparoid (heparinoid/ORG 10172) using a bolus to initiate therapy was tested in a randomized, double-blind, placebo-controlled trial.[607] The trial halted recruitment of patients with moderately severe stroke (NIHSS scores >15) because of an increased risk of symptomatic hemorrhage. Danaparoid did not lessen the risk of

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early recurrent stroke or neurological worsening or improve outcomes at 3 months. The trial included prespecified subgroup analyses among patients with different subtypes of ischemic stroke. The only subgroup that showed potential benefit from treatment was those subjects who had stroke secondary to large-artery atherosclerosis (>50% stenosis), in which favorable outcomes were noted in 64 of 119 patients treated with danaparoid (53.8%) and 41 of 108 patients given placebo (38.0%; P=0.023) at 7 days.[622] This finding is supported by the results of a study that found that the likelihood of early recurrent stroke was greatest among people with severe atherosclerotic disease of large arteries.[623] As a result, a randomized trial in Singapore and Hong Kong compared aspirin or nadroparin administered within 48 hours of stroke to Asian patients with occlusive disease of larger arteries.[624] Almost all of the patients had severe stenosis or occlusions of intracranial arteries, but the trial enrolled few patients with extracranial disease. No differences in the rate of hemorrhage or rates of favorable outcomes were found. Woessner et al[625] studied the usefulness of subcutaneously administered enoxaparin or adjusted-dose heparin in a multicenter trial that enrolled patients with either high-grade arterial stenoses or a cardioembolic source; no significant differences were noted between the 2 groups.

Bath et al[626] performed a meta-analysis of trials that tested aspirin or LWMHs. They found that the LMWHs significantly reduced the risk of venous thromboembolism but increased the risk of symptomatic bleeding. No differences were found in mortality, rate of recurrent stroke, or rate of neurological worsening. They concluded that LMWH should not replace aspirin in the routine management of patients with ischemic stroke. Another trial compared enoxaparin or UFH for prevention of thromboembolic events among patients with stroke that caused lower-limb paralysis; the 2 medications were equally effective.[627] Diener et al[628] compared certoparin or heparin in prevention of thromboembolic events after stroke. The LMWH was found to be at least as effective as UFH for prevention of these complications. In the Prevention of VTE After Acute Ischemic Stroke With LMWH Enoxaparin (PREVAIL) study, the usefulness of subcutaneous administration of either heparin or enoxaparin was tested for the prevention of symptomatic or asymptomatic DVT or pulmonary embolism (PE).[629] The risk of venous thromboembolism was significantly less with enoxaparin (68 [10%] versus 121 [18%]; risk ratio, 0.57; 95% CI, 0.44–0.76; P=0.001.) The rates of hemorrhage were similar in the 2 treatment groups. Overall, this study gives the strongest evidence of the superiority of LMWH in prevention of venous thromboembolism after ischemic stroke. In 2008, Sandercock et al[630] published an update of the Cochrane Systemic Review comparing the utility of UFH and LMWH. They found that the LMWHs were effective in lowering the risk of DVT, but the data were insufficient to determine whether these medications were superior to UFH when other potential therapeutic end points were examined.

Anticoagulants as an Adjunctive Therapy

The administration of either antiplatelet agents or anticoagulants is currently contraindicated during the first 24 hours after treatment with intravenous rtPA. The restriction is based on the clinical trial protocol used in the NINDS trials.[166] However, arterial reocclusion may follow successful recanalization with fibrinolysis.[290,593,594] In addition, cardiologists often prescribe anticoagulants and antiplatelet agents as part of a multimodality treatment regimen for management of acute coronary artery occlusions. Thus, there is interest in the use of an anticoagulant or antiplatelet agent that may maintain arterial patency after fibrinolytic therapy. The trials of intra-arterially administered r-pro-UK used heparin as part of the treatment regimen, and the control group received only heparin.[168,631,632] In the first study, both the success of recanalization and the risk of bleeding were increased among the subjects who received the larger of the 2 doses of adjunctive heparin. Intravenous heparin has been administered after administration of intravenous rtPA.[633,634] No increase in bleeding complications was reported. Heparin has been given in addition to abciximab with a reasonable degree of safety[635]; however, neither the safety nor efficacy of adjunctive anticoagulation has been established, and additional research is required.

Thrombin Inhibitors

Direct thrombin inhibitors may be useful in acute ischemic stroke because of their actions that limit thrombosis. These medications could be considered as an alternative to anticoagulants, and they could be administered to those people who develop heparin-associated thrombocytopenia. Dabigatran, a direct thrombin inhibitor, has been evaluated over the past decade for the prevention of thromboembolic events in patients after orthopedic procedures. More recently, in the RE-LY study (Randomized Evaluation of Long-term Anticoagulation Therapy), dabigatran demonstrated benefit compared with warfarin for the prevention of stroke or systemic embolization in patients with atrial fibrillation.[636] At lower doses, dabigatran was noninferior to warfarin while demonstrating fewer hemorrhagic complications. At higher doses, dabigatran was more effective than warfarin but had similar bleeding risk. In October 2010, the FDA approved the higher 150-mg twice-a-day dose for stroke prevention in patients with atrial fibrillation. For patients with impaired renal function, a lower 75-mg twice-a-day dose is recommended. A dose-escalation study of argatroban, also a direct thrombin inhibitor, found that it prolonged aPTT levels but did not increase mortality or the risk of serious bleeding.[637] A Japanese study retrospectively examined the impact of argatroban on outcomes among patients with cardioembolic stroke.[638] It concluded that argatroban may be superior to heparin in reducing mortality and improving outcomes after strokes. A single case in which argatroban was successfully administered in addition to intravenous and intra-arterial fibrinolysis was also reported.[637] Additional research is ongoing regarding the role of argatroban in the treatment of patients with acute stroke.

Conclusions and Recommendations

The results of several clinical trials demonstrate there is an increased risk of bleeding complications with early administration of either UFH or LMWH. Early administration of anticoagulants does not lessen the risk of early neurological worsening. Data indicate that early administration of UFH or LMWH does not lower the risk of early recurrent stroke,

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including among people with cardioembolic sources. Data are insufficient to indicate whether anticoagulants might be effective among some potentially high-risk groups, such as those people with intracardiac or intra-arterial thrombi. The effectiveness of urgent anticoagulation is not established for treatment of patients with arterial dissection or vertebrobasilar disease. The role of anticoagulants as an adjunct in addition to mechanical or pharmacological fibrinolysis has not been established.

Dabigatran was recently approved for the prevention of stroke and systemic embolism in patients with atrial fibrillation. The timing of initiation after stroke and the usefulness of other antithrombin medications have not been established.

Recommendations

1. **At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with acute ischemic stroke is not well established *(Class IIb; Level of Evidence B)*. These agents should be used in the setting of clinical trials.** (New recommendation)
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 *(Class IIb; Level of Evidence B)*.** (New recommendation)
3. **Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke, is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
4. **Urgent anticoagulation for the management of noncerebrovascular conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications *(Class III; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
5. **Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recommended *(Class III; Level of Evidence B)*.** (Unchanged from the previous guideline[13])

Antiplatelet Agents

Oral Agents

Aspirin is the antiplatelet agent that has been tested the most extensively. Two large trials each demonstrated a nonsignificant trend in reduction in death or disability when treatment with aspirin was begun within 48 hours of stroke.[605,606] A minor increase in bleeding complications was found. When the data from the 2 trials were combined, a modest but statistically significant benefit was noted with aspirin therapy. The primary effect was likely attributable to prevention of recurrent events. It is not clear whether aspirin limited the neurological consequences of the acute stroke itself.

There has been limited experience with the use of clopidogrel or dipyridamole in the setting of acute stroke. Initiation of treatment with clopidogrel in a daily dose of 75 mg does not produce maximal inhibition of platelet aggregation for ≈5 days.[639] This delay presents a problem for an early treatment effect in the management of patients with acute ischemic stroke. A bolus dose of 300 to 600 mg of clopidogrel rapidly inhibits platelet aggregation. A loading dose of clopidogrel followed by daily doses of 75 mg has been used to treat patients with acute myocardial ischemia. Suri et al[640] administered 600 mg of clopidogrel to 20 patients with a mean interval from stroke of 25 hours. No cases of neurological worsening or intracranial hemorrhage were reported. Another pilot study evaluated the administration of 325 mg of aspirin and 375 mg of clopidogrel to patients within 36 hours of a recent stroke or TIA.[641] The combination was found to be safe, and there was a suggestion that neurological deterioration could be prevented. A small Thai study reported the combination of aspirin and dipyridamole also could be administered safely within 48 hours of onset of stroke.[642] Overall, these data do not provide solid evidence about the utility of these antiplatelet agents in the management of patients with acute ischemic stroke.

More recently, 2 trials have investigated the early use of antithrombotic drugs in acute stroke. The EARLY trial was an open-label, randomized, multicenter German study of patients with acute ischemic stroke who received 100 mg of aspirin monotherapy or 25 mg of aspirin plus 200 mg of extended-release dipyridamole within 24 hours of stroke or TIA or after 7 days of aspirin monotherapy.[643] Of the 543 patients enrolled in both groups, 56% of patients given the combination regimen achieved an mRS of 0 or 1 at 90 days compared with 52% of patients who received aspirin monotherapy. Vascular adverse events, assessed as a composite end point, occurred in 10% and 15% of the early- and late-initiation groups respectively. The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) pilot trial also recruited patients with ischemic stroke or TIA in a similar study design but only enrolled patients with minor stroke (NIHSS score <4).[644] In a factorial design, patients were randomized to clopidogrel or placebo and simvastatin or placebo within 24 hours of their qualifying event. After enrolling 394 patients, the study was stopped prematurely because of the increased use of statins in general. Patients who received clopidogrel had a 90-day stroke risk of 7.1% compared with 10.8% in the placebo arm (adjusted risk ratio, −3.8%; P=0.019). Two patients who received clopidogrel developed intracranial hemorrhage compared with none in the placebo group. These 2 studies suggest that in patients who did receive fibrinolytic therapy, the early initiation of antithrombotic therapy for the secondary prevention of recurrent stroke appears to be as safe as later initiation.

Intravenous Antiplatelet Agents

Inhibitors of the platelet glycoprotein IIb/IIIa receptor are being considered for treatment of acute ischemic stroke because they may increase the rate of recanalization and improve patency of the microcirculation.[645,646] A series of studies evaluated one of these agents, abciximab. These included case reports and small clinical series; in some cases, the agent was given as monotherapy and in others as an adjunct, usually with pharmacological fibrinolysis or mechanical thrombectomy.[545,635,647–653] Abciximab also was tested in a clinical research program that included a dose-escalation study, a phase II dose-confirmation study, and a phase III clinical trial.[654–656] On the basis of the findings of the first 2 studies, the dose

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and regimen of abciximab used to treat patients with acute coronary lesions were found to have a reasonable safety profile.[654,655] In the phase II trial, there was a trend for an improvement in the rate of favorable outcomes among patients treated within 5 hours of stroke.[655] Unfortunately, interim analysis of the first 439 patients in the phase III trial did not demonstrate an acceptable risk-benefit ratio for treatment with abciximab, which led to the trial being halted.[656] As part of the phase III trial, the investigators also tested the use of abciximab for treatment of patients with stroke present on awakening. The trial found that the risk of bleeding with abciximab in this situation was beyond the desirable safety margins, and the trial halted recruitment of this group in advance of the remainder of the trial.[657]

Other parenterally administered glycoprotein IIb/IIIa receptor blockers also are being studied as monotherapy or as an adjunct to other recanalization interventions to treat patients with acute ischemic stroke. Most reports involve small series of patients who were treated with either tirofiban or eptifibatide.[658–663] Although the use of abciximab to treat acute ischemic stroke caused more hemorrhages, tirofiban did not increase the incidence of cerebral hemorrhagic transformation or parenchymal hemorrhage but may have lowered the mortality rate at 5 months in a phase II trial.[664] SaTIS (Safety of Tirofiban in Acute Ischemic Stroke) was a prospective, randomized, placebo-controlled, open-label treatment phase II trial that enrolled 260 patients at 11 centers. In this trial, ischemic stroke patients between 18 and 82 years old with an NIHSS score of 4 to 18 and within 3 to 22 hours of symptom onset were treated with intravenous tirofiban (0.4 μg/kg initial infusion over a 30-minute period, followed by 0.1 μg/kg continuous infusion for 48 hours). Approximately 1% of patients treated developed reversible thrombocytopenia. More patients in the placebo arm were taking aspirin. Of the 3 glycoprotein IIb/IIIa antagonists, tirofiban differs pharmacologically from abciximab and eptifibatide. Perhaps the relatively safer hemorrhagic profile demonstrated in SaTIS is related to tirofiban being a nonpeptide glycoprotein IIb/IIIa antagonist with a biological half-life of 4 to 8 hours and a return of platelet function in 2 hours when stopped.

Recently, the results of the Combined Approach to Lysis Utilizing Eptifibatide and rtPA in Acute Ischemic Stroke (CLEAR) trial were published.[532] This randomized, double-blind, dose-escalation study tested the combination of eptifibatide (75 mg/kg bolus and infusion 0.75 $mg \cdot kg^{-1} \cdot min^{-1}$) and rtPA either 0.3 mg/kg or 0.45 mg/kg IV compared with the conventional dose of intravenous rtPA alone. The study found the combination to be safe, although there was a trend toward better outcomes among those patients who received the conventional dose of intravenous rtPA alone. The investigators are currently conducting a follow-up phase II study, CLEAR-ER.

Most recently, Zinkstok and colleagues[665] compared the safety and efficacy of early administration of intravenous aspirin started within 90 minutes after initiation of intravenous rtPA therapy to intravenous rtPA alone in a multicenter, randomized, open-label study. In both groups, oral aspirin therapy was initiated 24 hours after intravenous rtPA. After 642 of a planned 800 patients were enrolled, the trial was terminated prematurely because of an excess of sICH in the aspirin treatment arm. Patients in the combined intravenous aspirin and rtPA group were more than twice as likely to develop sICH as the group given intravenous rtPA alone (4.3% versus 1.6% respectively; P=0.04). There was no significant difference in 90-day outcomes between the combined versus rtPA-alone groups (mRS score 0–2, 57.2% versus 54.0%, respectively).

Conclusions and Recommendations

Currently available data demonstrate a small but statistically significant decline in mortality and unfavorable outcomes with the administration of aspirin within 48 hours after stroke. It appears that the primary effects of aspirin are attributable to a reduction in early recurrent stroke. Data regarding the utility of other antiplatelet agents, including clopidogrel alone or in combination with aspirin, for the treatment of acute ischemic stroke are limited. In addition, data on the safety of antiplatelet agents when given within 24 hours of intravenous fibrinolysis are lacking. The relative indications for the long-term administration of antiplatelet agents to prevent recurrent stroke are included in other guideline and advisory statements.[302,666]

Research into intravenously administered antiplatelet agents is ongoing. An international trial did not demonstrate an acceptable safety/benefit profile for abciximab when it was administered within 6 hours of acute ischemic stroke. Other agents are being tested in conjunction with mechanical or pharmacological fibrinolysis. Considerably more research is needed to determine whether these agents have a role in the management of patients with acute ischemic stroke.

Recommendations

1. **Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients *(Class I; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
2. **The usefulness of clopidogrel for the treatment of acute ischemic stroke is not well established *(Class IIb; Level of Evidence C)*. Further research testing the usefulness of the emergency administration of clopidogrel in the treatment of patients with acute stroke is required.** (Revised from the previous guideline[13])
3. **The efficacy of intravenous tirofiban and eptifibatide is not well established, and these agents should be used only in the setting of clinical trials *(Class IIb; Level of Evidence C)*.** (New recommendation)
4. **Aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including intravenous rtPA *(Class III; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
5. **The administration of other intravenous antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended *(Class III; Level of Evidence B)*.** (Revised from the previous guideline[13]) **Further research testing the usefulness of emergency administration of these medications as a treatment option in patients with acute ischemic stroke is required.**
6. **The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of intravenous fibrinolysis is not recommended *(Class III; Level of Evidence C)*.** (Revised from the previous guideline[13])

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Volume Expansion, Vasodilators, and Induced Hypertension

Ischemic stroke results from occlusion of an artery with subsequent reduction in regional cerebral blood flow, demarcated into 2 distinct regions consisting of regional cerebral blood flow alterations: severe reduction (core) and moderate reduction (penumbra).[667,668] The penumbra remains viable for hours because some degree of blood flow is sustained through collateral supply and arteriolar dilation.[669,670] For >3 decades, investigators have studied interventions aimed at increasing cerebral perfusion in acute ischemic stroke by either improving flow through partially occluded vessels or improving flow through cerebral collateral circulation. These approaches have targeted acute alterations of blood rheology, expansion of blood volume, and increased global or local blood pressure. To date, no acute clinical trial has demonstrated unequivocal efficacy, but several ongoing trials may provide a new, widely applicable therapy for patients with ischemic stroke.

Hypervolemia and Hemodilution for Treatment of Acute Ischemic Stroke

Increased viscosity has been observed in the acute period of ischemic stroke because of volume depletion, leukocyte activation, red cell aggregation, elevated fibrinogen levels, and reduced red cell deformability.[671–675] A higher hematocrit is associated with reduced reperfusion, greater infarct size, and higher mortality among patients after ischemic stroke.[671,674] Hemodilution and volume expansion are proposed as treatment options to reduce the viscosity of blood, improve flow through collateral channels and microvascular circulation, and increase oxygen-carrying capacity.[676–682]

A meta-analysis of 18 trials[683] in which hemodilution was initiated within 72 hours of symptom onset was reported. A combination of phlebotomy and plasma volume expanders was used in 8 trials, and volume expansion alone was used in 10 trials. The plasma volume expander was dextran 40 in 12 trials, hydroxyethyl starch in 5 trials, and albumin in 1 trial. Hemodilution did not significantly reduce deaths within the first 4 weeks (OR, 1.1; 95% CI, 0.9–1.4) or within 3 to 6 months (OR, 1.0; 95% CI, 0.8–1.2). The proportion of patients with death, dependency, or institutionalization was similar in both groups (OR, 1.0; 95% CI, 0.8–1.2). There was no increased risk of serious cardiac events among patients with hemodilution.

Vasodilatation in Acute Ischemic Stroke

Techniques to promote vasodilation have been studied in acute stroke for >4 decades. Initially, vasodilatation was studied as a way to treat and prevent TIAs. More recently, vasodilation with methylxanthine derivatives, specifically pentoxifylline, propentofylline, and pentifylline, has been evaluated in the setting of acute ischemic stroke. In addition to the vasodilatation, the methylxanthine drugs may also reduce blood viscosity, increase erythrocyte flexibility, inhibit platelet aggregation, and decrease free radical production. Most methylxanthine-class trials have investigated the promotion of vasodilation in the subacute time frame. In a small randomized trial of 110 Chinese patients with acute cortical and lacunar strokes, Chan and Kay[684] initiated vasodilation using pentoxifylline in combination with aspirin within 36 to 48 hours from stroke onset and continued for 5 days. At 1 week, there was no difference in outcomes for patients with lacunar stroke between the treatment arms. They did report a statistically significant reduction in morbidity in patients with cortical strokes.[684] Subsequent studies have failed to reproduce this effect, and a Cochrane review of the 4 pentoxifylline trials and the 1 propentofylline study found there was not enough available evidence to reliably assess the effectiveness and safety of methylxanthine drugs in acute ischemic stroke.[685]

Induced Hypertension for the Management of Acute Ischemic Stroke

Increasing the systemic blood pressure may improve regional cerebral blood flow as a result of augmentation of flow through collaterals and arterioles that do not demonstrate an autoregulatory constrictive response to pathological vasodilation.[686–690] The clinical response is varied because of variations in collateral formation and preservation of autoregulatory vasoconstriction, systemic blood pressure response, and presence of a penumbra.

Rordorf et al[691] retrospectively reviewed a group of patients admitted with the diagnosis of ischemic stroke, of whom 33 were not given a pressor agent and 30 were treated with phenylephrine within 12 hours of symptom onset. There was no significant difference in morbidity or mortality between the 2 groups of patients. In 10 of 30 patients treated with induced hypertension, a systolic blood pressure threshold (mean 156 mm Hg) was identified below which ischemic deficits worsened and above which deficits improved. The mean number of stenotic/occluded arteries was greater in patients with an identified clinical blood pressure threshold for improvement subsequent to induced hypertension. A second pilot study[692] used phenylephrine to raise the systolic blood pressure in patients with acute stroke by 20%, not to exceed 200 mm Hg. Of 13 patients treated, 7 improved by 2 points on the NIHSS. No systemic or neurological complications were observed. Marzan et al[693] reported the results of induced hypertension (10%–20% of the initial value) using norepinephrine within a mean period of 13 hours after symptom onset. The dose was gradually reduced after 12 hours of administration and terminated when arterial blood pressure remained stable. Early (within 8 hours of initiation) neurological improvement by ≥2 points on the NIHSS was seen in 9 (27%) of 33 patients. Intracranial hemorrhage occurred in 2 patients. Hillis et al[694] randomized consecutive series of patients with large diffusion-perfusion mismatch to induced blood pressure elevation (n=9) or conventional management (n=6). Serial DWI and perfusion-weighted MRI studies were performed before and during the period of induced hypertension. Patients who were treated with induced hypertension showed significant improvement in NIHSS score from day 1 to day 3, cognitive score, and volume of hypoperfused tissue. High correlations were observed between the mean arterial pressure and accuracy on daily cognitive tests. Koenig et al[695] reported analysis of 100 patients who underwent perfusion-weighted MRI after acute ischemic stroke, of whom 46 were treated with induced hypertension with various vasopressors. The target mean

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arterial pressure augmentation of 10% to 20% above baseline was achieved in 35% of the 46 treated patients. Compared with 54 patients who underwent conventional treatment, NIHSS scores were similar during hospitalization and discharge, with no clear difference in rates of adverse events. Shah et al[696] reported 3 patients who received induced hypertension, not to exceed 180 mm Hg, after partial recanalization using intra-arterial fibrinolysis and noted favorable outcomes and no complications.

The available evidence suggests that a small subset of patients with ischemic stroke in the very acute period may benefit from modest (10%–20%) pharmacological elevation in systemic blood pressure. No clear criteria are validated for selection of such patients, although patients with large perfusion deficits caused by steno-occlusive disease who are not candidates for fibrinolytic and interventional treatments are the best studied, as well as those patients who demonstrate neurological change that correlates with systemic blood pressure changes. A short period (30–60 minutes) of a vasopressor infusion trial may help identify patients who are potential responders to such treatment.

Albumin for Treatment of Acute Ischemic Stroke

Albumin exerts its purported neuroprotective effect by reducing both endogenous and exogenous oxidative stress, maintaining plasma colloid oncotic pressure, and preserving microvascular integrity in focal cerebral ischemia.[697] In experimental models of focal ischemia, albumin reduces ischemic brain swelling, improves regional cerebral blood flow, reduces postischemic thrombosis, improves microvascular flow, and supplies free fatty acids to the postischemic brain.[672,698,699] In several observational studies,[700,701] low serum albumin at admission correlated with higher rates of death and disability among patients with ischemic stroke. Subsequently, the ALIAS (Albumin in Acute Stroke) Pilot Clinical Trial evaluated 6 doses (0.34–2.05 g/kg)[702,703] of 2-hour infusion of 25% human albumin beginning within 16 hours of stroke onset in patients with acute ischemic stroke. Eighty-two subjects received albumin, and 42 of those patients also received intravenous rtPA. The only albumin-related adverse event was mild or moderate pulmonary edema in 13% of the subjects, which confirms reasonable tolerability among patients with acute ischemic stroke without major dose-limiting complications. After adjustment for the intravenous rtPA effect, the probability of good outcome (defined as mRS score 0–1 or NIHSS score 0–1 at 3 months) at the highest 3 albumin tiers was 81% greater than in the lower-dose tiers and was 95% greater than in the comparable NINDS rtPA Stroke Trial historical cohort. The intravenous rtPA–treated subjects who received higher-dose albumin were 3 times more likely to achieve a good outcome than subjects receiving lower-dose albumin. The trial suggested that high-dose albumin treatment may be neuroprotective after ischemic stroke, with a synergistic effect between albumin and intravenous rtPA. A large, randomized, multicenter, placebo-controlled efficacy trial, the phase III ALIAS2 Trial,[704] compared 2.0 mg/kg of 25% albumin administered over 2 hours with placebo, with treatment initiated within 5 hours of stroke onset. The primary efficacy end point was either an NIHSS score of 0 to 1, an mRS score of 0 to 1, or both at 3 months.[704] An interim safety analysis of the first 436 subjects led to modifications in the study design to enhance safety and minimize development of congestive heart failure.[705] An exploratory efficacy analysis of the part 1 study data suggested a trend toward favorable outcomes in patients in the albumin arm.[706] In the fall of 2012, the study's data safety and monitoring board stopped recruitment after an interim analysis, and further results from the study are pending.

Mechanical Flow Augmentation

Mechanical methods to increase cerebral perfusion through Willisian and leptomeningeal collaterals offer the prospect of improving cerebral blood flow without the complications of vasopressor pharmacological agents. Data from animal models and from human research demonstrate that aortic occlusion, which is commonly performed by cross-clamping the descending aorta for vascular control during aortic surgery, results in net flow diversion to the cerebral from the lower-extremity circulatory beds, thereby increasing cerebral blood flow.[707–715] This evidence generated the development of a catheter-based device with 2 balloons near its distal tip placed in the infrarenal and suprarenal positions in the descending aorta (NeuroFlo device; CoAxia, Maple Grove, MN). After insertion via the femoral artery, the balloons are inflated sequentially up to ≈70% of the diameter of the aortic lumen over a period of 45 minutes to an hour, followed by removal.[716] A clinical feasibility study in acute ischemic stroke enrolled 17 patients up to 12 hours after symptom onset and showed an improvement in neurological symptoms in >50% of patients during treatment and at 24 hours.[717] A randomized controlled multicenter trial enrolling patients with ischemic stroke within 14 hours of symptom onset was completed in 2010. Results recently published in *Stroke* failed to show significant differences in clinical outcome, but no issues of safety were noted.[718,719] There was a statistically nonsignificant trend in lowering mortality in the treatment group compared with controls (11.3% versus 6.3%, respectively).

Another method that shows potential for augmenting cerebral blood flow is extracorporeal counterpulsation therapy, which is approved for patients with ischemic heart disease who have refractory angina. This therapy is provided by a device that inflates pneumatic cuffs on the lower extremities in sequential fashion during each cardiac cycle to augment diastolic flow in the coronary arteries and improve systolic unloading in the periphery.[720] There is also evidence that it may develop and recruit collateral vessels in ischemic myocardium.[721] In the cerebral bed, studies have demonstrated extracorporeal counterpulsation–induced diastolic augmentation of flow in the carotid arteries[722] and, more recently, the MCAs.[723] In addition, a small pilot trial of subacute extracorporeal counterpulsation in the first 2 months after stroke onset was encouraging.[724] On the basis of these findings, a randomized dose-ranging trial is ongoing in patients with acute ischemic stroke who are outside the therapeutic time window for intravenous fibrinolysis or endovascular therapy.

Augmentation of cerebral collateral blood flow is a compelling concept that may hold promise in the treatment of acute

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ischemic stroke. Although the aforementioned treatments appear to warrant further investigation, there are currently no data to support their use in this population of patients.

Recommendations

1. **In exceptional cases with systemic hypotension producing neurological sequelae, a physician may prescribe vasopressors to improve cerebral blood flow. If drug-induced hypertension is used, close neurological and cardiac monitoring is recommended *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
2. **The administration of high-dose albumin is not well established as a treatment for most patients with acute ischemic stroke until further definitive evidence regarding efficacy becomes available *(Class IIb; Level of Evidence B)*.** (New recommendation)
3. **At present, use of devices to augment cerebral blood flow for the treatment of patients with acute ischemic stroke is not well established *(Class IIb; Level of Evidence B)*. These devices should be used in the setting of clinical trials.** (New recommendation)
4. **The usefulness of drug-induced hypertension in patients with acute ischemic stroke is not well established *(Class IIb; Level of Evidence B)*.** (Revised from the previous guideline[13]) **Induced hypertension should be performed in the setting of clinical trials.**
5. **Hemodilution by volume expansion is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence A)*.** (Revised from the previous guideline[13])
6. **The administration of vasodilatory agents, such as pentoxifylline, is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence A)*.** (Unchanged from the previous guideline[13])

Neuroprotective Agents

Neuroprotection refers to the concept of applying a therapy that directly affects the brain tissue to salvage or delay the infarction of the still-viable ischemic penumbra, rather than reperfusing the tissue. Because many potential neuroprotective therapies are likely safe and potentially efficacious in hemorrhagic as well as ischemic stroke, the ideal neuroprotective therapy would be initiated as early as possible in the course of therapy, including in the prehospital setting, and be continued while other measures are instituted, such as brain imaging followed by fibrinolytic or endovascular revascularization.

Pharmacological Agents

Pharmacological agents that limit the cellular effects of acute ischemia or reperfusion may limit neurological injury after stroke. Potential therapeutic strategies include curbing the effects of excitatory amino acids, such as glutamate, transmembrane fluxes of calcium, intracellular activation of proteases, apoptosis, free radical damage, inflammatory responses, and membrane repair. More than 1000 published reports of various experimental neuroprotective treatments for acute stroke exist, culminating in well over 100 clinical trials.[725,726] Most clinical trials testing these therapies have produced disappointing results. In some circumstances, treated patients had worse outcomes than did control subjects, or the rates of adverse events were unacceptably high.[727] Most of the early neuroprotection studies initiated therapy past the commonly accepted 4- to 6-hour therapeutic window.[697] Although some of these clinical studies were small or poorly designed, others have been sufficiently large and methodologically strong to produce important information.[728] Newer agents and innovative clinical trial designs that adhere to the STAIR (Stroke Therapy Academic Industry Roundtable) criteria are needed to demonstrate that neuroprotective strategies could be helpful in treatment of stroke.[550]

Nimodipine is approved for the prevention of ischemic stroke among people with recent aneurysmal subarachnoid hemorrhage.[729] Nimodipine was tested in a large number of primary ischemic stroke clinical trials with generally negative results.[413,430,730–732] In some cases, outcomes were worse among patients treated with nimodipine than among control subjects.[430,732] Presumably, the higher rates of poor outcomes were secondary to the antihypertensive effects of nimodipine.[430] Trials of flunarizine, isradipine, and darodipine were also negative.[733–735] Although nicardipine is used to treat elevated blood pressure in the setting of stroke, the agent has had limited testing for neuroprotective treatment of the stroke itself.[736,737] A meta-analysis published in 2000 of the calcium channel–blocking agents found no evidence that this class of drug is effective in improving outcomes after ischemic stroke.[738]

Several *N*-methyl-D-aspartate antagonists have been tested in clinical trials, with largely negative results and increased rates of serious adverse events.[739–752] A 2003 systematic review of the excitatory amino acid modulator trials found no rates of improvements in either death or favorable outcomes with treatment.[753] Lubeluzole, which is thought to downregulate the glutamate-activated nitric oxide synthase pathway, was tested in several clinical trials, including one that evaluated the combination of the medication and intravenous rtPA.[754] Although a pilot study suggested safety and a reduction in deaths, subsequent larger clinical trials found no effects in reducing deaths or improving outcomes after stroke.[502,755,756] A subsequent analysis of the trials concluded that there was no evidence for the effectiveness of lubeluzole.[757]

Several trials tested the efficacy of clomethiazole, a γ-aminobutyric acid agonist, alone or in combination with intravenous rtPA.[758] The medication was also used to treat patients with hemorrhagic stroke.[759,760] Larger clinical trials failed to demonstrate the efficacy of clomethiazole in improving outcomes after ischemic stroke.[758,761–763] A randomized trial of diazepam, another γ-aminobutyric acid agonist, demonstrated no improvement in outcome at 3 months.[764] Although a dose-escalation study of naloxone found the medication to be safe, no signal of efficacy was noted.[765] Similarly, no benefit was noted in trials of the opioid antagonist nalmefene.[472,766]

Free radicals produced during cerebral ischemia are well-known mediators of neuronal injury. In initial studies, NXY-059, a free radical–trapping agent, demonstrated tolerability.[767] An initial pivotal trial showed potential in improving disability at 90 days, as measured by the mRS, and in reducing rates of intracranial bleeding[768]; however, a confirmatory pivotal trial in >3000 patients found no benefit on functional

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status at 90 days or on rates of intracranial hemorrhage.[769] A trial of tirilazad, a free radical scavenger agent that inhibits lipid peroxidation, was halted prematurely when an interim analysis failed to detect efficacy.[770,771] A review of all trials testing tirilazad, including in the treatment of subarachnoid hemorrhage, concluded that it did not improve outcomes.[772] A dose-escalation study of ebselen, an antioxidant, suggested that it might be safe and effective in improving outcomes after stroke.[773] A phase III trial completed enrollment in 2002, but no results were reported.[774] A small clinical trial found that edaravone, a free radical scavenger and antioxidant, might improve outcomes.[775] To date, none of these agents have sufficient data to support their use.

Trials of neuroprotective agents continue. A pilot study testing the combination of caffeine and alcohol when started within 6 hours of stroke found the intervention to be relatively safe.[776] Further evaluation of this intervention in combination with intravenous rtPA and with intravenous rtPA plus hypothermia is under way. Magnesium, an excitatory amino acid blocker, calcium channel blocker, and cerebral vasodilator, has been tested in a series of clinical studies. Although preliminary studies showed that magnesium was well tolerated and might improve outcomes, a subsequent larger clinical trial was negative.[777–780] One criticism of these early trials was that the agent was given up to 12 hours after onset of stroke. Subsequently, a study tested the safety and feasibility of very early magnesium sulfate administration by paramedics in the field to suspected stroke patients after informed consent was obtained by telephone. Of 20 patients enrolled (80% of whom had ischemic strokes), 70% received magnesium infusion within 2 hours of symptom onset.[781] A larger, phase III prehospital magnesium trial is currently under way.

Citicoline, a phospholipid precursor that appears to stabilize membranes, has been tested in several clinical studies.[782–784] The trials did not demonstrate treatment efficacy; however, a subsequent study-level meta-analysis suggested a net benefit of treatment in reducing disability.[785] A patient-level pooled analysis reported that patients with moderate to severe stroke might be helped if the medication were started within 24 hours of onset of symptoms.[786] The International Citicoline Trial on Acute Stroke (ICTUS), a large, European, multicenter randomized trial of citicoline, enrolled 2298 patients with moderate to severe ischemic strokes within 24 hours from symptom onset.[787] The trial was stopped prematurely in 2011 because of futility; no difference was found in the 90-day global outcome end point (OR, 1.03; 95% CI, 0.86–1.25; P=0.364).[788] Several trials of GM1-ganglioside, which also may stabilize membranes, have not demonstrated improved outcomes with treatment,[789–792] and a systematic review of this agent did not demonstrate any benefit from treatment.[793]

In addition to their low-density lipoprotein cholesterol–lowering effects, statins, or HMG-CoA reductase inhibitors, exert acute neuroprotective properties, including beneficial effects on endothelial function, cerebral blood flow, and inflammation. Formal dose-escalation trials are under way to evaluate statins as acute neuroprotective agents.[794] In a small, 89-patient randomized trial, patients already taking chronic statins at the time of ischemic stroke were randomized within 24 hours of onset to statin withdrawal for 3 days or to continued statin therapy. Among enrolled patients, median time from onset to inclusion was 6 hours. Brief withdrawal of statins during the acute period was associated with increased odds of death or dependency at 3 months.[795] Further study on the utility of early statin administration is needed.

Hematopoietic growth factors, in addition to regulating bone marrow, exert multiple potentially neuroprotective effects in the human brain. In a small pilot trial, erythropoietin was associated with a nonsignificant reduction in combined death and dependency[796]; however, preliminary data from a pivotal trial suggested that treatment with erythropoietin increased mortality.[797] Another phase I trial of erythropoietin in acute stroke is under way. Granulocyte colony-stimulating factor has been associated with a nonsignificant reduction in combined death and dependency in 2 small trials.[798]

Medications that reduce the inflammatory response to ischemia have also been evaluated. A randomized trial of enlimomab (an intercellular adhesion molecule-1 antagonist) found that the rates of poor outcomes, including death, were increased among patients who received the agent.[799] Another trial tested a neutrophil inhibitory factor; although the medication was safe, it did not improve outcomes.[800] A small study of cerebrolysin, with potential neurotrophic and neuroprotective actions, found that it was safe and might improve outcomes.[801] Preliminary studies of trafermin (basic fibroblast growth factor) showed that it was well tolerated but that there was a higher death rate among treated patients.[728,802] Other potentially neuroprotective therapies that are being tested include interferon-β, adenosine A1 receptor agonists, and nitric oxide synthase inhibitors.

Considerable experimental and clinical research is required before a pharmaceutical agent with identified neuroprotective effects can be recommended for treatment of patients with acute ischemic stroke. Several steps to improve preclinical and clinical research in neuroprotective agents, such as the STAIR guidelines, have been recommended.[803,804] It is hoped that ongoing studies of neuroprotective agents, potentially tested alone or in combination with measures to restore perfusion, will demonstrate safety and efficacy.

Hypothermia

Hypothermia has been shown to be neuroprotective in experimental and focal hypoxic brain injury models. Hypothermia may delay depletion of energy reserves, lessen intracellular acidosis, slow influx of calcium into ischemic cells, suppress production of oxygen free radicals, alter apoptotic signals, inhibit inflammation and cytokine production, and lessen the impact of excitatory amino acids.[805,806] Deep hypothermia is often administered to protect the brain in major operative procedures. Mild to moderate hypothermia is associated with improved neurological outcomes among patients with cardiac arrest, which led to hypothermia becoming the first neuroprotective strategy to be recommended by the AHA in comatose patients after cardiac arrest.[807–810] Conversely, a multicenter clinical trial found that mild hypothermia administered during surgery for treatment of a ruptured intracranial aneurysm did not improve outcomes after subarachnoid hemorrhage.[811]

Several small clinical studies have evaluated the feasibility of inducing modest hypothermia for treatment of patients

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with acute ischemic stroke.[812–818] Two small studies evaluated the utility of hypothermia in treating patients with malignant cerebral infarctions; results were mixed.[819,820] Potential side effects of therapeutic hypothermia include hypotension, cardiac arrhythmias, and pneumonia.[821] Den Hertog et al,[822] in a 2009 systematic review, found no indication of clinical benefit or harm from the use of hypothermia in stroke. A clinically significant effect could not be ruled out, however, and it was advised that large clinical trials were needed to assess the effect of hypothermia.[822]

Most pilot clinical trials to date have been designed to establish the safety and feasibility of various cooling techniques. These have typically used cohort or case-control groups for comparison of clinical efficacy. To date, no trial has produced Class I evidence, and none has had sufficient sample size to provide robust results. In studies investigating mild to moderate hypothermia induced by use of cooling blankets, the rate of cooling has been relatively slow, and shivering becomes an issue in nonparalyzed, non–mechanically ventilated patients. Moderate hypothermia, especially via endovascular techniques, can reach target temperatures more quickly, but this degree of hypothermia (32°C–33°C) appears to be associated with increased complications, including hypotension, cardiac arrhythmias, pneumonia, and thrombocytopenia. Patients with severe hemispheric strokes, especially with edema and mass effect, appear to be vulnerable to rebound increases in ICP when the rate of rewarming is relatively rapid. Mild or modest hypothermia (34°C–35°C) appears to produce fewer significant clinical complications.

Numerous questions remain unanswered related to the clinical use of hypothermia in acute focal cerebral ischemia. These include the therapeutic window for initiation of hypothermia, the speed of hypothermia induction, the level and duration of hypothermia, the rate of rewarming, and the most effective form of hypothermia delivery with the fewest complications. Additional questions to be addressed include proper or optimal patient selection, concomitant interventions such as fibrinolytics and hemicraniectomy, and whether hypothermia should be regional (cooling helmets or regional hypothermic saline infusions) or systemic (cooling blankets or endovascular catheters).

Lastly, many authors are promoting the investigation of hypothermia in conjunction with other potentially neuroprotective strategies. Synergistic effects of hypothermia with intravenous magnesium, caffeine, and alcohol have been proposed for study.[823,824] Ongoing feasibility and larger clinical trials of induced hypothermia, either alone or in combination with other therapies, will likely increase our understanding of the role of hypothermia in acute cerebral ischemia. Until then, there remains insufficient clinical evidence to establish a class of recommendation for induced hypothermia in acute stroke.

Hyperbaric Oxygen

Hyperbaric oxygen therapy (HBOT) is delivered in a specialized chamber pressurized to multiples of the ambient atmosphere (atmospheres absolute, or ATA; typically 1.5 to 3.0) and filled with oxygen to percentages up to 100%. This results in increasing the solubility of oxygen in plasma to a level adequate to support tissues with minimal extraction of the oxygen bound to hemoglobin.[825] Systemic harmful effects are generally limited to transient myopia, barotrauma of the middle ear or sinuses, and claustrophobia, but occasionally, HBOT may induce seizures.[825] HBOT may be used to treat patients with ischemic neurological symptoms secondary to air embolism or decompression sickness.[826,827] Although HBOT has generally conferred beneficial effects in preclinical acute cerebral ischemia studies,[828–833] clinical trials of HBOT in patients with acute stroke have been inconclusive or have shown that the intervention does not improve outcomes.[834–837] A meta-analysis found no evidence that HBOT improves clinical outcomes for acute stroke.[838] Delay from stroke onset to initiation of HBOT was an issue in these trials but is an intrinsic problem with HBOT, given the need for care delivery in a specialized chamber. At present, data do not support the routine use of hyperbaric oxygen in the treatment of patients with acute ischemic stroke.

Near-Infrared Laser Therapy

Application of a low-energy laser to the shaved skull to deliver energy in the near-infrared spectrum at a wavelength of 808 nm has been studied as a potential therapy for acute ischemic stroke.[839] The postulated mechanism of action is photobiostimulation, with near-infrared radiation absorbed by mitochondrial chromophores, which accelerates enzymatic activity, increases adenosine triphosphate production, and promotes tissue preservation in the ischemic penumbra and enhanced neurorecovery.[840–842]

Evidence of benefit in animal models[843–846] led to a safety and preliminary efficacy trial in 120 patients with acute ischemic stroke, which demonstrated statistically better outcomes in the treated patients as measured by the NIHSS, mRS, Barthel index, and Glasgow Outcome Scale.[847] A confirmatory trial enrolling 660 patients reported a positive trend but not a definitive benefit, and an additional pivotal trial using refined selection criteria is planned.[848] Thus far, however, the efficacy of near-infrared laser therapy has not been proven in acute ischemic stroke.

Recommendations

1. **Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable *(Class IIa; Level of Evidence B)*.** (New recommendation)
2. **The utility of induced hypothermia for the treatment of patients with ischemic stroke is not well established, and further trials are recommended *(Class IIb; Level of Evidence B)*.** (Revised from the previous guideline[13])
3. **At present, transcranial near-infrared laser therapy is not well established for the treatment of acute ischemic stroke *(Class IIb; Level of Evidence B)*, and further trials are recommended.** (New recommendation)
4. **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 *(Class III; Level of Evidence A)*.** (Revised from the previous guideline[13])

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5. **Data on the utility of hyperbaric oxygen are inconclusive, and some data imply that the intervention may be harmful. Thus, with the exception of stroke secondary to air embolization, this intervention is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence B)*.** (Unchanged from the previous guideline[13])

Surgical Interventions

Carotid Endarterectomy

Enthusiasm has grown over the past several years for early and sometimes immediate revascularization (emergent, typically within first 24 hours) with CEA in patients presenting with acute stroke or with stroke in evolution. Justification for this strategy is based on the reported risk of recurrent stroke for patients undergoing medical therapy while awaiting revascularization.[849,850]

In addition, there are theoretical benefits bestowed by (1) removal of the source of thromboembolic debris (thereby reducing chance of recurrent events, particularly in the case of "soft" or "ulcerated" plaque) and (2) restoring normal perfusion pressure to the ischemic penumbra in the brain. Data suggest that delaying CEA may reduce the potential benefit of revascularization by exposing certain patients to greater risk of recurrent stroke (up to 9.5% in the North American Symptomatic Carotid Endarterectomy Trial).[850a] Early CEA is believed to reduce that risk. Tempering the enthusiasm for early intervention are concerns regarding transformation of ischemic infarction to hemorrhagic infarction, as well as the potential to increase edema or produce hyperperfusion syndrome from sudden restoration of normal perfusion pressure to the brain. Sbarigia et al[851] enrolled 96 patients in a single-arm multicenter trial to evaluate the safety and efficacy of early CEA. Patients with very large ischemic strokes (NIHSS score >22) or with more than two thirds of the MCA territory involved with infarction were excluded. Mean time between onset of stroke and CEA was 1.5 days (±2 days). Overall 30-day morbidity/mortality was 7.3% (7/96). Most patients (85/96) demonstrated significant improvement; only 3% developed greater deficits, and no patients in this carefully selected cohort had hemorrhagic transformation or new cerebral infarction on CT. In another multicenter trial, Ballotta et al[852] performed early or urgent CEA (eg, within 2 weeks of acute stroke presentation; median time 8 days) on 102 patients with an mRS score <2. None of the subjects experienced new strokes, hemorrhagic conversions, or cerebral edema. Notably, case selection was limited to those with minor nondisabling stroke, who were neurologically stable, and with limited territorial infarct on CT or MRI. Case series in which more ill or neurologically unstable patients underwent early CEA demonstrated less favorable results. Huber et al[853] and Welsh et al[854] described combined stroke and death rates of 16% and 21%, respectively; their patients were more neurologically unstable, and some had complete carotid occlusion. Paty et al[855] showed that as infarct size increased by 1 cm in diameter, risk of permanent neurological impairment after CEA increased by a factor of 1.7. Thus, it would appear that early CEA may be appropriate for those with small, nondisabling stroke, with the goal of reducing ongoing thromboembolism or flow-limiting ischemia.

A systematic review by Rerkasem and Rothwell[856] of outcomes from a large number of publications specifically examined the influence of timing between onset of symptoms of TIA/stroke and subsequent CEA. These authors point out the paucity of data regarding optimal timing of CEA in general and specifically regarding outcomes for CEA for stroke-in-evolution or crescendo TIA. Existing studies have highly variable elements and definitions for these entities, and there is a lack of standardization across studies. Rerkasem and Rothwell's pooled analysis of results from 47 relevant studies published through 2008 demonstrated relatively high combined stroke and death rates for urgent CEA, 20.2% and 11.4%, in settings of stroke-in-evolution and crescendo TIA, respectively. There was no improvement in outcomes over time, because event rates from studies conducted before and after 2000 were not different. The incidence of stroke and death was significantly higher in patients who required emergent surgery for stroke-in-evolution or crescendo TIA than in patients with nonemergency CEA (OR, 4.6). All but 2 small studies in this analysis excluded patients who had major stroke; most patients had nondisabling stroke or variable deficits (crescendo TIA) as of the time of surgery. Emergent and urgent (days) surgery after large disabling stroke, regardless of carotid status, remains high risk.

Rerkasem and Rothwell[856] conclude the following: (1) Risks of emergency CEA are high in patients with unstable neurological status; (2) this risk must be balanced against the risk of neurological deterioration on medical therapy; (3) current evidence does not support emergent CEA for such patients; (4) improvements in intensive medical therapy may allow for stabilization of such patients; and (5) prospective randomized controlled trials of emergent or urgent versus delayed revascularization in patients with unstable neurological status (acute evolving stroke or crescendo TIA) are warranted. In contrast to patients with ongoing instability, data indicate that those patients who are neurologically stable after presenting with a nondisabling stroke or TIA may undergo surgery early on without any incremental risk compared with delayed surgery. Because the incidence of recurrent stroke or TIA is highest early after initial presentation, this subset of patients likely benefits from early revascularization. Data from large randomized trials show that the absolute benefit of CEA is highest during the initial 2 weeks after the event, provided the patient is not demonstrating instability. Rerkasem and Rothwell[856] highlight the need for additional carefully designed studies to compare alternative treatment algorithms for patients with acute neurological symptoms.

Most data available regarding the effectiveness of surgical treatment of patients with ischemic stroke or TIA do not pertain to CEA immediately after presentation but rather hours, days, or weeks after the initial event. Few data are available regarding emergency surgical intervention to treat or reverse the initial acute stroke. The most accepted and most common indication for immediate operation for acute stroke is in the setting of a new deficit that occurs immediately after CEA. Surgery in such instances is performed to correct a technical issue that resulted in attenuation of flow or acute thrombosis.

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Emergency CEA generally is not performed in other settings of acute ischemic stroke, especially when the deficit is large, because of the high risk of adverse events associated with acute restoration of flow to damaged tissue. The exception to this might be when either clinical parameters or DWI suggests that the actual infarcted area is small and the penumbra is large, which indicates that reperfusion of a severe carotid narrowing might enable recovery of tissue in the ischemic zone.

Emergent CEA is sometimes advocated for patients with intraluminal mobile or sessile thrombus associated with an atherosclerotic plaque at the carotid bifurcation. The indications for this are controversial. The morbidity associated with surgery appears to be high among patients who already have intraluminal thrombus demonstrated by cerebral angiography.[857–860] Although some groups report low rates of complications and good neurological outcomes with immediate surgery,[857–859] others have reported better results when the patients are treated initially with anticoagulants followed by delayed operation.[860]

Other Surgical Procedures (Extracranial-Intracranial Bypass)

Extracranial-intracranial bypass for the treatment of ischemic stroke has not been shown to be of benefit. Rare reports of improvement with early bypass surgery exist,[861,862] as do reports of no improvement and hemorrhagic complications.[863] Reports of the early use of surgical embolectomy exist,[864,865] but endovascular approaches appear to provide a better alternative in most situations.[866,867]

Conclusions and Recommendations

Emergent CEA and other operations for treatment of patients with acute ischemic stroke may have serious risks, and the indications must be considered carefully for each individual patient. Furthermore, optimal timing for revascularization after presentation with acute stroke or TIA remains to be defined and likely will vary depending on several factors, including size of infarct, presence and size of residual penumbra, stability of neurological status, and general medical condition of the patient. Additional randomized clinical trials should be designed and undertaken to examine the safety and efficacy of CEA in various subsets of patients with acute stroke, to establish the optimal timing for revascularization, and to define its role in the emergency management of stroke.

Recommendations

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 *(Class IIb; Level of Evidence B)*.** (New recommendation)
2. **In patients with unstable neurological status (either stroke-in-evolution or crescendo TIA), the efficacy of emergent or urgent CEA is not well established *(Class IIb; Level of Evidence B)*.** (New recommendation)

Admission to the Hospital and General Acute Treatment (After Hospitalization)

Key to safe and effective stroke care, especially after intravenous or intra-arterial recanalization, is rapid hospital admission or interhospital transfer to a stroke unit or neurocritical care unit. Approximately 25% of patients may have neurological worsening during the first 24 to 48 hours after stroke, and it is difficult to predict which patients will deteriorate.[868–872] In addition to the potential progression of the initial stroke, the need to prevent neurological or medical complications also means that patients with acute stroke should be admitted to the hospital in almost all circumstances.[873–877] The goals of treatment after admission to the hospital are to (1) observe for changes in the patient's condition that might prompt initiation of medical or surgical interventions, (2) provide observation and treatment to reduce the likelihood of bleeding complications after the use of intravenous rtPA, (3) facilitate medical or surgical measures aimed at improving outcome after stroke, (4) begin measures to prevent subacute complications, (5) initiate long-term therapies to prevent recurrent stroke, and (6) start efforts to restore neurological function through rehabilitation and good supportive care. The importance of dedicated stroke nursing care in the management of stroke patients cannot be overstated. The 2009 scientific statement from the AHA by Summers et al, entitled "Comprehensive Overview of Nursing and Interdisciplinary Care of the Acute Ischemic Stroke Patient," is an excellent resource detailing such care.[878]

Specialized Stroke Care Units

Numerous studies, performed mainly in Europe and Canada, demonstrate the utility of comprehensive stroke units in lessening the rates of mortality and morbidity after stroke.[879–892] The positive effects persist for years. The benefits from treatment in a stroke unit are comparable to the effects achieved with intravenous administration of rtPA.[893] European stroke units usually do not include intensive care unit–level treatment, including ventilatory assistance. Regular communications and coordinated care are also key aspects of the stroke unit. Standardized stroke orders or integrated stroke pathways improve adherence to best practices for treatment of patients with stroke.[894–898] An observational study of New York State stroke data found transport and admission to a PSC compared with nondesignated hospitals led to lower overall 30-day mortality rates (10.1% versus 12.5%) and increased use of fibrinolytic therapy (4.8% versus 1.7%).[48] Additional studies have shown that participation in the GWTG-Stroke program has produced improved care processes and sustained increased adherence to stroke performance measures.[87,88]

Studies demonstrating the benefit of CSCs lag those of PSC effectiveness. An observational study of clinical registries and a linked administrative database in 333 hospitals in Finland demonstrated improved mortality and clinical outcomes when patients were cared for in stroke centers compared with general hospitals.[41] The number needed to treat for the prevention of 1 death or institutional care at 1 year was 29 for CSCs and 40 for PSCs compared with nonstroke centers. Prior epidemiological work demonstrated that patients admitted on the weekend had higher mortality. A prospective registry study

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suggested that CSCs with 24/7 specialized care may ameliorate this occurrence, but additional prospective studies must be performed.[899] Given the challenges of building effective stroke systems, continued research is required to identify the best means for triaging patients and integrating nonstroke centers with PSCs and CSCs.

General Stroke Care

Most of the individual components of general medical management after admission to the hospital have not been tested in clinical studies.[873,874,876,900,901] Thus, recommendations are based on customary care and the findings from multiple randomized trials that efficient delivery of the combination of these treatments in a stroke unit yields better outcomes than does less organized delivery of these therapies in general medical wards. Medical and nursing management focuses on prevention of subacute complications. Sixty-three percent of patients have ≥1 complication after acute stroke even when cared for in specialized units. The most common complications during the first week in a Norwegian stroke unit were pain, fever, progressing stroke, and UTI. There were low incidences of immobility complications such as DVT and PE in the specialized unit.[902] The patient's neurological status and vital signs are assessed frequently during the first 24 hours after admission. Stroke severity is associated with the development of complications, which most commonly occur in the first 4 days.[902] Most patients are first treated with bed rest, but mobilization usually begins as soon as the patient's condition is considered stable. A Very Early Rehabilitation Trial for Stroke (AVERT) is a large randomized controlled trial that is mobilizing stroke patients within the first 24 hours.[903] In the pilot trial, the intervention appeared safe and feasible. Some patients may have neurological worsening on movement to an upright posture. Thus, close observation should be included during the transition to sitting or standing. Early mobilization is favored because it lessens the likelihood of complications such as pneumonia, DVT, PE, and pressure sores.[901] In addition, prolonged immobility may lead to contractures, orthopedic complications, or pressure palsies.[876,904,905] Frequent turning, the use of alternating pressure mattresses, and close surveillance of the skin help to prevent pressure sores. Measures to avoid falls are also important considerations.[906]

Nutrition and Hydration

Sustaining nutrition is important because dehydration or malnutrition may slow recovery.[907,908] Dehydration is a potential cause of DVT after stroke. Impairments of swallowing are associated with a high risk of pneumonia.[909] Some patients cannot receive food or fluids orally because of impairments in swallowing or mental status. Patients with infarctions of the brain stem, multiple strokes, major hemispheric lesions, or depressed consciousness are at greatest risk for aspiration. Swallowing impairments are associated with an increased risk of death.[910] An abnormal gag reflex, impaired voluntary cough, dysphonia, incomplete oral-labial closure, a high NIHSS score, or cranial nerve palsies should alert the care team to the risk of dysphagia.[9-1-1–913] A preserved gag reflex may not indicate safety with swallowing.[914] The patient may be placed on a strict nothing-by-mouth order until an assessment of the ability to swallow is completed. Studies have shown that other healthcare providers can safely perform the initial screening before the speech language pathologist assessment.[903,915,916] In a prospective 15-hospital study, use of a formal dysphagia screening protocol, which incorporated an evidence-based screening tool, was associated with improved compliance with dysphagia screenings and a significantly reduced risk of pneumonia.[917] The Toronto Bedside Swallowing Screening test, an evidence-based tool for swallow assessment, has been evaluated successfully for interrater reliability and predictive validity.[918] A water swallow test performed at the bedside is a useful screening tool. A wet voice after swallowing is a predictor of a high risk for aspiration. Clinical signs may not identify patients at risk for aspiration, and further testing, including a video fluoroscopic evaluation of swallow or a fiber optic endoscopic evaluation of swallow, may be performed if indicated.[919–921]

Most patients are treated initially with intravenous fluids. Intravenous hyperalimentation is rarely necessary. When necessary, a nasogastric (NG) or nasoduodenal tube may be inserted to provide feedings and to facilitate administration of medications.[922] Placement of a percutaneous endoscopic gastrostomy (PEG) tube is performed to treat patients who will need prolonged tube feedings.[923] Although this device usually requires less care, complications, including involuntary removal of the tube or peritonitis, may occur.[924] The risk of aspiration pneumonia is not eliminated by the use of an NG or PEG tube.

The Feed or Ordinary Diet (FOOD) trials examined (1) the effect of administration of nutritional supplements in outcomes of patients with stroke who could swallow, (2) the effect of initiation of NG feeding started within 7 days of stroke compared with later intervals on outcomes, and (3) the effect of PEG feedings on outcomes compared with NG feedings during the first 2 to 3 weeks after onset.[925–928] The results showed that supplemental nutrition was not necessary, that early NG tube feeding may substantially decrease the risk of death, and that early feeding via an NG tube resulted in better functional outcomes than feeding by PEG,[925,926] although many long-term care facilities will not accept patients with an NG tube as the means for providing nutrition.

Bowel management to avoid constipation and fecal impaction or diarrhea is also a component of ancillary care.[929] Constipation occurs in 30% to 60% of patients 4 weeks after stroke, and in patients with moderate stroke severity, constipation was associated with poor outcomes at 12 weeks.[930] Some feedings administered via a PEG or NG tube may cause osmotic gradients that lead to diarrhea.

Infections

Pneumonia, which is most likely to occur in seriously affected, immobile patients and those who are unable to cough, is an important cause of death after stroke.[876,909,931–933] Aslanyan et al[931] found that the development of pneumonia was associated with an increased risk of death (hazard ratio, 2.2; 95% CI, 1.5–3.3) or unfavorable outcome (OR, 3.8; 95% CI, 2.2–6.7). Stroke-associated pneumonia increases length of stay, mortality, and hospital costs.[934] Immobility and atelectasis can lead to development of pneumonia. Early mobility and good pulmonary care can help prevent pneumonia.[934] Preventive measures in intubated patients include ventilation in a semirecumbent

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position, positioning of the airway, suctioning, early mobility, and shortened use of intubation if feasible.[935] Measures to treat nausea and vomiting may also lower the risk of aspiration pneumonia. Exercise and encouragement to take deep breaths may help to lessen the development of atelectasis. The appearance of fever after stroke should prompt a search for pneumonia, and appropriate antibiotic therapy should be administered promptly. In one study, prophylactic administration of levofloxacin was not successful in lessening the risk of pneumonia or other infections in the first days after stroke.[936]

UTIs are common, occurring in 15% to 60% of stroke patients; they independently predict worse outcomes and can lead to bacteremia or sepsis as a potential complication.[874,931,937–939] Urinalysis for evidence of infection should be performed whenever a patient develops a fever after stroke. Some patients, especially those with major impairments, are at high risk for urinary incontinence.[940] Indwelling catheters should be avoided if possible but may be required in the acute phase of stroke. The catheter should be removed as soon as the patient is medically and neurologically stable. Intermittent catheterization may lessen the risk of infection. External catheters, incontinence pants, and intermittent catheterization are alternatives to an indwelling catheter. The patient should be assessed for UTI if there is a change in level of consciousness and no other cause of neurological deterioration is identified. A urinalysis and urine culture should be obtained if UTI is suspected.[13,931,932,940] Acidification of the urine may lessen the risk of infection, and anticholinergic agents may help in recovery of bladder function. Although prophylactic administration of antibiotics usually is not done, appropriate antibiotics should be prescribed for patients with evidence of UTI.

DVT and PE

PE accounts for 10% of deaths after stroke, and the complication may be detected in 1% of patients who have had a stroke.[941] Indredavik and colleagues[902] found PE in <2.5% of patients during the first week in a specialized stroke unit. DVT and PE were more likely to occur in the first 3 months after stroke, with an incidence of 2.5% and 1.2%, respectively.[902] Pulmonary emboli generally arise from venous thrombi that develop in a paralyzed lower extremity or pelvis. Besides being associated with a life-threatening pulmonary event, symptomatic DVT also slows recovery and rehabilitation after stroke. The risk of DVT is highest amongst immobilized and older patients with severe stroke.[942–946]

The options for lowering the risk of DVT include early mobilization, administration of antithrombotic agents, and the use of external compression devices. Anticoagulants are given to prevent DVT and PE among seriously ill patients. Much of the support for the use of anticoagulants comes from clinical studies testing these agents in the treatment of bedridden patients other than those with stroke.[947,948] A meta-analysis demonstrated that these medications were effective among patients with stroke.[949] Several clinical trials have demonstrated the utility of heparin and LMWH.[947,950] The results of the PREVAIL Trial showed that a 40-mg injection of enoxaparin once daily was more effective than 5000 IU of UFH twice a day for prevention of DVT in ischemic stroke patients.[629] The risk of serious bleeding complications was relatively low.[951] Long-term treatment usually involves the use of oral anticoagulants such as warfarin. Ridker et al[952] found that low-intensity warfarin therapy was effective in preventing recurrent venous thromboembolism. Aspirin also may be effective for patients who have contraindications to anticoagulants, although direct comparisons with anticoagulants are limited.[606,953,954] Experience evaluating the use of external compression of the veins in the lower extremities, such as stockings or alternating pressure devices, in stroke patients is limited, and potential for skin damage is a concern.[955–957] Patients with PE from thrombi in the lower extremities and a contraindication for antithrombotic treatment may require placement of a device to filter the inferior vena cava.

Cardiovascular Monitoring and Treatment

As described in the "General Supportive Care and Treatment of Acute Complications" section, careful cardiovascular monitoring of patients presenting with acute stroke, particularly those with large deficits and right hemispheric strokes, is essential. These patients are at risk for myocardial ischemia, congestive heart failure, atrial fibrillation, and significant arrhythmias. The continuation of cardiac monitoring started in the ED for the first 24 hours after stroke may detect intermittent atrial fibrillation not apparent at presentation and the development of potentially lethal early arrhythmias.[134,136,958] Longer monitoring may be required, with either 24-hour Holter monitoring or event-looped recording for several days to detect more occult arrhythmias.[134,959] Routine prophylactic treatment of potential cardiac arrhythmias has not been shown to be beneficial, but clinically significant cardiac arrhythmias may compromise cerebral perfusion and should be treated accordingly.

In ischemic stroke patients with known atrial fibrillation or other conditions that require anticoagulation, few data are available to provide guidance as to when and how to reinitiate anticoagulation. In a study of the initiation of anticoagulation after hemorrhagic stroke, warfarin resumption during the acute hospitalization did not produce an increase in bleeding and mortality.[960] Individual patient characteristics, such as indication for anticoagulation, volume of ischemic injury, age, reperfusion use, and anticoagulation drug, may contribute to the decision about when to initiate anticoagulation.

Other Care

After stabilization of the patient's condition, secondary prevention measures to prevent long-term complications are begun, and measures to provide rehabilitation, patient and family education, and family support are started. AHA/ASA guidelines on secondary prevention and rehabilitation provide a framework for these activities.[879,961,962] Other risk factors that must be treated include diabetes mellitus, hypertension, and codeveloping heart disease. Lifestyle changes must be evaluated and included in education about secondary stroke prevention. Changes in activity will reflect the patient's neurological impairments and overall health.

Conclusions and Recommendations

The management of stroke patients after hospital admission remains a key component of overall treatment and is as

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important as the acutely administered therapies. The components of this aspect of treatment dovetail with the acute interventions to restore perfusion. In addition, these components of management can be performed on all stroke patients. These therapies can improve outcomes by lessening complications and enhancing recovery from stroke.

Recommendations

1. **The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation is recommended *(Class I; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
2. **Patients with suspected pneumonia or UTIs should be treated with appropriate antibiotics *(Class I; Level of Evidence A)*.** (Revised from the previous guideline)
3. **Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent DVT *(Class I; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
4. **The use of standardized stroke care order sets is recommended to improve general management *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
5. **Assessment of swallowing before the patient begins eating, drinking, or receiving oral medications is recommended *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
6. **Patients who cannot take solid food and liquids orally should receive NG, nasoduodenal, or PEG tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing *(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])
7. **Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
8. **Treatment of concomitant medical diseases is recommended *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
9. **Early institution of interventions to prevent recurrent stroke is recommended *(Class I; Level of Evidence C)*.** (Unchanged from the previous guideline[13])
10. **The use of aspirin is reasonable for treatment of patients who cannot receive anticoagulants for DVT prophylaxis *(Class IIa; Level of Evidence A)*.** (Revised from the previous guideline[13])
11. **In selecting between NG and PEG tube routes of feeding in patients who cannot take solid food or liquids orally, it is reasonable to prefer NG tube feeding until 2 to 3 weeks after stroke onset *(Class IIa; Level of Evidence B)*.** (Revised from the previous guideline[13])
12. **The use of intermittent external compression devices is reasonable for treatment of patients who cannot receive anticoagulants *(Class IIa; Level of Evidence B)*.** (Revised from the previous guideline[13])
13. **Routine use of nutritional supplements has not been shown to be beneficial *(Class III; Level of Evidence B)*.** (Revised from the previous guideline[13])
14. **Routine use of prophylactic antibiotics has not been shown to be beneficial *(Class III; Level of Evidence B)*.** (Revised from the previous guideline[13])
15. **Routine placement of indwelling bladder catheters is not recommended because of the associated risk of catheter-associated UTIs *(Class III; Level of Evidence C)*.** (Unchanged from the previous guideline[13])

Treatment of Acute Neurological Complications

Deterioration after initial stroke assessment is common, occurring in 25% of patients.[868,872] In the group with clinical deterioration, one third occurs because of stroke progression, one third because of brain edema, 10% because of hemorrhage, and 11% because of recurrent ischemia. The potential for life-threatening deterioration highlights the need for close observation and assessment, again, best provided in dedicated stroke or neurocritical units. Given the complexity of severe stroke and potential complications, multidisciplinary care teams composed of neurologists, neurointensivists, and neurosurgeons, as well as dedicated stroke nursing, are required to optimally manage these complex patients.

Ischemic Brain Edema

Acute cerebral infarction is often followed by a delayed deterioration caused by edema of the infarcted tissue.[158,963,964] Depending on stroke location, infarct volume, patient age, and degree of preexisting atrophy, edema may produce a range of clinical findings from being clinically silent and not associated with new neurological symptoms to precipitous fatal deterioration.[965,966] Although the cytotoxic edema normally peaks 3 to 4 days after injury,[965–967] early reperfusion of a large volume of necrotic tissue can accelerate the edema to a potentially critical level within the first 24 hours, a circumstance termed *malignant edema*.[968] In patients with severe stroke or posterior fossa infarctions, careful observation is required for early intervention to address potentially life-threatening edema.

Medical Management of Cerebral Edema

Cerebral edema will occur in all infarcts but especially in large-volume infarcts. Several medical interventions have been suggested to minimize edema development, such as restriction of free water to avoid hypo-osmolar fluid, avoidance of excess glucose administration, minimization of hypoxemia and hypercarbia, and treatment of hyperthermia. Antihypertensive agents, particularly those that induce cerebral vasodilatation, should be avoided. To assist in venous drainage, the head of the bed can be elevated at 20° to 30°. The goal of these interventions is to reduce or minimize edema formation before it produces clinically significant increases in ICP.

When edema produces increased ICP, standard ICP management practices should be initiated.[969] ICP management strategies are similar to those used in traumatic brain injury and spontaneous intracranial hemorrhage, including hyperventilation, hypertonic saline, osmotic diuretics, intraventricular drainage of cerebrospinal fluid, and decompressive surgery.[970,971] No evidence indicates that hyperventilation, corticosteroids in conventional or large doses, diuretics, mannitol, or glycerol or other measures that reduce ICP alone improve outcome in patients with ischemic brain swelling. Mannitol 0.25 to 0.5 g/kg IV administered over 20 minutes lowers ICP and can be given every 6 hours. The usual maximal dose is

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2 g/kg. In a preliminary study by Koenig et al,[972] use of hypertonic saline in patients with clinical transtentorial herniation caused by various supratentorial lesions, including ischemic and hemorrhagic stroke, was associated with a rapid decrease in ICP. This stroke-specific study complements very supportive data from the traumatic brain injury literature. Hyperventilation of intubated patients induces cerebral vasoconstriction, which causes a reduction in cerebral blood volume, thus lowering ICP. The target of hyperventilation is mild hypocapnia (P_{co_2} 30–35 mm Hg), but even after this goal is reached, the benefit is short-lived. Despite intensive medical management, the death rate in patients with increased ICP remains as high as 50% to 70%; thus, these interventions should be considered temporizing, extending the window for definitive treatments.

Decompressive Surgery

Hemispheric infarction, often caused by proximal large-vessel occlusions (internal carotid, carotid terminus, proximal MCA), is associated with a large volume of infarction that often involves tissue above and below the sylvian fissure.[158,964,973] Patients with imaging studies that demonstrate the early appearance of CT scan hypodensity,[158] restricted diffusion,[974,975] or an absence of perfusion[244] in more than two thirds of the MCA territory are at increased risk of delayed herniation. Clinical deterioration is often rapid, with brain stem compression first causing deterioration of consciousness, which may be followed rapidly by a failure of upper brain stem function.[965,966] Deterioration of consciousness in this setting is associated with a 50% to 70% likelihood of mortality despite maximal medical management.[963,976] Brain stem compression is commonly accompanied by secondary involvement of the frontal and occipital lobes, presumably attributable to anterior cerebral and posterior cerebral artery compression against dural structures.[977,978] The resulting secondary infarctions greatly limit the potential for a meaningful clinical recovery or even survival.

The role of neurosurgical intervention for the treatment of supratentorial infarction has been controversial. Previously, the long-term functional benefit of surgical decompression was debated, although surgical decompression can reduce mortality from 80% to ≈20%.[979–982] Because secondary infarctions limit the potential for recovery, earlier intervention, that is, before signs of herniation, is often recommended on the basis of the volume of tissue that is infarcted and the degree of midline shift.[983,984] The merger of 3 randomized controlled trials published in 2007 demonstrated the potential benefit of decompressive surgery. In the study, surgery was performed within 48 hours of stroke onset in patients with malignant infarctions who were 18 to 60 years of age. Surgical decompression reduced mortality from 78% to 29% and significantly increased favorable outcomes.[985] Equal benefit was observed in patients with dominant and nondominant hemisphere infarctions. Age impacted outcome, with older patients having worse outcomes.[986] The authors stressed, "The decision to perform decompressive surgery should, however, be made on an individual basis in every case".[987–989] Although the surgery may be recommended for treatment of seriously affected patients, the physician should advise the patient's family about the potential outcomes, including survival with severe disability.

When a large infarction of the cerebellum occurs, delayed swelling commonly follows. Although the early symptoms may be limited to impaired function of the cerebellum, edema can cause brain stem compression and can progress very rapidly to a loss of brain stem function. Emergent posterior fossa decompression with partial removal of the infarcted tissue is often lifesaving and produces a clinical outcome with a reasonable quality of life.[990–992]

Hemorrhagic Transformation

Ischemic infarction is frequently accompanied by petechial hemorrhage without associated neurological deterioration in patients who are not treated with recanalization strategies.[993,994] Symptomatic hemorrhage, however, occurs in ≈5% to 6% of patients after use of intravenous rtPA and intra-arterial recanalization strategies and anticoagulant use.[480,995–997] Strict adherence to fibrinolytic administration and posttreatment protocols minimizes these risks. Hemorrhagic transformation can also occur in patients who did not undergo reperfusion therapies and who require similar vigilance, especially those patients with larger strokes, of older age, and with a cardioembolic pathogenesis. Signs and symptoms of sICH resemble those of patients with spontaneous ICH, such as worsening neurological symptoms, decreasing mental status, headache, increased blood pressure and pulse, and vomiting.[470] Similarly, health providers' vigilance to immediately detect hemorrhagic complications may allow timely interventions to mitigate the hemorrhage.

Most sICHs occur within the first 24 hours after intravenous rtPA; the vast majority of fatal hemorrhages occur within the first 12 hours.[470] If a patient demonstrates signs of symptomatic hemorrhage, any remaining intravenous rtPA should be withheld. A standardized guideline for managing fibrinolytic-associated hemorrhages does not exist. Given insights from clinical trials, protocols call for an emergent noncontrast CT scan and blood samples for a complete blood count, coagulation parameters (PT, PTT, INR), type and screen, and fibrinogen levels. Concurrently, other causes of neurological worsening, such as hemodynamic instability, are pursued. Although no study has been conducted to determine the best way to manage post–intravenous rtPA hemorrhage, many rtPA-associated hemorrhage protocols call for the use of cryoprecipitate to restore decreased fibrinogen levels. A recent case report described the use of tranexamic acid in the treatment of an intravenous rtPA–associated hemorrhage in a Jehovah's Witness stroke patient. After administration, no further hematoma expansion was noted.[998] Further studies are clearly warranted to define the optimal way to manage fibrinolytic-associated hemorrhages.

Although definitive data from clinical trials are lacking, surgical hematoma evacuation may be considered depending on the size and location of the hemorrhage and the patient's overall medical and neurological condition. Evacuation of a large hemorrhage may be lifesaving, whereas smaller hematomas may be tolerated without clinical relevance.[999] As with cerebral edema, cerebellar hemorrhagic conversion is more likely to become symptomatic.[1000]

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Seizures

The reported incidence of seizures after ischemic infarction varies greatly, with most reports indicating an incidence <10%.[1001,1002] An increased incidence of seizures after ischemic infarction is reported in patients with hemorrhagic transformation.[1003] A great variance is also reported in the incidence of recurrent and late-onset seizures.[1004,1005] With few data available on the efficacy of anticonvulsants in the treatment of seizures in stroke patients, current recommendations are based on the established management of seizures that may complicate any neurological illness. No studies to date have demonstrated a benefit of prophylactic anticonvulsant use after ischemic stroke, and little information exists on indications for the long-term use of anticonvulsants after a seizure.

Palliative Care

Although the role of palliative care for patients with cancer is widely accepted, many (especially elderly) patients who survive massive hemispheric or brain stem strokes may be candidates for palliative care. Although this topic has not been examined extensively, the appropriate integration of palliative care in one medical center suggests that although the need for such referral was less than for cancer victims, there still exists a real need for many stroke patients.[1006] Early discussions with the patient and family can ensure any prior do-not-resuscitate or limitations-of-care orders are respected. Additionally, it is critical to conduct discussions with patients and families regarding poststroke prognosis to allow them to make informed decisions regarding any new do-not-resuscitate or limitations-of-care orders.

Recommendations

1. **Patients with major infarctions are at high risk for complicating brain edema and increased ICP. 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 *(Class I; Level of Evidence A)*. Early transfer of patients at risk for malignant brain edema to an institution with neurosurgical expertise should be considered.** (Revised from the previous guideline[13])
2. **Decompressive surgical evacuation of a space-occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression *(Class I; Level of Evidence B)*.** (Revised from the previous guideline[13])
3. **Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially lifesaving *(Class I; Level of Evidence B)*. Advanced patient age and patient/family valuations of achievable outcome states may affect decisions regarding surgery.** (Revised from the previous guideline[13])
4. **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 *(Class I; Level of Evidence B)*.** (Unchanged from the previous guideline[13])
5. **Placement of a ventricular drain is useful in patients with acute hydrocephalus secondary to ischemic stroke *(Class I; Level of Evidence C)*.** (Revised from the previous guideline[13])
6. **Although aggressive medical measures have been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, the usefulness of these measures is not well established *(Class IIb; Level of Evidence C)*.** (Revised from the previous guideline[13])
7. **Because of lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) are not recommended for treatment of cerebral edema and increased ICP complicating ischemic stroke *(Class III; Level of Evidence A)*.** (Unchanged from the previous guideline[13])
8. **Prophylactic use of anticonvulsants is not recommended *(Class III; Level of Evidence C)*.** (Unchanged from the previous guideline[13])

Disclosures

Writing Group Disclosures

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*Modest.

†Significant.

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J. Mocco	Vanderbilt University	State of Florida, Dept of Health, James and Esther King Early Career Grant†	None	University of Wisconsin, for serving on the Consensus to Establish Consistent Angiographic Evaluation Criteria in Acute Ischemic Stroke*	None	Lazarus Effect, Inc*	Codman Neurovascular Acute Ischemic Stroke Advisory Board–no funds received by myself for participation*	None

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*Modest.

† Significant.

References

1. Stroke drops to fourth leading cause of death in 2008 [news release]. Atlanta, GA: Centers for Disease Control and Prevention; December 9, 2010. http://www.cdc.gov/media/pressrel/2010/r101209.html. Accessed June 20, 2011.
2. Schwamm LH, Audebert HJ, Amarenco P, Chumbler NR, Frankel MR, George MG, Gorelick PB, Horton KB, Kaste M, Lackland DT, Levine SR, Meyer BC, Meyers PM, Patterson V, Stranne SK, White CJ; American Heart Association Stroke Council; Council on Epidemiology and Prevention; Interdisciplinary Council on Peripheral Vascular Disease; Council on Cardiovascular Radiology and Intervention. Recommendations for the implementation of telemedicine within stroke systems of care: a policy statement from the American Heart Association. *Stroke*. 2009;40:2635–2660.
3. Schwamm LH, Holloway RG, Amarenco P, Audebert HJ, Bakas T, Chumbler NR, Handschu R, Jauch EC, Knight WA 4th, Levine SR, Mayberg M, Meyer BC, Meyers PM, Skalabrin E, Wechsler LR; American Heart Association Stroke Council; Interdisciplinary Council on Peripheral Vascular Disease. A review of the evidence for the use of telemedicine within stroke systems of care: a scientific statement from the American Heart Association/American Stroke Association. *Stroke*. 2009;40:2616–2634.
4. Schwamm LH, Pancioli A, Acker A3rd, Goldstein A, Zorowitz A, Shephard A, Moyer A, Gorman A, Johnston A, Duncan A, Gorelick A, Frank A, Stranne A, Smith A, Federspiel A, Horton A, Magnis A, Adams A; American Stroke Association's Task Force on the Development of Stroke Systems. Recommendations for the establishment of stroke systems of care: recommendations from the American Stroke Association's Task Force on the Development of Stroke Systems. *Stroke*. 2005;36:690–703.
5. Acker JE 3rd, Pancioli AM, Crocco TJ, Eckstein MK, Jauch EC, Larrabee H, Meltzer NM, Mergendahl WC, Munn JW, Prentiss SM, Sand C, Saver JL, Eigel B, Gilpin BR, Schoeberl M, Solis P, Bailey JR, Horton KB, Stranne SK; American Heart Association; American Stroke Association Expert Panel on Emergency Medical Services Systems, Stroke Council. Implementation strategies for emergency medical services within stroke systems of care: a policy statement from the American Heart Association/American Stroke Association Expert Panel on Emergency Medical Services Systems and the Stroke Council. *Stroke*. 2007;38:3097–3115.
6. Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, Hatsukami TS, Higashida RT, Johnston SC, Kidwell CS, Lutsep HL, Miller E, Sacco RL. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. *Stroke*. 2009;40:2276–2293.
7. Goldstein LB, Bushnell CD, Adams RJ, Appel LJ, Braun LT, Chaturvedi S, Creager MA, Culebras A, Eckel RH, Hart RG, Hinchey JA, Howard VJ, Jauch EC, Levine SR, Meschia JF, Moore WS, Nixon JV, Pearson TA; American Heart Association Stroke Council; Council on Cardiovascular Nursing; Council on Epidemiology and Prevention; Council for High Blood Pressure Research, Council on Peripheral Vascular Disease, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the primary prevention of stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2011;42:e26]. *Stroke*. 2011;42:517–584.
8. Roach ES, Golomb MR, Adams R, Biller J, Daniels S, Deveber G, Ferriero D, Jones BV, Kirkham FJ, Scott RM, Smith ER; American Heart Association Stroke Council; Council on Cardiovascular Disease in the Young. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young [published correction appears in *Stroke*. 2009;40:e8–e10]. *Stroke*. 2008;39:2644–2691.
9. Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, Hobson R, Kidwell CS, Koroshetz WJ, Mathews V, Villablanca P, Warach S, Walters B; American Heart Association Council on Cardiovascular Radiology and Intervention, Stroke Council, and the Interdisciplinary Council on Peripheral Vascular Disease. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. *Stroke*. 2009;40:3646–3678.
10. Leifer D, Bravata DM, Connors JJ 3rd, Hinchey JA, Jauch EC, Johnston SC, Latchaw R, Likosky W, Ogilvy C, Qureshi AI, Summers D, Sung GY, Williams LS, Zorowitz R; American Heart Association Special Writing Group of the Stroke Council; Atherosclerotic Peripheral Vascular Disease Working Group; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing. Metrics for measuring quality of care in comprehensive stroke centers: detailed follow-up to Brain Attack Coalition comprehensive stroke center recommendations: a statement for healthcare professionals from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2011;42:e369]. *Stroke*. 2011;42:849–877.

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11. Adams H, Adams R, Del Zoppo G, Goldstein LB; Stroke Council of the American Heart Association; American Stroke Association. Guidelines for the early management of patients with ischemic stroke: 2005 guidelines update: a scientific statement from the Stroke Council of the American Heart Association/American Stroke Association. *Stroke*. 2005;36:916–923.
12. Adams HP Jr, Brott TG, Furlan AJ, Gomez CR, Grotta J, Helgason CM, Kwiatkowski T, Lyden PD, Marler JR, Torner J, Feinberg W, Mayberg M, Thies W. Guidelines for thrombolytic therapy for acute stroke: a supplement to the guidelines for the management of patients with acute ischemic stroke: a statement for healthcare professionals from a Special Writing Group of the Stroke Council, American Heart Association. *Circulation*. 1996;94:1167–1174.
13. Adams HP Jr, del Zoppo G, Alberts MJ, Bhatt DL, Brass L, Furlan A, Grubb RL, Higashida RT, Jauch EC, Kidwell C, Lyden PD, Morgenstern LB, Qureshi AI, Rosenwasser RH, Scott PA, Wijdicks EF; American Heart Association; American Stroke Association Stroke Council; Clinical Cardiology Council; Cardiovascular Radiology and Intervention Council; Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups. Guidelines for the early management of adults with ischemic stroke: a guideline from the American Heart Association/American Stroke Association Stroke Council, Clinical Cardiology Council, Cardiovascular Radiology and Intervention Council, and the Atherosclerotic Peripheral Vascular Disease and Quality of Care Outcomes in Research Interdisciplinary Working Groups [published corrections appear in *Stroke*. 2007;38:e38 and *Stroke*. 2007;38:e96]. *Stroke*. 2007;38:1655–1711.
14. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association [published correction appears in *Stroke*. 2010;41:e562]. *Stroke*. 2009;40:2945–2948.
15. Jauch EC, Cucchiara B, Adeoye O, Meurer W, Brice J, Chan YY, Gentile N, Hazinski MF. Part 11: adult stroke: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [published correction appears in *Circulation*. 2011;124:e404]. *Circulation*. 2010;122(suppl 3):S818–S828.
16. Jurkowski JM, Maniccia DM, Dennison BA, Samuels SJ, Spicer DA. Awareness of necessity to call 9-1-1 for stroke symptoms, upstate New York. *Prev Chronic Dis*. 2008;5:A41.
17. Mosley I, Nicol M, Donnan G, Patrick I, Dewey H. Stroke symptoms and the decision to call for an ambulance. *Stroke*. 2007;38:361–366.
18. Chiti A, Fanucchi S, Sonnoli C, Barni S, Orlandi G. Stroke symptoms and the decision to call for an ambulance: turn on people's minds! *Stroke*. 2007;38:e58–e59.
19. California Acute Stroke Pilot Registry (CASPR) Investigators. Prioritizing interventions to improve rates of thrombolysis for ischemic stroke. *Neurology*. 2005;64:654–659.
20. Morgenstern LB, Staub L, Chan W, Wein TH, Bartholomew LK, King M, Felberg RA, Burgin WS, Groff J, Hickenbottom SL, Saldin K, Demchuk AM, Kalra A, Dhingra A, Grotta JC. Improving delivery of acute stroke therapy: the TLL Temple Foundation Stroke Project. *Stroke*. 2002;33:160–166.
21. Williams O, Noble JM. "Hip-hop" stroke: a stroke educational program for elementary school children living in a high-risk community. *Stroke*. 2008;39:2809–2816.
22. Morgenstern LB, Gonzales NR, Maddox KE, Brown DL, Karim AP, Espinosa N, Moyé LA, Pary JK, Grotta JC, Lisabeth LD, Conley KM. A randomized, controlled trial to teach middle school children to recognize stroke and call 9-1-1: the Kids Identifying and Defeating Stroke project. *Stroke*. 2007;38:2972–2978.
23. Kleindorfer DO, Miller R, Moomaw CJ, Alwell K, Broderick JP, Khoury J, Woo D, Flaherty ML, Zakaria T, Kissela BM. Designing a message for public education regarding stroke: does FAST capture enough stroke? *Stroke*. 2007;38:2864–2868.
24. Wall HK, Beagan BM, O'Neill J, Foell KM, Boddie-Willis CL. Addressing stroke signs and symptoms through public education: the Stroke Heroes Act FAST campaign. *Prev Chronic Dis*. 2008;5:A49.
25. Mohammad YM. Mode of arrival to the emergency department of stroke patients in the United States. *J Vasc Interv Neurol*. 2008;1:83–86.
26. Abdullah AR, Smith EE, Biddinger PD, Kalenderian D, Schwamm LH. Advance hospital notification by EMS in acute stroke is associated with shorter door-to-computed tomography time and increased likelihood of administration of tissue-plasminogen activator. *Prehosp Emerg Care*. 2008;12:426–431.
27. Brice JH, Evenson KR, Lellis JC, Rosamond WD, Aytur SA, Christian JB, Morris DL. Emergency medical services education, community outreach, and protocols for stroke and chest pain in North Carolina. *Prehosp Emerg Care*. 2008;12:366–371.
28. Tsai AW. Prehospital and emergency department capacity for acute stroke care in Minnesota. *Prev Chronic Dis*. 2008;5:A55.
29. Evenson KR, Brice JH, Rosamond WD, Lellis JC, Christian JB, Morris DL. Statewide survey of 9-1-1 communication centers on acute stroke and myocardial infarction. *Prehosp Emerg Care*. 2007;11:186–191.
30. Rosamond WD, Evenson KR, Schroeder EB, Morris DL, Johnson AM, Brice JH. Calling emergency medical services for acute stroke: a study of 9-1-1 tapes. *Prehosp Emerg Care*. 2005;9:19–23.
31. Reginella RL, Crocco T, Tadros A, Shackleford A, Davis SM. Predictors of stroke during 9-1-1 calls: opportunities for improving EMS response. *Prehosp Emerg Care*. 2006;10:369–373.
32. Ramanujam P, Castillo E, Patel E, Vilke G, Wilson MP, Dunford JV. Prehospital transport time intervals for acute stroke patients. *J Emerg Med*. 2009;37:40–45.
33. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Vanden Hoek TL, Kronick SL. Part 9: post-cardiac arrest care: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [published corrections appear in *Circulation*. 2011;123:e237 and *Circulation*. 2011;124:e403]. *Circulation*. 2010;122(suppl 3):S768–S786.
34. Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field: prospective validation of the Los Angeles prehospital stroke screen (LAPSS). *Stroke*. 2000;31:71–76.
35. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med*. 1999;33:373–378.
36. McKinney JS, Mylavarapu K, Lane J, Roberts V, Ohman-Strickland P, Merlin MA. Hospital prenotification of stroke patients by emergency medical services improves stroke time targets. *J Stroke Cerebrovasc Dis*. 2013;22:113–118.
37. Patel MD, Rose KM, O'Brien EC, Rosamond WD. Prehospital notification by emergency medical services reduces delays in stroke evaluation: findings from the North Carolina stroke care collaborative. *Stroke*. 2011;42:2263–2268.
38. Kim SK, Lee SY, Bae HJ, Lee YS, Kim SY, Kang MJ, Cha JK. Prehospital notification reduced the door-to-needle time for iv t-PA in acute ischaemic stroke [published correction appears in *Eur J Neurol*. 2010;17:170]. *Eur J Neurol*. 2009;16:1331–1335.
39. Svenson JE, O'Connor JE, Lindsay MB. Is air transport faster? A comparison of air versus ground transport times for interfacility transfers in a regional referral system. *Air Med J*. 2006;25:170–172.
40. Chalela JA, Kasner SE, Jauch EC, Pancioli AM. Safety of air medical transportation after tissue plasminogen activator administration in acute ischemic stroke. *Stroke*. 1999;30:2366–2368.
41. Meretoja A, Roine RO, Kaste M, Linna M, Roine S, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Effectiveness of primary and comprehensive stroke centers: PERFECT stroke: a nationwide observational study from Finland. *Stroke*. 2010;41:1102–1107.
42. Smith EE, Hassan KA, Fang J, Selchen D, Kapral MK, Saposnik G; Registry of the Canadian Stroke Network (RCSN); Stroke Outcome Research Canada (SORCan) Working Group. Do all ischemic stroke subtypes benefit from organized inpatient stroke care? *Neurology*. 2010;75:456–462.
43. Alberts MJ, Hademenos G, Latchaw RE, Jagoda A, Marler JR, Mayberg MR, Starke RD, Todd HW, Viste KM, Girgus M, Shephard T, Emr M, Shwayder P, Walker MD. Recommendations for the establishment of primary stroke centers: Brain Attack Coalition. *JAMA*. 2000;283:3102–3109.
44. The Joint Commission. Facts about Primary Stroke Center Certification. February 16, 2011. http://www.jointcommission.org/facts_about_primary_stroke_center_certification/. Accessed June 20, 2011.
45. Audebert HJ, Schenkel J, Heuschmann PU, Bogdahn U, Haberl RL; Telemedic Pilot Project for Integrative Stroke Care Group. Effects of the implementation of a telemedical stroke network: the Telemedic Pilot Project for Integrative Stroke Care (TEMPiS) in Bavaria, Germany. *Lancet Neurol*. 2006;5:742–748.

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46. Sung SF, Ong CT, Wu CS, Hsu YC, Su YH. Increased use of thrombolytic therapy and shortening of in-hospital delays following acute ischemic stroke: experience on the establishment of a primary stroke center at a community hospital. *Acta Neurol Taiwan*. 2010;19:246–252.
47. Rose KM, Rosamond WD, Huston SL, Murphy CV, Tegeler CH. Predictors of time from hospital arrival to initial brain-imaging among suspected stroke patients: the North Carolina Collaborative Stroke Registry. *Stroke*. 2008;39:3262–3267.
48. Xian Y, Holloway RG, Chan PS, Noyes K, Shah MN, Ting HH, Chappel AR, Peterson ED, Friedman B. Association between stroke center hospitalization for acute ischemic stroke and mortality. *JAMA*. 2011;305:373–380.
49. Gropen TI, Gagliano PJ, Blake CA, Sacco RL, Kwiatkowski T, Richmond NJ, Leifer D, Libman R, Azhar S, Daley MB; NYSDOH Stroke Center Designation Project Workgroup. Quality improvement in acute stroke: the New York State Stroke Center Designation Project. *Neurology*. 2006;67:88–93.
50. Stradling D, Yu W, Langdorf ML, Tsai F, Kostanian V, Hasso AN, Welbourne SJ, Schooley Y, Fisher MJ, Cramer SC. Stroke care delivery before vs after JCAHO stroke center certification. *Neurology*. 2007;68:469–470.
51. Alberts MJ, Latchaw RE, Selman WR, Shephard T, Hadley MN, Brass LM, Koroshetz W, Marler JR, Booss J, Zorowitz RD, Croft JB, Magnis E, Mulligan D, Jagoda A, O'Connor R, Cawley CM, Connors JJ, Rose-DeRenzy JA, Emr M, Warren M, Walker MD; Brain Attack Coalition. Recommendations for comprehensive stroke centers: a consensus statement from the Brain Attack Coalition. *Stroke*. 2005;36:1597–1616.
52. Cramer SC, Stradling D, Brown DM, Carrillo-Nunez IM, Ciabarra A, Cummings M, Dauben R, Lombardi DL, Patel N, Traynor EN, Waldman S, Miller K, Stratton SJ. Organization of a United States county system for comprehensive acute stroke care. *Stroke*. 2012;43:1089–1093.
53. McKinney JS, Deng Y, Kasner SE, Kostis JB; Myocardial Infarction Data Acquisition System (MIDAS 15) Study Group. Comprehensive stroke centers overcome the weekend versus weekday gap in stroke treatment and mortality. *Stroke*. 2011;42:2403–2409.
54. Suarez JI. Outcome in neurocritical care: advances in monitoring and treatment and effect of a specialized neurocritical care team. *Crit Care Med*. 2006;34(suppl):S232–S238.
55. Rincon F, Mayer SA. Neurocritical care: a distinct discipline? *Curr Opin Crit Care*. 2007;13:115–121.
56. Suarez JI, Zaidat OO, Suri MF, Feen ES, Lynch G, Hickman J, Georgiadis A, Selman WR. Length of stay and mortality in neurocritically ill patients: impact of a specialized neurocritical care team. *Crit Care Med*. 2004;32:2311–2317.
57. Hemphill JC 3rd, Barton CW, Morabito D, Manley GT. Influence of data resolution and interpolation method on assessment of secondary brain insults in neurocritical care. *Physiol Meas*. 2005;26:373–386.
58. Hess DC, Wang S, Gross H, Nichols FT, Hall CE, Adams RJ. Telestroke: extending stroke expertise into underserved areas. *Lancet Neurol*. 2006;5:275–278.
59. Demaerschalk BM. Telemedicine or telephone consultation in patients with acute stroke. *Curr Neurol Neurosci Rep*. 2011;11:42–51.
60. Ickenstein GW, Horn M, Schenkel J, Vatankhah B, Bogdahn U, Haberl R, Audebert HJ. The use of telemedicine in combination with a new stroke-code-box significantly increases t-PA use in rural communities. *Neurocrit Care*. 2005;3:27–32.
61. Switzer JA, Hess DC. Development of regional programs to speed treatment of stroke. *Curr Neurol Neurosci Rep*. 2008;8:35–42.
62. Switzer JA, Hall C, Gross H, Waller J, Nichols FT, Wang S, Adams RJ,Hess DC. A web-based telestroke system facilitates rapid treatment of acute ischemic stroke patients in rural emergency departments. *J Emerg Med*. 2009;36:12–18.
63. Audebert HJ, Kukla C, Vatankhah B, Gotzler B, Schenkel J, Hofer S, Fürst A, Haberl RL. Comparison of tissue plasminogen activator administration management between Telestroke Network hospitals and academic stroke centers: the Telemedical Pilot Project for Integrative Stroke Care in Bavaria/Germany. *Stroke*. 2006;37:1822–1827.
64. Sairanen T, Soinila S, Nikkanen M, Rantanen K, Mustanoja S, Färkkilä M, Pieninkeroinen I, Numminen H, Baumann P, Valpas J, Kuha T, Kaste M, Tatlisumak T; Finnish Telestroke Task Force. Two years of Finnish Telestroke: thrombolysis at spokes equal to that at the hub. *Neurology*. 2011;76:1145–1152.
65. Demaerschalk BM, Hwang HM, Leung G. Cost analysis review of stroke centers, telestroke, and rt-PA. *Am J Manag Care*. 2010;16:537–544.
66. Schwab S, Vatankhah B, Kukla C, Hauchwitz M, Bogdahn U, Fürst A, Audebert HJ,Horn M; TEMPiS Group. Long-term outcome after thrombolysis in telemedical stroke care. *Neurology*. 2007;69:898–903.
67. Meyer BC, Raman R, Hemmen T, Obler R, Zivin JA, Rao R, Thomas RG,Lyden PD. Efficacy of site-independent telemedicine in the STRokE DOC trial: a randomised, blinded, prospective study. *Lancet Neurol*. 2008;7:787–795.
68. Demaerschalk BM, Bobrow BJ, Raman R, Kiernan TE, Aguilar MI, Ingall TJ, Dodick DW, Ward MP, Richemont PC, Brazdys K, Koch TC, Miley ML, Hoffman Snyder CR, Corday DA, Meyer BC; STRokE DOC AZ TIME Investigators. Stroke team remote evaluation using a digital observation camera in Arizona: the initial Mayo Clinic experience trial. *Stroke*. 2010;41:1251–1258.
69. Waite K, Silver F, Jaigobin C, Black S, Lee L, Murray B, Danyliuk P, Brown EM. Telestroke: a multi-site, emergency-based telemedicine service in Ontario. *J Telemed Telecare*. 2006;12:141–145.
70. Smith EE, Dreyer P, Prvu-Bettger J, Abdullah AR, Palmeri G, Goyette L, McElligott C,Schwamm LH. Stroke center designation can be achieved by small hospitals: the Massachusetts experience. *Crit Pathw Cardiol*. 2008;7:173–177.
71. Thrall JH. Teleradiology: part I: history and clinical applications. *Radiology*. 2007;243:613–617.
72. *Medicare Payment of Telemedicine and Telehealth Services.* Washington, DC: American Telemedicine Association; 2007.
73. *Medicare Guide to Rural Health Services Information for Providers, Suppliers, and Physicians.* Baltimore, MD: Centers for Medicare and Medicaid Services; 2007.
74. Existing requirements for telemedicine practitioners explained. *Jt Comm Perspect*. 2003;23:4.
75. Kidwell CS, Alger JR, Di Salle F, Starkman S, Villablanca P, Bentson J, Saver JL. Diffusion MRI in patients with transient ischemic attacks. *Stroke*. 1999;30:1174–1180.
76. Noguchi K, Ogawa T, Inugami A, Toyoshima H, Sugawara S, Hatazawa J, Fujita H,Shimosegawa I,Kanno I,Okudera T. Acute subarachnoid hemorrhage: MR imaging with fluid-attenuated inversion recovery pulse sequences. *Radiology*. 1995;196:773–777.
77. Sames TA, Storrow AB, Finkelstein JA, Magoon MR. Sensitivity of new-generation computed tomography in subarachnoid hemorrhage. *Acad Emerg Med*. 1996;3:16–20.
78. Tomura N, Uemura K, Inugami A, Fujita H, Higano S, Shishido F. Early CT finding in cerebral infarction: obscuration of the lentiform nucleus. *Radiology*. 1988;168:463–467.
79. Phabphal K, Hirunpatch S. The effectiveness of low-cost teleconsultation for emergency head computer tomography in patients with suspected stroke. *J Telemed Telecare*. 2008;14:439–442.
80. Mitchell JR, Sharma P, Modi J, Simpson M, Thomas M, Hill MD, Goyal M. A smartphone client-server teleradiology system for primary diagnosis of acute stroke. *J Med Internet Res*. 2011;13:e31.
81. Anderson ER, Smith B, Ido M, Frankel M. Remote assessment of stroke using the iPhone 4. *J Stroke Cerebrovasc Dis*. Published online before print October 21, 2011. doi:10.1016/j.jstrokecerebrovascdis.2011.09.013. http://www.strokejournal.org/article/S1052-3057(11)00255-2/abstract. Accessed January 26, 2013.
82. Johnston KC, Worrall BB; Teleradiology Assessment of Computerized Tomographs Online Reliability Study. Teleradiology Assessment of Computerized Tomographs Online Reliability Study (TRACTORS) for acute stroke evaluation. *Telemed J E Health*. 2003;9:227–233.
83. Reeves MJ, Broderick JP, Frankel M, LaBresh KA, Schwamm L, Moomaw CJ, Weiss P, Katzan I, Arora S, Heinrich JP, Hickenbottom S, Karp H, Malarcher A, Mensah G, Reeves MJ; Paul Coverdell Prototype Registries Writing Group. The Paul Coverdell National Acute Stroke Registry: initial results from four prototypes. *Am J Prev Med*. 2006;31(suppl 2):S202–S209.
84. Stoeckle-Roberts S, Reeves MJ, Jacobs BS, Maddox K, Choate L, Wehner S, Mullard AJ. Closing gaps between evidence-based stroke care guidelines and practices with a collaborative quality improvement project. *Jt Comm J Qual Patient Saf*. 2006;32:517–527.
85. Centers for Disease Control and Prevention (CDC). Use of a registry to improve acute stroke care: seven states, 2005–2009. *MMWR Morb Mortal Wkly Rep*. 2011;60:206–210.
86. American Heart Association and American Stroke Association. Performance Achievement. Get With The Guidelines. http://www.heart.org/HEARTORG/HealthcareProfessional/GetWithTheGuidelinesHFStroke/GetWithTheGuidelinesStrokeHomePage/Get-With-The-Guidelines-Stroke-Home-Page_UCM_306098_SubHomePage.jsp. Accessed January 21, 2013.

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87. Schwamm LH, Fonarow GC, Reeves MJ, Pan W, Frankel MR, Smith EE, Ellrodt G,Cannon CP,Liang L,Peterson E,Labresh KA. Get With the Guidelines-Stroke is associated with sustained improvement in care for patients hospitalized with acute stroke or transient ischemic attack. *Circulation*. 2009;119:107–115.
88. LaBresh KA, Reeves MJ, Frankel MR, Albright D, Schwamm LH. Hospital treatment of patients with ischemic stroke or transient ischemic attack using the "Get With The Guidelines" program. *Arch Intern Med*. 2008;168:411–417.
89. Fonarow GC, Reeves MJ, Smith EE, Saver JL, Zhao X, Olson DW, Peterson EE, Schwamm LH; GWTG-Stroke Steering Committee and Investigators. Characteristics, performance measures, and in-hospital outcomes of the first one million stroke and transient ischemic attack admissions in Get With The Guidelines-Stroke. *Circ Cardiovasc Qual Outcomes*. 2010;3:291–302.
90. Reeves MJ, Fonarow GC, Zhao X, Smith EE, Schwamm LH; Get With The Guidelines-Stroke Steering Committee & Investigators. Quality of care in women with ischemic stroke in the GWTG program. *Stroke*. 2009;40:1127–1133.
91. Fonarow GC, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. *Circulation*. 2011;123:750–758.
92. Hacke W, Donnan G, Fieschi C, Kaste M, von Kummer R, Broderick JP, Brott T, Frankel M, Grotta JC, Haley EC Jr, Kwiatkowski T, Levine SR, Lewandowski C, Lu M, Lyden P, Marler JR, Patel S, Tilley BC, Albers G, Bluhmki E, Wilhelm M, Hamilton S; ATLANTIS Trials Investigators; ECASS Trials Investigators; NINDS rt-PA Study Group Investigators. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.
93. Marler JR, Tilley BC, Lu M, Brott TG, Lyden PC, Grotta JC, Broderick JP, Levine SR, Frankel MP, Horowitz SH, Haley EC Jr, Lewandowski CA, Kwiatkowski TP. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology*. 2000;55:1649–1655.
94. National Institute of Neurological Disorders and Stroke Symposium. *Improving the chain of recovery for acute stroke in your community: task force reports*. Bethesda, MD: National Institutes of Health, Department of Health and Human Services; 2003.
95. Marler JR, Jones PW, Emr M, eds. *Setting New Directions for Stroke Care: Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke*. Bethesda, MD: National Institute of Neurological Disorders and Stroke; 1997.
96. Bock BF. *Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke: Response System for Patients Presenting With Acute Stroke.* http://www.ninds.nih.gov/news_and_events/proceedings/stroke_proceedings/bock.htm. Accessed August 23, 2011.
97. Asimos AW, Norton HJ, Price MF, Cheek WM. Therapeutic yield and outcomes of a community teaching hospital code stroke protocol. *Acad Emerg Med*. 2004;11:361–370.
98. Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic accuracy of stroke referrals from primary care, emergency room physicians, and ambulance staff using the face arm speech test. *Stroke*. 2003;34:71–76.
99. Nor AM, McAllister C, Louw SJ, Dyker AG, Davis M, Jenkinson D, Ford GA. Agreement between ambulance paramedic- and physician-recorded neurological signs with Face Arm Speech Test (FAST) in acute stroke patients. *Stroke*. 2004;35:1355–1359.
100. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, Davis M,Ford GA. The Recognition of Stroke in the Emergency Room (ROSIER) scale: development and validation of a stroke recognition instrument. *Lancet Neurol*. 2005;4:727–734.
101. Josephson SA, Hills NK, Johnston SC. NIH Stroke Scale reliability in ratings from a large sample of clinicians. *Cerebrovasc Dis*. 2006;22:389–395.
102. Lyden P, Raman R, Liu L, Emr M, Warren M, Marler J. National Institutes of Health Stroke Scale certification is reliable across multiple venues. *Stroke*. 2009;40:2507–2511.
103. NINDS t-PA Stroke Study Group. Generalized efficacy of t-PA for acute stroke: subgroup analysis of the NINDS t-PA Stroke Trial. *Stroke*. 1997;28:2119–2125.
104. Adams HP Jr, Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, Woolson RF,Hansen MD. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53:126–131.
105. Frankel MR, Morgenstern LB, Kwiatkowski T, Lu M, Tilley BC, Broderick JP, Libman R, Levine SR, Brott T. Predicting prognosis after stroke: a placebo group analysis from the National Institute of Neurological Disorders and Stroke rt-PA Stroke Trial. *Neurology*. 2000;55:952–959.
106. Winkler DT, Fluri F, Fuhr P, Wetzel SG, Lyrer PA, Ruegg S, Engelter ST. Thrombolysis in stroke mimics: frequency, clinical characteristics, and outcome. *Stroke*. 2009;40:1522–1525.
107. Scott PA, Silbergleit R. Misdiagnosis of stroke in tissue plasminogen activator-treated patients: characteristics and outcomes. *Ann Emerg Med*. 2003;42:611–618.
108. Chernyshev OY, Martin-Schild S, Albright KC, Barreto A, Misra V, Acosta I, Grotta JC, Savitz SI. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. *Neurology*. 2010;74:1340–1345.
109. Saver JL, Barsan WG. Swift or sure? The acceptable rate of neurovascular mimics among IV tPA-treated patients. *Neurology*. 2010;74:1336–1337.
110. Kothari RU, Brott T, Broderick JP, Hamilton CA. Emergency physicians: accuracy in the diagnosis of stroke. *Stroke*. 1995;26:2238–2241.
111. Morgenstern LB, Lisabeth LD, Mecozzi AC, Smith MA, Longwell PJ, McFarling DA, Risser JM. A population-based study of acute stroke and TIA diagnosis. *Neurology*. 2004;62:895–900.
112. Akins PT, Delemos C, Wentworth D, Byer J, Schorer SJ, Atkinson RP. Can emergency department physicians safely and effectively initiate thrombolysis for acute ischemic stroke? *Neurology*. 2000;55:1801–1805.
113. Lopez-Yunez AM, Bruno A, Williams LS, Yilmaz E, Zurrú C, Biller J. Protocol violations in community-based rTPA stroke treatment are associated with symptomatic intracerebral hemorrhage. *Stroke*. 2001;32:12–16.
114. Rymer MM, Thurtchley D, Summers D; America Brain and Stroke Institute Stroke Team. Expanded modes of tissue plasminogen activator delivery in a comprehensive stroke center increases regional acute stroke interventions. *Stroke*. 2003;34:e58–e60.
115. Smith RW, Scott PA, Grant RJ, Chudnofsky CR, Frederiksen SM. Emergency physician treatment of acute stroke with recombinant tissue plasminogen activator: a retrospective analysis. *Acad Emerg Med*. 1999;6:618–625.
116. Wang DZ, Rose JA, Honings DS, Garwacki DJ, Milbrandt JC. Treating acute stroke patients with intravenous tPA: the OSF Stroke Network experience. *Stroke*. 2000;31:77–81.
117. Tanne D, Bates VE, Verro P, Kasner SE, Binder JR, Patel SC, Mansbach HH, Daley S, Schultz LR, Karanjia PN, Scott P, Dayno JM, Vereczkey-Porter K, Benesch C, Book D, Coplin WM, Dulli D, Levine SR. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey: the t-PA Stroke Survey Group. *Neurology*. 1999;53:424–427.
118. Katzan IL, Furlan AJ, Lloyd LE, Frank JI, Harper DL, Hinchey JA, Hammel JP,Qu A,Sila CA. Use of tissue-type plasminogen activator for acute ischemic stroke: the Cleveland area experience. *JAMA*. 2000;283:1151–1158.
119. Bravata DM, Kim N, Concato J, Krumholz HM, Brass LM. Thrombolysis for acute stroke in routine clinical practice. *Arch Intern Med*. 2002;162:1994–2001.
120. Katzan IL, Hammer MD, Furlan AJ, Hixson ED, Nadzam DM; Cleveland Clinic Health System Stroke Quality Improvement Team. Quality improvement and tissue-type plasminogen activator for acute ischemic stroke: a Cleveland update. *Stroke*. 2003;34:799–800.
121. Meurer WJ, Caveney AF, Lo A, Zhang L, Frederiksen SM, Sandretto AM, Silbergleit R, Scott PA. Lack of association between pretreatment neurology consultation and subsequent protocol deviation in tissue plasminogen activator-treated patients with stroke. *Stroke*. 2010;41:2098–2101.
122. Scott PA, Frederiksen SM, Kalbfleisch JD, Xu Z, Meurer WJ, Caveney AF, Sandretto A, Holden AB, Haan MN, Hoeffner EG, Ansari SA, Lambert DP, Jaggi M, Barsan WG, Silbergleit R. Safety of intravenous thrombolytic use in four emergency departments without acute stroke teams. *Acad Emerg Med*. 2010;17:1062–1071.
123. Kerr G, Ray G, Wu O, Stott DJ, Langhorne P. Elevated troponin after stroke: a systematic review. *Cerebrovasc Dis*. 2009;28:220–226.
124. James P, Ellis CJ, Whitlock RM, McNeil AR, Henley J, Anderson NE. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. *BMJ*. 2000;320:1502–1504.
125. Di Angelantonio E, Fiorelli M, Toni D, Sacchetti ML, Lorenzano S, Falcou A, Ciarla MV, Suppa M, Bonanni L, Bertazzoni G, Aguglia F,

Downloaded from http://stroke.ahajournals.org/ at Wayne State University on February 18, 2013

Argentino C. Prognostic significance of admission levels of troponin I in patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatr*. 2005;76:76–81.
126. Jensen JK, Kristensen SR, Bak S, Atar D, Høilund-Carlsen PF, Mickley H. Frequency and significance of troponin T elevation in acute ischemic stroke. *Am J Cardiol*. 2007;99:108–112.
127. Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology*. 2006;66:1325–1329.
128. Blommel ML, Blommel AL. Dabigatran etexilate: A novel oral direct thrombin inhibitor. *Am J Health Syst Pharm*. 2011;68:1506–1519.
129. Westover AN, McBride S, Haley RW. Stroke in young adults who abuse amphetamines or cocaine: a population-based study of hospitalized patients. *Arch Gen Psychiatry*. 2007;64:495–502.
130. Rost NS, Masrur S, Pervez MA, Viswanathan A, Schwamm LH. Unsuspected coagulopathy rarely prevents IV thrombolysis in acute ischemic stroke. *Neurology*. 2009;73:1957–1962.
131. Cucchiara BL, Jackson B, Weiner M, Messe SR. Usefulness of checking platelet count before thrombolysis in acute ischemic stroke. *Stroke*. 2007;38:1639–1640.
132. Sagar G, Riley P, Vohrah A. Is admission chest radiography of any clinical value in acute stroke patients? *Clin Radiol*. 1996;51:499–502.
133. Goldstein LB. Stroke code chest radiographs are not useful. *Cerebrovasc Dis*. 2007;24:460–462.
134. Lazzaro MA, Krishnan K, Prabhakaran S. Detection of atrial fibrillation with concurrent Holter monitoring and continuous cardiac telemetry following ischemic stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis*. 2012;21:89–93.
135. Vingerhoets F, Bogousslavsky J, Regli F, Van Melle G. Atrial fibrillation after acute stroke. *Stroke*. 1993;24:26–30.
136. Christensen H, Fogh Christensen A, Boysen G. Abnormalities on ECG and telemetry predict stroke outcome at 3 months. *J Neurol Sci*. 2005;234:99–103.
137. Dimant J, Grob D. Electrocardiographic changes and myocardial damage in patients with acute cerebrovascular accidents. *Stroke*. 1977;8:448–455.
138. Oppenheimer SM. Neurogenic cardiac effects of cerebrovascular disease. *Curr Opin Neurol*. 1994;7:20–24.
139. Oppenheimer SM, Hachinski VC. The cardiac consequences of stroke. *Neurol Clin*. 1992;10:167–176.
140. Kidwell CS, Villablanca JP, Saver JL. Advances in neuroimaging of acute stroke. *Curr Atheroscler Rep*. 2000;2:126–135.
141. Schellinger PD, Bryan RN, Caplan LR, Detre JA, Edelman RR, Jaigobin C, Kidwell CS, Mohr JP, Sloan M, Sorensen AG, Warach S; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Evidence-based guideline: the role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology [published correction appears in *Neurology*. 2010;75:938]. *Neurology*. 2010;75:177–185.
142. von Kummer R, Bourquain H, Bastianello S, Bozzao L, Manelfe C, Meier D, Hacke W. Early prediction of irreversible brain damage after ischemic stroke at CT. *Radiology*. 2001;219:95–100.
143. The European Stroke Organisation (ESO) Executive Committee and the ESO Writing Committee. Guidelines for management of ischaemic stroke and transient ischaemic attack 2008. *Cerebrovasc Dis*. 2008;25:457–507.
144. Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke: potential contributing factors in the European Cooperative Acute Stroke Study. *Stroke*. 1997;28:957–960.
145. Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, Erilä T, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Köhrmann M, Larrue V, Lees KR, Machnig T, Roine RO, Toni D, Vanhooren G; Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy Investigators. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITS-MOST). *Stroke*. 2008;39:3316–3322.
146. Demchuk AM, Hill MD, Barber PA, Silver B, Patel SC, Levine SR; NINDS rtPA Stroke Study Group, NIH. Importance of early ischemic computed tomography changes using ASPECTS in NINDS rtPA Stroke Study. *Stroke*. 2005;36:2110–2115.
147. Dzialowski I, Hill MD, Coutts SB, Demchuk AM, Kent DM, Wunderlich O, von Kummer R. Extent of early ischemic changes on computed tomography (CT) before thrombolysis: prognostic value of the Alberta Stroke Program Early CT Score in ECASS II. *Stroke*. 2006;37:973–978.
148. Patel SC, Levine SR, Tilley BC, Grotta JC, Lu M, Frankel M, Haley EC Jr, Brott TG, Broderick JP, Horowitz S, Lyden PD, Lewandowski CA, Marler JR, Welch KM; National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA*. 2001;286:2830–2838.
149. Truwit CL, Barkovich AJ, Gean-Marton A, Hibri N, Norman D. Loss of the insular ribbon: another early CT sign of acute middle cerebral artery infarction. *Radiology*. 1990;176:801–806.
150. von Kummer R, Meyding-Lamade U, Forsting M, Rosin L, Rieke K, Hacke W, Sartor K. Sensitivity and prognostic value of early CT in occlusion of the middle cerebral artery trunk. *AJNR Am J Neuroradiol*. 1994;15:9–15.
151. Barber PA, Demchuk AM, Zhang J, Buchan AM. Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy: ASPECTS Study Group: Alberta Stroke Programme Early CT Score [published correction appears in *Lancet*. 2000;355:2170]. *Lancet*. 2000;355:1670–1674.
152. Demchuk AM, Coutts SB. Alberta Stroke Program Early CT Score in acute stroke triage. *Neuroimaging Clin N Am*. 2005;15:409–419, xii.
153. Kalafut MA, Schriger DL, Saver JL, Starkman S. Detection of early CT signs of >1/3 middle cerebral artery infarctions: interrater reliability and sensitivity of CT interpretation by physicians involved in acute stroke care. *Stroke*. 2000;31:1667–1671.
154. Demaerschalk BM, Silver B, Wong E, Merino JG, Tamayo A, Hachinski V. ASPECT scoring to estimate >1/3 middle cerebral artery territory infarction. *Can J Neurol Sci*. 2006;33:200–204.
155. Pexman JH, Barber PA, Hill MD, Sevick RJ, Demchuk AM, Hudon ME, Hu WY,Buchan AM. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol*. 2001;22:1534–1542.
156. Lev MH, Farkas J, Gemmete JJ, Hossain ST, Hunter GJ, Koroshetz WJ, Gonzalez RG. Acute stroke: improved nonenhanced CT detection: benefits of soft-copy interpretation by using variable window width and center level settings. *Radiology*. 1999;213:150–155.
157. Moulin T, Cattin F, Crépin-Leblond T, Tatu L, Chavot D, Piotin M, Viel JF,Rumbach L,Bonneville JF. Early CT signs in acute middle cerebral artery infarction: predictive value for subsequent infarct locations and outcome. *Neurology*. 1996;47:366–375.
158. Manno EM, Nichols DA, Fulgham JR, Wijdicks EF. Computed tomographic determinants of neurologic deterioration in patients with large middle cerebral artery infarctions. *Mayo Clin Proc*. 2003;78:156–160.
159. Smith WS, Tsao JW, Billings ME, Johnston SC, Hemphill JC 3rd, Bonovich DC, Dillon WP. Prognostic significance of angiographically confirmed large vessel intracranial occlusion in patients presenting with acute brain ischemia. *Neurocrit Care*. 2006;4:14–17.
160. Tomsick T, Brott T, Barsan W, Broderick J, Haley EC, Spilker J, Khoury J. Prognostic value of the hyperdense middle cerebral artery sign and stroke scale score before ultraearly thrombolytic therapy. *AJNR Am J Neuroradiol*. 1996;17:79–85.
161. Flacke S, Urbach H, Keller E, Träber F, Hartmann A, Textor J, Gieseke J, Block W, Folkers PJ, Schild HH. Middle cerebral artery (MCA) susceptibility sign at susceptibility-based perfusion MR imaging: clinical importance and comparison with hyperdense MCA sign at CT. *Radiology*. 2000;215:476–482.
162. Barber PA, Demchuk AM, Hudon ME, Pexman JH, Hill MD, Buchan AM. Hyperdense sylvian fissure MCA "dot" sign: a CT marker of acute ischemia. *Stroke*. 2001;32:84–88.
163. Leary MC, Kidwell CS, Villablanca JP, Starkman S, Jahan R, Duckwiler GR, Gobin YP, Sykes S, Gough KJ, Ferguson K, Llanes JN, Masamed R, Tremwel M, Ovbiagele B, Vespa PM, Vinuela F, Saver JL. Validation of computed tomographic middle cerebral artery "dot" sign: an angiographic correlation study. *Stroke*. 2003;34:2636–2640.
164. Arnold M, Nedeltchev K, Schroth G, Baumgartner RW, Remonda L, Loher TJ, Stepper F, Sturzenegger M, Schuknecht B, Mattle HP. Clinical and radiological predictors of recanalisation and outcome of 40 patients with acute basilar artery occlusion treated with intra-arterial thrombolysis. *J Neurol Neurosurg Psychiatr*. 2004;75:857–862.
165. Goldmakher GV, Camargo EC, Furie KL, Singhal AB, Roccatagliata L, Halpern EF, Chou MJ, Biagini T, Smith WS, Harris GJ, Dillon WP, Gonzalez RG, Koroshetz WJ, Lev MH. Hyperdense basilar artery sign on unenhanced CT predicts thrombus and outcome in acute posterior circulation stroke. *Stroke*. 2009;40:134–139.
166. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med*. 1995;333:1581–1587.

Downloaded from http://stroke.ahajournals.org/ at Wayne State University on February 18, 2013

167. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Höxter G, Mahagne M-H, Hennerici M. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke: the European Cooperative Acute Stroke Study (ECASS). *JAMA*. 1995;274:1017–1025.
168. Furlan A, Higashida R, Wechsler L, Gent M, Rowley H, Kase C, Pessin M, Ahuja A, Callahan F, Clark WM, Silver F, Rivera F. Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial: Prolyse in Acute Cerebral Thromboembolism. *JAMA*. 1999;282:2003–2011.
169. Hacke W, Kaste M, Bluhmki E, Brozman M, Dávalos A, Guidetti D, Larrue V, Lees KR, Medeghri Z, Machnig T, Schneider D,von Kummer R, Wahlgren N, Toni D; ECASS Investigators. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.
170. Ogawa A, Mori E, Minematsu K, Taki W, Takahashi A, Nemoto S, Miyamoto S,Sasaki M,Inoue T; MELT Japan Study Group. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. *Stroke*. 2007;38:2633–2639.
171. Mohr JP, Biller J, Hilal SK, Yuh WT, Tatemichi TK, Hedges S, Tali E, Nguyen H, Mun I, Adams HP Jr, Grimsman K, Marler JR. Magnetic resonance versus computed tomographic imaging in acute stroke. *Stroke*. 1995;26:807–812.
172. Barber PA, Darby DG, Desmond PM, Gerraty RP, Yang Q, Li T, Jolley D, Donnan GA, Tress BM, Davis SM. Identification of major ischemic change: diffusion-weighted imaging versus computed tomography. *Stroke*. 1999;30:2059–2065.
173. Fiebach JB, Schellinger PD, Jansen O, Meyer M, Wilde P, Bender J, Schramm P, Jüttler E, Oehler J, Hartmann M, Hähnel S, Knauth M, Hacke W, Sartor K. CT and diffusion-weighted MR imaging in randomized order: diffusion-weighted imaging results in higher accuracy and lower interrater variability in the diagnosis of hyperacute ischemic stroke. *Stroke*. 2002;33:2206–2210.
174. González RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. *Radiology*. 1999;210:155–162.
175. Ay H, Buonanno FS, Rordorf G, Schaefer PW, Schwamm LH, Wu O, Gonzalez RG, Yamada K, Sorensen GA, Koroshetz WJ. Normal diffusion-weighted MRI during stroke-like deficits. *Neurology*. 1999;52:1784–1792.
176. Barber PA, Darby DG, Desmond PM, Yang Q, Gerraty RP, Jolley D, Donnan GA, Tress BM, Davis SM. Prediction of stroke outcome with echoplanar perfusion- and diffusion-weighted MRI. *Neurology*. 1998;51:418–426.
177. Lee LJ, Kidwell CS, Alger J, Starkman S, Saver JL. Impact on stroke subtype diagnosis of early diffusion-weighted magnetic resonance imaging and magnetic resonance angiography. *Stroke*. 2000;31:1081–1089.
178. Lövblad KO, Laubach HJ, Baird AE, Curtin F, Schlaug G, Edelman RR, Warach S. Clinical experience with diffusion-weighted MR in patients with acute stroke. *AJNR Am J Neuroradiol*. 1998;19:1061–1066.
179. Lutsep HL, Albers GW, DeCrespigny A, Kamat GN, Marks MP, Moseley ME. Clinical utility of diffusion-weighted magnetic resonance imaging in the assessment of ischemic stroke. *Ann Neurol*. 1997;41:574–580.
180. van Everdingen KJ, van der Grond J, Kappelle LJ, Ramos LM, Mali WP. Diffusion-weighted magnetic resonance imaging in acute stroke. *Stroke*. 1998;29:1783–1790.
181. Warach S, Chien D, Li W, Ronthal M, Edelman RR. Fast magnetic resonance diffusion-weighted imaging of acute human stroke. *Neurology*. 1992;42:1717–1723.
182. Albers GW, Lansberg MG, Norbash AM, Tong DC, O'Brien MW, Woolfenden AR, Marks MP,Moseley ME. Yield of diffusion-weighted MRI for detection of potentially relevant findings in stroke patients. *Neurology*. 2000;54:1562–1567.
183. Bryan RN, Levy LM, Whitlow WD, Killian JM, Preziosi TJ, Rosario JA. Diagnosis of acute cerebral infarction: comparison of CT and MR imaging. *AJNR Am J Neuroradiol*. 1991;12:611–620.
184. Perkins CJ, Kahya E, Roque CT, Roche PE, Newman GC. Fluid-attenuated inversion recovery and diffusion- and perfusion-weighted MRI abnormalities in 117 consecutive patients with stroke symptoms. *Stroke*. 2001;32:2774–2781.
185. Wiener JI, King JT Jr, Moore JR, Lewin JS. The value of diffusion-weighted imaging for prediction of lasting deficit in acute stroke: an analysis of 134 patients with acute neurologic deficits. *Neuroradiology*. 2001;43:435–441.
186. Arauz A, Murillo L, Cantú C, Barinagarrementeria F, Higuera J. Prospective study of single and multiple lacunar infarcts using magnetic resonance imaging: risk factors, recurrence, and outcome in 175 consecutive cases. *Stroke*. 2003;34:2453–2458.
187. Ay H, Oliveira-Filho J, Buonanno FS, Ezzeddine M, Schaefer PW, Rordorf G, Schwamm LH,Gonzalez RG,Koroshetz WJ. Diffusion-weighted imaging identifies a subset of lacunar infarction associated with embolic source. *Stroke*. 1999;30:2644–2650.
188. Baird AE, Lövblad KO, Schlaug G, Edelman RR, Warach S. Multiple acute stroke syndrome: marker of embolic disease? *Neurology*. 2000; 54:674–678.
189. Caso V, Budak K, Georgiadis D, Schuknecht B, Baumgartner RW. Clinical significance of detection of multiple acute brain infarcts on diffusion weighted magnetic resonance imaging. *J Neurol Neurosurg Psychiatr*. 2005;76:514–518.
190. Etgen T, Gräfin von Einsiedel H, Röttinger M, Winbeck K, Conrad B, Sander D. Detection of acute brainstem infarction by using DWI/MRI. *Eur Neurol*. 2004;52:145–150.
191. Gerraty RP, Parsons MW, Barber PA, Darby DG, Desmond PM, Tress BM, Davis SM. Examining the lacunar hypothesis with diffusion and perfusion magnetic resonance imaging. *Stroke*. 2002;33:2019–2024.
192. Keir SL, Wardlaw JM, Bastin ME, Dennis MS. In which patients is diffusion-weighted magnetic resonance imaging most useful in routine stroke care? *J Neuroimaging*. 2004;14:118–122.
193. Mullins ME, Schaefer PW, Sorensen AG, Halpern EF, Ay H, He J, Koroshetz WJ,Gonzalez RG. CT and conventional and diffusion-weighted MR imaging in acute stroke: study in 691 patients at presentation to the emergency department. *Radiology*. 2002;224:353–360.
194. Seifert T, Enzinger C, Storch MK, Pichler G, Niederkorn K, Fazekas F. Acute small subcortical infarctions on diffusion weighted MRI: clinical presentation and aetiology. *J Neurol Neurosurg Psychiatr*. 2005;76:1520–1524.
195. Takahashi K, Kobayashi S, Matui R, Yamaguchi S, Yamashita K. The differences of clinical parameters between small multiple ischemic lesions and single lesion detected by diffusion-weighted MRI. *Acta Neurol Scand*. 2002;106:24–29.
196. Wessels T, Röttger C, Jauss M, Kaps M, Traupe H, Stolz E. Identification of embolic stroke patterns by diffusion-weighted MRI in clinically defined lacunar stroke syndromes. *Stroke*. 2005;36:757–761.
197. Wityk RJ, Goldsborough MA, Hillis A, Beauchamp N, Barker PB, Borowicz LM Jr, McKhann GM. Diffusion- and perfusion-weighted brain magnetic resonance imaging in patients with neurologic complications after cardiac surgery. *Arch Neurol*. 2001;58:571–576.
198. Lefkowitz D, LaBenz M, Nudo SR, Steg RE, Bertoni JM. Hyperacute ischemic stroke missed by diffusion-weighted imaging. *AJNR Am J Neuroradiol*. 1999;20:1871–1875.
199. Wang PY, Barker PB, Wityk RJ, Ulug AM, van Zijl PC, Beauchamp NJ Jr. Diffusion-negative stroke: a report of two cases. *AJNR Am J Neuroradiol*. 1999;20:1876–1880.
200. Kidwell CS, Saver JL, Mattiello J, Starkman S, Vinuela F, Duckwiler G, Gobin YP, Jahan R, Vespa P, Kalafut M, Alger JR. Thrombolytic reversal of acute human cerebral ischemic injury shown by diffusion/perfusion magnetic resonance imaging. *Ann Neurol*. 2000;47:462–469.
201. Sanossian N, Saver JL, Alger JR, Kim D, Duckwiler GR, Jahan R, Vinuela F, Ovbiagele B, Liebeskind DS. Angiography reveals that fluid-attenuated inversion recovery vascular hyperintensities are due to slow flow, not thrombus. *AJNR Am J Neuroradiol*. 2009;30:564–568.
202. Arakawa S, Wright PM, Koga M, Phan TG, Reutens DC, Lim I, Gunawan MR, Ma H, Perera N, Ly J, Zavala J, Fitt G, Donnan GA. Ischemic thresholds for gray and white matter: a diffusion and perfusion magnetic resonance study. *Stroke*. 2006;37:1211–1216.
203. Baird AE, Benfield A, Schlaug G, Siewert B, Lövblad KO, Edelman RR, Warach S. Enlargement of human cerebral ischemic lesion volumes measured by diffusion-weighted magnetic resonance imaging. *Ann Neurol*. 1997;41:581–589.
204. Bammer R, Moseley ME. Perfusion magnetic resonance and the perfusion/diffusion mismatch in stroke. In: Latchaw RE, Kucharczyk J, Moseley ME, eds. *Imaging of the Nervous System: Diagnostic and Therapeutic Applications.* Philadelphia, PA: Elsevier Mosby; 2005:227–248.
205. Beaulieu C, de Crespigny A, Tong DC, Moseley ME, Albers GW, Marks MP. Longitudinal magnetic resonance imaging study of perfusion and diffusion in stroke: evolution of lesion volume and correlation with clinical outcome. *Ann Neurol*. 1999;46:568–578.
206. Christensen S, Parsons M, De Silva D, Ebinger M, Butcher J, Fink J, Davis S. Optimal mismatch definitions for detecting treatment response in acute stroke. *Cerebrovasc Dis*. 2008;25(suppl 2):33.

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207. Kakuda W, Lansberg MG, Thijs VN, Kemp SM, Bammer R, Wechsler LR, Moseley ME, Marks MP, Albers GW; DEFUSE Investigators. Optimal definition for PWI/DWI mismatch in acute ischemic stroke patients [published correction appears in *J Cereb Blood Flow Metab*. 2008;28:1272]. *J Cereb Blood Flow Metab*. 2008;28:887–891.
208. Moseley ME, Bammer R. Diffusion-weighted magnetic resonance imaging. In: Latchaw RE, Kucharczyk J, Moseley ME, eds. *Imaging of the Nervous System: Diagnostic and Therapeutic Applications.* Philadelphia, PA: Elsevier Mosby; 2005:227–248.
209. Murphy BD, Fox AJ, Lee DH, Sahlas DJ, Black SE, Hogan MJ, Coutts SB, Demchuk AM, Goyal M, Aviv RI, Symons S, Gulka IB, Beletsky V, Pelz D, Hachinski V, Chan R, Lee TY. Identification of penumbra and infarct in acute ischemic stroke using computed tomography perfusion-derived blood flow and blood volume measurements. *Stroke*. 2006;37:1771–1777.
210. Schaefer PW, Roccatagliata L, Ledezma C, Hoh B, Schwamm LH, Koroshetz W, Gonzalez RG,Lev MH. First-pass quantitative CT perfusion identifies thresholds for salvageable penumbra in acute stroke patients treated with intra-arterial therapy. *AJNR Am J Neuroradiol*. 2006;27:20–25.
211. Shellock FG, Kanal E. Guidelines and recommendations for MR imaging safety and patient management, III: questionnaire for screening patients before MR procedures: the SMRI Safety Committee. *J Magn Reson Imaging*. 1994;4:749–751.
212. Sobesky J, Zaro Weber O, Lehnhardt FG, Hesselmann V, Neveling M, Jacobs A, Heiss WD. Does the mismatch match the penumbra? Magnetic resonance imaging and positron emission tomography in early ischemic stroke. *Stroke*. 2005;36:980–985.
213. Thomalla G, Schwark C, Sobesky J, Bluhmki E, Fiebach JB, Fiehler J, Zaro Weber O, Kucinski T, Juettler E, Ringleb PA, Zeumer H, Weiller C, Hacke W, Schellinger PD, Röther J; MRI in Acute Stroke Study Group of the German Competence Network Stroke. Outcome and symptomatic bleeding complications of intravenous thrombolysis within 6 hours in MRI-selected stroke patients: comparison of a German multicenter study with the pooled data of ATLANTIS, ECASS, and NINDS tPA trials. *Stroke*. 2006;37:852–858.
214. Tong DC, Yenari MA, Albers GW, O'Brien M, Marks MP, Moseley ME. Correlation of perfusion- and diffusion-weighted MRI with NIHSS score in acute (<6.5 hour) ischemic stroke. *Neurology*. 1998;50:864–870.
215. Warach S. New imaging strategies for patient selection for thrombolytic and neuroprotective therapies. *Neurology*. 2001;57(suppl 2):S48–S52.
216. Warach S. Measurement of the ischemic penumbra with MRI: it's about time. *Stroke*. 2003;34:2533–2534.
217. Deleted in proof.
218. Wintermark M, Albers GW, Alexandrov AV, Alger JR, Bammer R, Baron JC, Davis S, Demaerschalk BM, Derdeyn CP, Donnan GA, Eastwood JD, Fiebach JB, Fisher M, Furie KL, Goldmakher GV, Hacke W, Kidwell CS, Kloska SP, Köhrmann M, Koroshetz W, Lee TY, Lees KR, Lev MH, Liebeskind DS, Ostergaard L, Powers WJ, Provenzale J, Schellinger P, Silbergleit R, Sorensen AG, Wardlaw J, Wu O, Warach S. Acute stroke imaging research roadmap. *Stroke*. 2008;39:1621–1628.
219. Wintermark M, Flanders AE, Velthuis B, Meuli R, van Leeuwen M, Goldsher D, Pineda C, Serena J, van der Schaaf I, Waaijer A, Anderson J, Nesbit G, Gabriely I, Medina V, Quiles A, Pohlman S, Quist M, Schnyder P, Bogousslavsky J, Dillon WP, Pedraza S. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke*. 2006;37:979–985.
220. Wu O, Christensen S, Hjort N, Dijkhuizen RM, Kucinski T, Fiehler J, Thomalla G, Röther J, Østergaard L. Characterizing physiological heterogeneity of infarction risk in acute human ischaemic stroke using MRI. *Brain*. 2006;129(pt 9):2384–2393.
221. Coutts SB, Hill MD, Simon JE, Sohn CH, Scott JN, Demchuk AM; VISION Study Group. Silent ischemia in minor stroke and TIA patients identified on MR imaging. *Neurology*. 2005;65:513–517.
222. Cucchiara BL, Messe SR, Taylor RA, Pacelli J, Maus D, Shah Q, Kasner SE. Is the ABCD score useful for risk stratification of patients with acute transient ischemic attack? *Stroke*. 2006;37:1710–1714.
223. Restrepo L, Jacobs MA, Barker PB, Wityk RJ. Assessment of transient ischemic attack with diffusion- and perfusion-weighted imaging. *AJNR Am J Neuroradiol*. 2004;25:1645–1652.
224. Bradley WG Jr, Schmidt PG. Effect of methemoglobin formation on the MR appearance of subarachnoid hemorrhage. *Radiology*. 1985;156:99–103.
225. Edelman RR, Johnson K, Buxton R, Shoukimas G, Rosen BR, Davis KR, Brady TJ. MR of hemorrhage: a new approach. *AJNR Am J Neuroradiol*. 1986;7:751–756.
226. Gomori JM, Grossman RI, Goldberg HI, Zimmerman RA, Bilaniuk LT. Intracranial hematomas: imaging by high-field MR. *Radiology*. 1985;157:87–93.
227. Hayman LA, Taber KH, Ford JJ, Bryan RN. Mechanisms of MR signal alteration by acute intracerebral blood: old concepts and new theories. *AJNR Am J Neuroradiol*. 1991;12:899–907.
228. Kidwell CS, Chalela JA, Saver JL, Starkman S, Hill MD, Demchuk AM,Butman JA,Patronas N,Alger JR,Latour LL,Luby ML,Baird AE,Leary MC, Tremwel M,Ovbiagele B, Fredieu A, Suzuki S, Villablanca JP,Davis S,Dunn B,Todd JW,Ezzeddine MA, Haymore J,Lynch JK,Davis L, Warach S. Comparison of MRI and CT for detection of acute intracerebral hemorrhage. *JAMA*. 2004;292:1823–1830.
229. Linfante I, Llinas RH, Caplan LR, Warach S. MRI features of intracerebral hemorrhage within 2 hours from symptom onset. *Stroke*. 1999;30:2263–2267.
230. Patel MR, Edelman RR, Warach S. Detection of hyperacute primary intraparenchymal hemorrhage by magnetic resonance imaging. *Stroke*. 1996;27:2321–2324.
231. Schellinger PD, Jansen O, Fiebach JB, Hacke W, Sartor K. A standardized MRI stroke protocol: comparison with CT in hyperacute intracerebral hemorrhage. *Stroke*. 1999;30:765–768.
232. Fiebach JB, Schellinger PD, Gass A, Kucinski T, Siebler M, Villringer A, Olkers P, Hirsch JG, Heiland S, Wilde P, Jansen O, Röther J, Hacke W, Sartor K; Kompetenznetzwerk Schlaganfall B5. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: a multicenter study on the validity of stroke imaging. *Stroke*. 2004;35:502–506.
233. Chalela JA, Kang DW, Warach S. Multiple cerebral microbleeds: MRI marker of a diffuse hemorrhage-prone state. *J Neuroimaging*. 2004;14:54–57.
234. Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K, Leary MC, Starkman S, Gobin YP, Jahan R, Vespa P, Liebeskind DS, Alger JR, Vinuela F. Magnetic resonance imaging detection of microbleeds before thrombolysis: an emerging application. *Stroke*. 2002;33:95–98.
235. Wong KS, Chan YL, Liu JY, Gao S, Lam WW. Asymptomatic microbleeds as a risk factor for aspirin-associated intracerebral hemorrhages. *Neurology*. 2003;60:511–513.
236. Kakuda W, Thijs VN, Lansberg MG, Bammer R, Wechsler L, Kemp S, Moseley ME, Marks MP, Albers GW; DEFUSE Investigators. Clinical importance of microbleeds in patients receiving IV thrombolysis. *Neurology*. 2005;65:1175–1178.
237. Kharitonova T, Thorén M, Ahmed N, Wardlaw JM, von Kummer R, Thomassen L, Wahlgren N; SITS investigators. Disappearing hyperdense middle cerebral artery sign in ischaemic stroke patients treated with intravenous thrombolysis: clinical course and prognostic significance. *J Neurol Neurosurg Psychiatr*. 2009;80:273–278.
238. Linfante I, Llinas RH, Selim M, Chaves C, Kumar S, Parker RA, Caplan LR,Schlaug G. Clinical and vascular outcome in internal carotid artery versus middle cerebral artery occlusions after intravenous tissue plasminogen activator. *Stroke*. 2002;33:2066–2071.
239. Manelfe C, Larrue V, von Kummer R, Bozzao L, Ringleb P, Bastianello S, Iweins F,Lesaffre E. Association of hyperdense middle cerebral artery sign with clinical outcome in patients treated with tissue plasminogen activator. *Stroke*. 1999;30:769–772.
240. Tan IY, Demchuk AM, Hopyan J, Zhang L, Gladstone D, Wong K, Martin M, Symons SP, Fox AJ, Aviv RI. CT angiography clot burden score and collateral score: correlation with clinical and radiologic outcomes in acute middle cerebral artery infarct. *AJNR Am J Neuroradiol*. 2009;30:525–531.
241. Nichols C, Khoury J, Brott T, Broderick J. Intravenous recombinant tissue plasminogen activator improves arterial recanalization rates and reduces infarct volumes in patients with hyperdense artery sign on baseline computed tomography. *J Stroke Cerebrovasc Dis*. 2008;17:64–68.
242. Lev MH, Farkas J, Rodriguez VR, Schwamm LH, Hunter GJ, Putman CM, Rordorf GA, Buonanno FS, Budzik R, Koroshetz WJ, Gonzalez RG. CT angiography in the rapid triage of patients with hyperacute stroke to intraarterial thrombolysis: accuracy in the detection of large vessel thrombus. *J Comput Assist Tomogr*. 2001;25:520–528.
243. Lin K, Rapalino O, Law M, Babb JS, Siller KA, Pramanik BK. Accuracy of the Alberta Stroke Program Early CT Score during the first 3 hours of middle cerebral artery stroke: comparison of noncontrast CT, CT

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angiography source images, and CT perfusion. *AJNR Am J Neuroradiol*. 2008;29:931–936.
244. Ryoo JW, Na DG, Kim SS, Lee KH, Lee SJ, Chung CS, Choi DS. Malignant middle cerebral artery infarction in hyperacute ischemic stroke: evaluation with multiphasic perfusion computed tomography maps. *J Comput Assist Tomogr*. 2004;28:55–62.
245. Mattle HP, Arnold M, Georgiadis D, Baumann C, Nedeltchev K, Benninger D, Remonda L, von Büdingen C, Diana A, Pangalu A, Schroth G, Baumgartner RW. Comparison of intraarterial and intravenous thrombolysis for ischemic stroke with hyperdense middle cerebral artery sign. *Stroke*. 2008;39:379–383.
246. Zaidat OO, Suarez JI, Santillan C, Sunshine JL, Tarr RW, Paras VH, Selman WR,Landis DM. Response to intra-arterial and combined intravenous and intra-arterial thrombolytic therapy in patients with distal internal carotid artery occlusion. *Stroke*. 2002;33:1821–1826.
247. Sims JR, Rordorf G, Smith EE, Koroshetz WJ, Lev MH, Buonanno F, Schwamm LH. Arterial occlusion revealed by CT angiography predicts NIH stroke score and acute outcomes after IV tPA treatment. *AJNR Am J Neuroradiol*. 2005;26:246–251.
248. Coutts SB, Lev MH, Eliasziw M, Roccatagliata L, Hill MD, Schwamm LH, Pexman JH, Koroshetz WJ, Hudon ME, Buchan AM, Gonzalez RG, Demchuk AM. ASPECTS on CTA source images versus unenhanced CT: added value in predicting final infarct extent and clinical outcome. *Stroke*. 2004;35:2472–2476.
249. Torres-Mozqueda F, He J, Yeh IB, Schwamm LH, Lev MH, Schaefer PW, González RG. An acute ischemic stroke classification instrument that includes CT or MR angiography: the Boston Acute Stroke Imaging Scale. *AJNR Am J Neuroradiol*. 2008;29:1111–1117.
250. Ezzeddine MA, Lev MH, McDonald CT, Rordorf G, Oliveira-Filho J, Aksoy FG, Farkas J, Segal AZ, Schwamm LH, Gonzalez RG, Koroshetz WJ. CT angiography with whole brain perfused blood volume imaging: added clinical value in the assessment of acute stroke. *Stroke*. 2002;33:959–966.
251. Riedel CH, Zimmermann P, Jensen-Kondering U, Stingele R, Deuschl G, Jansen O. The importance of size: successful recanalization by intravenous thrombolysis in acute anterior stroke depends on thrombus length. *Stroke*. 2011;42:1775–1777.
252. Esteban JM, Cervera V. Perfusion CT and angio CT in the assessment of acute stroke. *Neuroradiology*. 2004;46:705–715.
253. Bash S, Villablanca JP, Jahan R, Duckwiler G, Tillis M, Kidwell C, Saver J,Sayre J. Intracranial vascular stenosis and occlusive disease: evaluation with CT angiography, MR angiography, and digital subtraction angiography. *AJNR Am J Neuroradiol*. 2005;26:1012–1021.
254. Graf J, Skutta B, Kuhn FP, Ferbert A. Computed tomographic angiography findings in 103 patients following vascular events in the posterior circulation: potential and clinical relevance. *J Neurol*. 2000;247:760–766.
255. Moll R, Dinkel HP. Value of the CT angiography in the diagnosis of common carotid artery bifurcation disease: CT angiography versus digital subtraction angiography and color flow Doppler. *Eur J Radiol*. 2001;39:155–162.
256. Suwanwela NC, Phanthumchinda K, Suwanwela N. Transcranial Doppler sonography and CT angiography in patients with atherothrombotic middle cerebral artery stroke. *AJNR Am J Neuroradiol*. 2002;23:1352–1355.
257. Nguyen-Huynh MN, Wintermark M, English J, Lam J, Vittinghoff E, Smith WS, Johnston SC. How accurate is CT angiography in evaluating intracranial atherosclerotic disease? *Stroke*. 2008;39:1184–1188.
258. Hirai T, Korogi Y, Ono K, Nagano M, Maruoka K, Uemura S, Takahashi M. Prospective evaluation of suspected stenoocclusive disease of the intracranial artery: combined MR angiography and CT angiography compared with digital subtraction angiography. *AJNR Am J Neuroradiol*. 2002;23:93–101.
259. Lev MH, Segal AZ, Farkas J, Hossain ST, Putman C, Hunter GJ, Budzik R, Harris GJ, Buonanno FS, Ezzeddine MA, Chang Y, Koroshetz WJ, Gonzalez RG, Schwamm LH. Utility of perfusion-weighted CT imaging in acute middle cerebral artery stroke treated with intra-arterial thrombolysis: prediction of final infarct volume and clinical outcome. *Stroke*. 2001;32:2021–2028.
260. Skutta B, Fürst G, Eilers J, Ferbert A, Kuhn FP. Intracranial stenoocclusive disease: double-detector helical CT angiography versus digital subtraction angiography. *AJNR Am J Neuroradiol*. 1999;20:791–799.
261. Schramm P, Schellinger PD, Fiebach JB, Heiland S, Jansen O, Knauth M, Hacke W,Sartor K. Comparison of CT and CT angiography source images with diffusion-weighted imaging in patients with acute stroke within 6 hours after onset. *Stroke*. 2002;33:2426–2432.
262. Schramm P, Schellinger PD, Klotz E, Kallenberg K, Fiebach JB, Külkens S, Heiland S, Knauth M, Sartor K. Comparison of perfusion computed tomography and computed tomography angiography source images with perfusion-weighted imaging and diffusion-weighted imaging in patients with acute stroke of less than 6 hours' duration. *Stroke*. 2004;35:1652–1658.
263. Aviv RI, Shelef I, Malam S, Chakraborty S, Sahlas DJ, Tomlinson G, Symons S, Fox AJ. Early stroke detection and extent: impact of experience and the role of computed tomography angiography source images. *Clin Radiol*. 2007;62:447–452.
264. Schellinger PD, Jansen O, Fiebach JB, Pohlers O, Ryssel H, Heiland S, Steiner T,Hacke W,Sartor K. Feasibility and practicality of MR imaging of stroke in the management of hyperacute cerebral ischemia. *AJNR Am J Neuroradiol*. 2000;21:1184–1189.
265. Yucel EK, Anderson CM, Edelman RR, Grist TM, Baum RA, Manning WJ, Culebras A, Pearce W. AHA scientific statement: magnetic resonance angiography: update on applications for extracranial arteries. *Circulation*. 1999;100:2284–2301.
266. Qureshi AI, Isa A, Cinnamon J, Fountain J, Ottenlips JR, Braimah J, Frankel MR. Magnetic resonance angiography in patients with brain infarction. *J Neuroimaging*. 1998;8:65–70.
267. Babikian VL, Pochay V, Burdette DE, Brass ML. Transcranial Doppler sonographic monitoring in the intensive care unit. *J Intensive Care Med*. 1991;6:36–44.
268. Newell DW, Aaslid R. Transcranial Doppler: clinical and experimental uses. *Cerebrovasc Brain Metab Rev*. 1992;4:122–143.
269. Baumgartner RW, Mattle HP, Aaslid R. Transcranial color-coded duplex sonography, magnetic resonance angiography, and computed tomography angiography: methods, applications, advantages, and limitations. *J Clin Ultrasound*. 1995;23:89–111.
270. de Bray JM, Joseph PA, Jeanvoine H, Maugin D, Dauzat M, Plassard F. Transcranial Doppler evaluation of middle cerebral artery stenosis. *J Ultrasound Med*. 1988;7:611–616.
271. Demchuk AM, Christou I, Wein TH, Felberg RA, Malkoff M, Grotta JC, Alexandrov AV. Accuracy and criteria for localizing arterial occlusion with transcranial Doppler. *J Neuroimaging*. 2000;10:1–12.
272. Rorick MB, Nichols FT, Adams RJ. Transcranial Doppler correlation with angiography in detection of intracranial stenosis. *Stroke*. 1994;25:1931–1934.
273. Sloan MA, Alexandrov AV, Tegeler CH, Spencer MP, Caplan LR, Feldmann E, Wechsler LR, Newell DW, Gomez CR, Babikian VL, Lefkowitz D, Goldman RS, Armon C, Hsu CY, Goodin DS; Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment: transcranial Doppler ultrasonography: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology*. 2004;62:1468–1481.
274. Wong KS, Li H, Lam WW, Chan YL, Kay R. Progression of middle cerebral artery occlusive disease and its relationship with further vascular events after stroke. *Stroke*. 2002;33:532–536.
275. Zanette EM, Fieschi C, Bozzao L, Roberti C, Toni D, Argentino C, Lenzi GL. Comparison of cerebral angiography and transcranial Doppler sonography in acute stroke. *Stroke*. 1989;20:899–903.
276. Feldmann E, Wilterdink JL, Kosinski A, Lynn M, Chimowitz MI, Sarafin J, Smith HH, Nichols F, Rogg J, Cloft HJ, Wechsler L, Saver J, Levine SR, Tegeler C, Adams R, Sloan M; Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) Trial Investigators. The Stroke Outcomes and Neuroimaging of Intracranial Atherosclerosis (SONIA) trial. *Neurology*. 2007;68:2099–2106.
277. Imray CH, Tiivas CA. Are some strokes preventable? The potential role of transcranial Doppler in transient ischaemic attacks of carotid origin. *Lancet Neurol*. 2005;4:580–586.
278. Markus HS, Droste DW, Kaps M, Larrue V, Lees KR, Siebler M, Ringelstein EB. Dual antiplatelet therapy with clopidogrel and aspirin in symptomatic carotid stenosis evaluated using Doppler embolic signal detection: the Clopidogrel and Aspirin for Reduction of Emboli in Symptomatic Carotid Stenosis (CARESS) trial. *Circulation*. 2005;111:2233–2240.
279. Poppert H, Sadikovic S, Sander K, Wolf O, Sander D. Embolic signals in unselected stroke patients: prevalence and diagnostic benefit. *Stroke*. 2006;37:2039–2043.
280. Alexandrov AV, Molina CA, Grotta JC, Garami Z, Ford SR, Alvarez-Sabin J, Montaner J, Saqqur M, Demchuk AM, Moyé LA, Hill MD, Wojner AW; CLOTBUST Investigators. Ultrasound-enhanced systemic thrombolysis for acute ischemic stroke. *N Engl J Med*. 2004;351:2170–2178.

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281. Saqqur M, Molina CA, Salam A, Siddiqui M, Ribo M, Uchino K, Calleja S, Garami Z, Khan K, Akhtar N, O'Rourke F, Shuaib A, Demchuk AM, Alexandrov AV; CLOTBUST Investigators. Clinical deterioration after intravenous recombinant tissue plasminogen activator treatment: a multicenter transcranial Doppler study. *Stroke*. 2007;38:69–74.
282. Saqqur M, Uchino K, Demchuk AM, Molina CA, Garami Z, Calleja S, Akhtar N, Orouk FO,Salam A,Shuaib A,Alexandrov AV; CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke*. 2007;38:948–954.
283. Alexandrov AV, Wojner AW, Grotta JC; CLOTBUST Investigators. CLOTBUST: design of a randomized trial of ultrasound-enhanced thrombolysis for acute ischemic stroke. *J Neuroimaging*. 2004;14:108–112.
284. Christou I, Alexandrov AV, Burgin WS, Wojner AW, Felberg RA, Malkoff M, Grotta JC. Timing of recanalization after tissue plasminogen activator therapy determined by transcranial Doppler correlates with clinical recovery from ischemic stroke. *Stroke*. 2000;31:1812–1816.
285. Demchuk AM, Burgin WS, Christou I, Felberg RA, Barber PA, Hill MD, Alexandrov AV. Thrombolysis In Brain Ischemia (TIBI) transcranial Doppler flow grades predict clinical severity, early recovery, and mortality in patients treated with intravenous tissue plasminogen activator. *Stroke*. 2001;32:89–93.
286. Karnik R, Stelzer P, Slany J. Transcranial Doppler sonography monitoring of local intra-arterial thrombolysis in acute occlusion of the middle cerebral artery. *Stroke*. 1992;23:284–287.
287. Qureshi AI, Siddiqui AM, Kim SH, Hanel RA, Xavier AR, Kirmani JF, Suri MF,Boulos AS,Hopkins LN. Reocclusion of recanalized arteries during intra-arterial thrombolysis for acute ischemic stroke. *AJNR Am J Neuroradiol*. 2004;25:322–328.
288. Rubiera M, Alvarez-Sabín J, Ribo M, Montaner J, Santamarina E, Arenillas JF, Huertas R, Delgado P, Purroy F, Molina CA. Predictors of early arterial reocclusion after tissue plasminogen activator-induced recanalization in acute ischemic stroke. *Stroke*. 2005;36:1452–1456.
289. Saqqur M, Tsivgoulis G, Molina CA, Demchuk AM, Shuaib A, Alexandrov AV; CLOTBUST Investigators. Residual flow at the site of intracranial occlusion on transcranial Doppler predicts response to intravenous thrombolysis: a multi-center study. *Cerebrovasc Dis*. 2009;27:5–12.
290. Alexandrov AV, Grotta JC. Arterial reocclusion in stroke patients treated with intravenous tissue plasminogen activator. *Neurology*. 2002;59:862–867.
291. Daffertshofer M, Gass A, Ringleb P, Sitzer M, Sliwka U, Els T, Sedlaczek O, Koroshetz WJ, Hennerici MG. Transcranial low-frequency ultrasound-mediated thrombolysis in brain ischemia: increased risk of hemorrhage with combined ultrasound and tissue plasminogen activator: results of a phase II clinical trial. *Stroke*. 2005;36:1441–1446.
292. Barr JD. Cerebral angiography in the assessment of acute cerebral ischemia: guidelines and recommendations. *J Vasc Interv Radiol*. 2004;15(pt 2):S57–S66.
293. Citron SJ, Wallace RC, Lewis CA, Dawson RC, Dion JE, Fox AJ, Manzione JV, Payne CS, Rivera FJ, Russell EJ, Sacks D, Yakes WF, Bakal CW; Society of Interventional Radiology; American Society of Interventional and Therapeutic Neuroradiology; American Society of Neuroradiology. Quality improvement guidelines for adult diagnostic neuroangiography: cooperative study between ASITN, ASNR, and SIR [republished from *AJNR Am J Neuroradiol* . 2000;21:146–150 and *J Vasc Interv Radiol*. 2000;11:129–134]. *J Vasc Interv Radiol*. 2003;14(pt 2):S257–S262.
294. Culebras A, Kase CS, Masdeu JC, Fox AJ, Bryan RN, Grossman CB, Lee DH,Adams HP,Thies W. Practice guidelines for the use of imaging in transient ischemic attacks and acute stroke: a report of the Stroke Council, American Heart Association. *Stroke*. 1997;28:1480–1497.
295. Räsänen HT, Manninen HI, Vanninen RL, Vainio P, Berg M, Saari T. Mild carotid artery atherosclerosis: assessment by 3-dimensional time-of-flight magnetic resonance angiography, with reference to intravascular ultrasound imaging and contrast angiography. *Stroke*. 1999;30:827–833.
296. Schenk EA, Bond MG, Aretz TH, Angelo JN, Choi HY, Rynalski T, Gustafson NF, Berson AS, Ricotta JJ, Goodison MW. Multicenter validation study of real-time ultrasonography, arteriography, and pathology: pathologic evaluation of carotid endarterectomy specimens. *Stroke*. 1988;19:289–296.
297. Trystram D, Dormont D, Gobin Metteil MP, Iancu Gontard D, Meder JF. Imaging of cervical arterial dissections: multi-center study and review of the literature [in French]. *J Neuroradiol*. 2002;29:257–263.
298. Warren DJ, Hoggard N, Walton L, Radatz MW, Kemeny AA, Forster DM, Wilkinson ID, Griffiths PD. Cerebral arteriovenous malformations: comparison of novel magnetic resonance angiographic techniques and conventional catheter angiography. *Neurosurgery*. 2001;48:973–982.
299. Hankey GJ, Warlow CP, Sellar RJ. Cerebral angiographic risk in mild cerebrovascular disease. *Stroke*. 1990;21:209–222.
300. Kaufmann TJ, Huston J 3rd, Mandrekar JN, Schleck CD, Thielen KR, Kallmes DF. Complications of diagnostic cerebral angiography: evaluation of 19,826 consecutive patients. *Radiology*. 2007;243:812–819.
301. Willinsky RA, Taylor SM, TerBrugge K, Farb RI, Tomlinson G, Montanera W. Neurologic complications of cerebral angiography: prospective analysis of 2,899 procedures and review of the literature. *Radiology*. 2003;227:522–528.
302. Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Sacco RL, Schwamm LH; American Heart Association; American Stroke Association. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack [published correction appears in *Stroke*. 2010;41:e455]. *Stroke*. 2008;39:1647–1652.
303. Buskens E, Nederkoorn PJ, Buijs-Van Der Woude T, Mali WP, Kappelle LJ, Eikelboom BC, Van Der Graaf Y,Hunink MG. Imaging of carotid arteries in symptomatic patients: cost-effectiveness of diagnostic strategies. *Radiology*. 2004;233:101–112.
304. Lovett JK, Dennis MS, Sandercock PA, Bamford J, Warlow CP, Rothwell PM. Very early risk of stroke after a first transient ischemic attack. *Stroke*. 2003;34:e138–e140.
305. Rothwell PM, Giles MF, Flossmann E, Lovelock CE, Redgrave JN, Warlow CP, Mehta Z. A simple score (ABCD) to identify individuals at high early risk of stroke after transient ischaemic attack. *Lancet*. 2005;366:29–36.
306. Johnston DC, Goldstein LB. Clinical carotid endarterectomy decision making: noninvasive vascular imaging versus angiography. *Neurology*. 2001;56:1009–1015.
307. Nederkoorn PJ, Mali WP, Eikelboom BC, Elgersma OE, Buskens E, Hunink MG, Kappelle LJ, Buijs PC,Wüst AF, van der Lugt A, van der Graaf Y. Preoperative diagnosis of carotid artery stenosis: accuracy of noninvasive testing. *Stroke*. 2002;33:2003–2008.
308. Flis CM, Jäger HR, Sidhu PS. Carotid and vertebral artery dissections: clinical aspects, imaging features and endovascular treatment. *Eur Radiol*. 2007;17:820–834.
309. Goyal MS, Derdeyn CP. The diagnosis and management of supraaortic arterial dissections. *Curr Opin Neurol*. 2009;22:80–89.
310. Lev MH, Romero JM, Goodman DN, Bagga R, Kim HY, Clerk NA, Ackerman RH,Gonzalez RG. Total occlusion versus hairline residual lumen of the internal carotid arteries: accuracy of single section helical CT angiography. *AJNR Am J Neuroradiol*. 2003;24:1123–1129.
311. Carroll BA. Duplex sonography in patients with hemispheric symptoms. *J Ultrasound Med*. 1989;8:535–540.
312. Widjaja E, Manuel D, Hodgson TJ, Connolly DJ, Coley SC, Romanowski CA, Gaines P, Cleveland T, Thomas S, Griffiths PD, Doyle C, Venables GS; Sheffield Stroke Prevention Group. Imaging findings and referral outcomes of rapid assessment stroke clinics. *Clin Radiol*. 2005;60:1076–1082.
313. Alexandrov AV, Vital D, Brodie DS, Hamilton P, Grotta JC. Grading carotid stenosis with ultrasound: an interlaboratory comparison. *Stroke*. 1997;28:1208–1210.
314. Alexandrov AV, Brodie DS, McLean A, Hamilton P, Murphy J, Burns PN. Correlation of peak systolic velocity and angiographic measurement of carotid stenosis revisited. *Stroke*. 1997;28:339–342.
315. Ranke C, Trappe HJ. Blood flow velocity measurements for carotid stenosis estimation: interobserver variation and interequipment variability. *VASA*. 1997;26:210–214.
316. Curley PJ, Norrie L, Nicholson A, Galloway JM, Wilkinson AR. Accuracy of carotid duplex is laboratory specific and must be determined by internal audit. *Eur J Vasc Endovasc Surg*. 1998;15:511–514.
317. Kuntz KM, Polak JF, Whittemore AD, Skillman JJ, Kent KC. Duplex ultrasound criteria for the identification of carotid stenosis should be laboratory specific. *Stroke*. 1997;28:597–602.
318. Blakeley DD, Oddone EZ, Hasselblad V, Simel DL, Matchar DB. Noninvasive carotid artery testing: a meta-analytic review. *Ann Intern Med*. 1995;122:360–367.
319. Long A, Lepoutre A, Corbillon E, Branchereau A. Critical review of non- or minimally invasive methods (duplex ultrasonography, MR- and CT-angiography) for evaluating stenosis of the proximal internal carotid artery. *Eur J Vasc Endovasc Surg*. 2002;24:43–52.

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320. Nederkoorn PJ, Elgersma OE, van der Graaf Y, Eikelboom BC, Kappelle LJ, Mali WP. Carotid artery stenosis: accuracy of contrast-enhanced MR angiography for diagnosis. *Radiology*. 2003;228:677–682.
321. Lubezky N, Fajer S, Barmeir E, Karmeli R. Duplex scanning and CT angiography in the diagnosis of carotid artery occlusion: a prospective study. *Eur J Vasc Endovasc Surg*. 1998;16:133–136.
322. Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV. Management and outcomes of transient ischemic attacks in Ontario. *CMAJ*. 2004;170:1099–1104.
323. Anderson GB, Ashforth R, Steinke DE, Ferdinandy R, Findlay JM. CT angiography for the detection and characterization of carotid artery bifurcation disease. *Stroke*. 2000;31:2168–2174.
324. Berg MH, Manninen HI, Räsänen HT, Vanninen RL, Jaakkola PA. CT angiography in the assessment of carotid artery atherosclerosis. *Acta Radiol*. 2002;43:116–124.
325. Leclerc X, Godefroy O, Lucas C, Benhaim JF, Michel TS, Leys D, Pruvo JP. Internal carotid arterial stenosis: CT angiography with volume rendering. *Radiology*. 1999;210:673–682.
326. Randoux B, Marro B, Koskas F, Duyme M, Sahel M, Zouaoui A, Marsault C. Carotid artery stenosis: prospective comparison of CT, three-dimensional gadolinium-enhanced MR, and conventional angiography. *Radiology*. 2001;220:179–185.
327. Cosottini M, Pingitore A, Puglioli M, Michelassi MC, Lupi G, Abbruzzese A, Calabrese R, Lombardi M, Parenti G, Bartolozzi C. Contrast-enhanced three-dimensional magnetic resonance angiography of atherosclerotic internal carotid stenosis as the noninvasive imaging modality in revascularization decision making. *Stroke*. 2003;34:660–664.
328. Goyal M, Nicol J, Gandhi D. Evaluation of carotid artery stenosis: contrast-enhanced magnetic resonance angiography compared with conventional digital subtraction angiography. *Can Assoc Radiol J*. 2004;55:111–119.
329. Huston J 3rd, Fain SB, Wald JT, Luetmer PH, Rydberg CH, Covarrubias DJ, Riederer SJ, Bernstein MA, Brown RD, Meyer FB, Bower TC, Schleck CD. Carotid artery: elliptic centric contrast-enhanced MR angiography compared with conventional angiography. *Radiology*. 2001;218:138–143.
330. Remonda L, Heid O, Schroth G. Carotid artery stenosis, occlusion, and pseudo-occlusion: first-pass, gadolinium-enhanced, three-dimensional MR angiography: preliminary study. *Radiology*. 1998;209:95–102.
331. Serfaty JM, Chirossel P, Chevallier JM, Ecochard R, Froment JC, Douek PC. Accuracy of three-dimensional gadolinium-enhanced MR angiography in the assessment of extracranial carotid artery disease. *AJR Am J Roentgenol*. 2000;175:455–463.
332. Westwood ME, Kelly S, Berry E, Bamford JM, Gough MJ, Airey CM, Meaney JF, Davies LM, Cullingworth J, Smith MA. Use of magnetic resonance angiography to select candidates with recently symptomatic carotid stenosis for surgery: systematic review. *BMJ*. 2002;324:198.
333. Berletti R, Cavagna E, Cimini N, Moretto G, Schiavon F. Dissection of epiaortic vessels: clinical appearance and potentiality of imaging techniques [in English, Italian]. *Radiol Med*. 2004;107:35–46.
334. Clifton AG. MR angiography. *Br Med Bull*. 2000;56:367–377.
335. Patel MR, Edelman RR. MR angiography of the head and neck. *Top Magn Reson Imaging*. 1996;8:345–365.
336. Phan T, Huston J 3rd, Bernstein MA, Riederer SJ, Brown RD Jr. Contrast-enhanced magnetic resonance angiography of the cervical vessels: experience with 422 patients. *Stroke*. 2001;32:2282–2286.
337. Okumura A, Araki Y, Nishimura Y, Iwama T, Kaku Y, Furuichi M, Sakai N. The clinical utility of contrast-enhanced 3D MR angiography for cerebrovascular disease. *Neurol Res*. 2001;23:767–771.
338. Gelal FM, Kitis O, Calli C, Yunten N, Vidinli BD, Uygur M. Craniocervical artery dissection: diagnosis and follow-up with MR imaging and MR angiography. *Med Sci Monit*. 2004;10:MT109-MT116.
339. Keller E, Flacke S, Gieseke J, Sommer T, Brechtelsbauer D, Gass S, Pauleit D,Textor J,Schild HH. Craniocervical dissections: study strategies in MR imaging and MR angiography [in German]. *Rofo*. 1997;167:565–571.
340. Agarwal P, Kumar S, Hariharan S, Eshkar N, Verro P, Cohen B, Sen S. Hyperdense middle cerebral artery sign: can it be used to select intra-arterial versus intravenous thrombolysis in acute ischemic stroke? *Cerebrovasc Dis*. 2004;17:182–190.
341. Bendszus M, Urbach H, Ries F, Solymosi L. Outcome after local intra-arterial fibrinolysis compared with the natural course of patients with a dense middle cerebral artery on early CT. *Neuroradiology*. 1998;40:54–58.
342. Dittrich R, Kloska SP, Fischer T, Nam E, Ritter MA, Seidensticker P, Heindel W, Nabavi DG, Ringelstein EB. Accuracy of perfusion-CT in predicting malignant middle cerebral artery brain infarction. *J Neurol*. 2008;255:896–902.
343. Kakuda W, Hamilton S, Thijs VN, Lansberg MG, Kemp S, Skalabrin E, Albers GW; DEFUSE Investigators. Optimal outcome measures for detecting clinical benefits of early reperfusion: insights from the DEFUSE Study. *J Stroke Cerebrovasc Dis*. 2008;17:235–240.
344. Olivot JM, Mlynash M, Thijs VN, Kemp S, Lansberg MG, Wechsler L, Schlaug G, Bammer R, Marks MP, Albers GW. Relationships between infarct growth, clinical outcome, and early recanalization in diffusion and perfusion imaging for understanding stroke evolution (DEFUSE). *Stroke*. 2008;39:2257–2263.
345. Albers GW, Thijs VN, Wechsler L, Kemp S, Schlaug G, Skalabrin E, Bammer R, Kakuda W, Lansberg MG, Shuaib A, Coplin W, Hamilton S, Moseley M, Marks MP; DEFUSE Investigators. Magnetic resonance imaging profiles predict clinical response to early reperfusion: the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke evolution (DEFUSE) study. *Ann Neurol*. 2006;60:508–517.
346. Davis SM, Donnan GA, Parsons MW, Levi C, Butcher KS, Peeters A, Barber PA, Bladin C, De Silva DA, Byrnes G, Chalk JB, Fink JN, Kimber TE, Schultz D, Hand PJ, Frayne J, Hankey G, Muir K, Gerraty R, Tress BM, Desmond PM; EPITHET Investigators. Effects of alteplase beyond 3 h after stroke in the Echoplanar Imaging Thrombolytic Evaluation Trial (EPITHET): a placebo-controlled randomised trial. *Lancet Neurol*. 2008;7:299–309.
347. Furlan AJ, Eyding D, Albers GW, Al-Rawi Y, Lees KR, Rowley HA, Sachara C, Soehngen M, Warach S, Hacke W; DEDAS Investigators. Dose Escalation of Desmoteplase for Acute Ischemic Stroke (DEDAS): evidence of safety and efficacy 3 to 9 hours after stroke onset. *Stroke*. 2006;37:1227–1231.
348. Grotta J. Neuroprotection is unlikely to be effective in humans using current trial designs. *Stroke*. 2002;33:306–307.
349. Hacke W, Albers G, Al-Rawi Y, Bogousslavsky J, Davalos A, Eliasziw M, Fischer M, Furlan A, Kaste M, Lees KR, Soehngen M, Warach S; DIAS Study Group. The Desmoteplase in Acute Ischemic Stroke Trial (DIAS): a phase II MRI-based 9-hour window acute stroke thrombolysis trial with intravenous desmoteplase. *Stroke*. 2005;36:66–73.
350. Heiss WD, Huber M, Fink GR, Herholz K, Pietrzyk U, Wagner R, Wienhard K. Progressive derangement of periinfarct viable tissue in ischemic stroke. *J Cereb Blood Flow Metab*. 1992;12:193–203.
351. Gleason S, Furie KL, Lev MH, O'Donnell J, McMahon PM, Beinfeld MT, Halpern E, Mullins M, Harris G, Koroshetz WJ, Gazelle GS. Potential influence of acute CT on inpatient costs in patients with ischemic stroke. *Acad Radiol*. 2001;8:955–964.
352. Smith WS, Roberts HC, Chuang NA, Ong KC, Lee TJ, Johnston SC, Dillon WP. Safety and feasibility of a CT protocol for acute stroke: combined CT, CT angiography, and CT perfusion imaging in 53 consecutive patients. *AJNR Am J Neuroradiol*. 2003;24:688–690.
353. Josephson SA, Dillon WP, Smith WS. Incidence of contrast nephropathy from cerebral CT angiography and CT perfusion imaging. *Neurology*. 2005;64:1805–1806.
354. Aspelin P, Aubry P, Fransson SG, Strasser R, Willenbrock R, Berg KJ; Nephrotoxicity in High-Risk Patients Study of Iso-Osmolar and Low-Osmolar Non-Ionic Contrast Media Study Investigators. Nephrotoxic effects in high-risk patients undergoing angiography. *N Engl J Med*. 2003;348:491–499.
355. Rudnick MR, Goldfarb S. Pathogenesis of contrast-induced nephropathy: experimental and clinical observations with an emphasis on the role of osmolality. *Rev Cardiovasc Med*. 2003;4(suppl 5):S28–S33.
356. Krol AL, Dzialowski I, Roy J, Puetz V, Subramaniam S, Coutts SB, Demchuk AM. Incidence of radiocontrast nephropathy in patients undergoing acute stroke computed tomography angiography [published correction appears in *Stroke*. 2007;38:e97]. *Stroke*. 2007;38:2364–2366.
357. Wintermark M, Reichhart M, Cuisenaire O, Maeder P, Thiran JP, Schnyder P, Bogousslavsky J,Meuli R. Comparison of admission perfusion computed tomography and qualitative diffusion- and perfusion-weighted magnetic resonance imaging in acute stroke patients. *Stroke*. 2002;33:2025–2031.
358. Wintermark M, Reichhart M, Thiran JP, Maeder P, Chalaron M, Schnyder P, Bogousslavsky J,Meuli R. Prognostic accuracy of cerebral blood flow measurement by perfusion computed tomography, at the time of emergency room admission, in acute stroke patients. *Ann Neurol*. 2002;51:417–432.
359. Roberts HC, Roberts TP, Smith WS, Lee TJ, Fischbein NJ, Dillon WP. Multisection dynamic CT perfusion for acute cerebral ischemia: the "toggling-table" technique. *AJNR Am J Neuroradiol*. 2001;22:1077–1080.

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360. Kribben A, Witzke O, Hillen U, Barkhausen J, Daul AE, Erbel R. Nephrogenic systemic fibrosis: pathogenesis, diagnosis, and therapy. *J Am Coll Cardiol*. 2009;53:1621–1628.
361. Perez-Rodriguez J, Lai S, Ehst BD, Fine DM, Bluemke DA. Nephrogenic systemic fibrosis: incidence, associations, and effect of risk factor assessment: report of 33 cases. *Radiology*. 2009;250:371–377.
362. Butcher K, Parsons M, Allport L, Lee SB, Barber PA, Tress B, Donnan GA,Davis SM; EPITHET Investigators. Rapid assessment of perfusion-diffusion mismatch. *Stroke*. 2008;39:75–81.
363. Butcher KS, Lee SB, Parsons MW, Allport L, Fink J, Tress B, Donnan G,Davis SM; EPITHET Investigators. Differential prognosis of isolated cortical swelling and hypoattenuation on CT in acute stroke. *Stroke*. 2007;38:941–947.
364. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, Kaste M, Lipka LJ, Pedraza S, Ringleb PA, Rowley HA, Schneider D, Schwamm LH, Leal JS, Söhngen M, Teal PA, Wilhelm-Ogunbiyi K, Wintermark M, Warach S. Intravenous desmoteplase in patients with acute ischaemic stroke selected by MRI perfusion-diffusion weighted imaging or perfusion CT (DIAS-2): a prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2009;8:141–150.
365. Sulter G, Elting JW, Stewart R, den Arend A, De Keyser J. Continuous pulse oximetry in acute hemiparetic stroke. *J Neurol Sci*. 2000;179(S 1–2):65–69.
366. Roffe C, Sills S, Halim M, Wilde K, Allen MB, Jones PW, Crome P. Unexpected nocturnal hypoxia in patients with acute stroke. *Stroke*. 2003;34:2641–2645.
367. Aviv JE, Martin JH, Sacco RL, Zagar D, Diamond B, Keen MS, Blitzer A. Supraglottic and pharyngeal sensory abnormalities in stroke patients with dysphagia. *Ann Otol Rhinol Laryngol*. 1996;105:92–97.
368. Milhaud D, Popp J, Thouvenot E, Heroum C, Bonafé A. Mechanical ventilation in ischemic stroke. *J Stroke Cerebrovasc Dis*. 2004;13:183–188.
369. Siccoli MM, Valko PO, Hermann DM, Bassetti CL. Central periodic breathing during sleep in 74 patients with acute ischemic stroke: neurogenic and cardiogenic factors. *J Neurol*. 2008;255:1687–1692.
370. Nachtmann A, Siebler M, Rose G, Sitzer M, Steinmetz H. Cheyne-Stokes respiration in ischemic stroke. *Neurology*. 1995;45:820–821.
371. Rowat AM, Wardlaw JM, Dennis MS, Warlow CP. Patient positioning influences oxygen saturation in the acute phase of stroke. *Cerebrovasc Dis*. 2001;12:66–72.
372. Wojner-Alexander AW, Garami Z, Chernyshev OY, Alexandrov AV. Heads down: flat positioning improves blood flow velocity in acute ischemic stroke. *Neurology*. 2005;64:1354–1357.
373. Schwarz S, Georgiadis D, Aschoff A, Schwab S. Effects of body position on intracranial pressure and cerebral perfusion in patients with large hemispheric stroke. *Stroke*. 2002;33:497–501.
374. Chatterton HJ, Pomeroy VM, Connolly MJ, Faragher EB, Clayton L, Tallis RC. The effect of body position on arterial oxygen saturation in acute stroke. *J Gerontol A Biol Sci Med Sci*. 2000;55:M239–M244.
375. Elizabeth J, Singarayar J, Ellul J, Barer D, Lye M. Arterial oxygen saturation and posture in acute stroke. *Age Ageing*. 1993;22:269–272.
376. Pang JA, Yeung VT, Zhang YG. Do postural changes affect gas exchange in acute hemiplegia? *Br J Clin Pract*. 1988;42:501–502.
377. Tyson SF, Nightingale P. The effects of position on oxygen saturation in acute stroke: a systematic review. *Clin Rehabil*. 2004;18:863–871.
378. Rangel-Castilla L, Rangel-Castillo L, Gopinath S, Robertson CS. Management of intracranial hypertension [published correction appears in *Neurol Clin*. 2008;26:xvii]. *Neurol Clin*. 2008;26:521–541, x.
379. Singhal AB, Benner T, Roccatagliata L, Koroshetz WJ, Schaefer PW, Lo EH, Buonanno FS,Gonzalez RG, Sorensen AG. A pilot study of normobaric oxygen therapy in acute ischemic stroke. *Stroke*. 2005;36:797–802.
380. Singhal AB, Ratai E, Benner T, Vangel M, Lee V, Koroshetz WJ, Schaefer PW, Sorensen AG, Gonzalez RG. Magnetic resonance spectroscopy study of oxygen therapy in ischemic stroke. *Stroke*. 2007;38:2851–2854.
381. Chiu EH, Liu CS, Tan TY, Chang KC. Venturi mask adjuvant oxygen therapy in severe acute ischemic stroke. *Arch Neurol*. 2006;63:741–744.
382. Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke*. 1999;30:2033–2037.
383. Doggett DL, Tappe KA, Mitchell MD, Chapell R, Coates V, Turkelson CM. Prevention of pneumonia in elderly stroke patients by systematic diagnosis and treatment of dysphagia: an evidence-based comprehensive analysis of the literature. *Dysphagia*. 2001;16:279–295.
384. Grotta J, Pasteur W, Khwaja G, Hamel T, Fisher M, Ramirez A. Elective intubation for neurologic deterioration after stroke. *Neurology*. 1995;45:640–644.
385. Foerch C, Kessler KR, Steckel DA, Steinmetz H, Sitzer M. Survival and quality of life outcome after mechanical ventilation in elderly stroke patients. *J Neurol Neurosurg Psychiatr*. 2004;75:988–993.
386. Bushnell CD, Phillips-Bute BG, Laskowitz DT, Lynch JR, Chilukuri V, Borel CO. Survival and outcome after endotracheal intubation for acute stroke. *Neurology*. 1999;52:1374–1381.
387. Holloway RG, Benesch CG, Burgin WS, Zentner JB. Prognosis and decision making in severe stroke. *JAMA*. 2005;294:725–733.
388. Golestanian E, Liou JI, Smith MA. Long-term survival in older critically ill patients with acute ischemic stroke. *Crit Care Med*. 2009;37:3107–3113.
389. Azzimondi G, Bassein L, Nonino F, Fiorani L, Vignatelli L, Re G, D'Alessandro R. Fever in acute stroke worsens prognosis: a prospective study. *Stroke*. 1995;26:2040–2043.
390. Boysen G, Christensen H. Stroke severity determines body temperature in acute stroke. *Stroke*. 2001;32:413–417.
391. Castillo J, Dávalos A, Marrugat J, Noya M. Timing for fever-related brain damage in acute ischemic stroke. *Stroke*. 1998;29:2455–2460.
392. Ginsberg MD, Busto R. Combating hyperthermia in acute stroke: a significant clinical concern. *Stroke*. 1998;29:529–534.
393. Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome: a meta-analysis of studies in patients. *Stroke*. 2000;31:410–414.
394. Kammersgaard LP, Jørgensen HS, Rungby JA, Reith J, Nakayama H, Weber UJ, Houth J, Olsen TS. Admission body temperature predicts long-term mortality after acute stroke: the Copenhagen Stroke Study. *Stroke*. 2002;33:1759–1762.
395. Reith J, Jørgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, Olsen TS. Body temperature in acute stroke: relation to stroke severity, infarct size, mortality, and outcome. *Lancet*. 1996;347:422–425.
396. Wang Y, Lim LL, Levi C, Heller RF, Fisher J. Influence of admission body temperature on stroke mortality. *Stroke*. 2000;31:404–409.
397. Zaremba J. Hyperthermia in ischemic stroke. *Med Sci Monit*. 2004;10:RA148-RA153.
398. Prasad K, Krishnan PR. Fever is associated with doubling of odds of short-term mortality in ischemic stroke: an updated meta-analysis. *Acta Neurol Scand*. 2010;122:404–408.
399. Jørgensen HS, Reith J, Nakayama H, Kammersgaard LP, Raaschou HO, Olsen TS. What determines good recovery in patients with the most severe strokes? The Copenhagen Stroke Study. *Stroke*. 1999;30:2008–2012.
400. Sulter G, Elting JW, Maurits N, Luijckx GJ, Luyckx GJ, De Keyser J. Acetylsalicylic acid and acetaminophen to combat elevated body temperature in acute ischemic stroke [published correction appears in *Cerebrovasc Dis*. 2008;26:570]. *Cerebrovasc Dis*. 2004;17:118–122.
401. Kasner SE, Wein T, Piriyawat P, Villar-Cordova CE, Chalela JA, Krieger DW, Morgenstern LB, Kimmel SE, Grotta JC. Acetaminophen for altering body temperature in acute stroke: a randomized clinical trial. *Stroke*. 2002;33:130–134.
402. Dippel DW, van Breda EJ, van Gemert HM, van der Worp HB, Meijer RJ, Kappelle LJ, Koudstaal PJ. Effect of paracetamol (acetaminophen) on body temperature in acute ischemic stroke: a double-blind, randomized phase II clinical trial. *Stroke*. 2001;32:1607–1612.
403. Dippel DW, van Breda EJ, van der Worp HB, van Gemert HM, Meijer RJ, Kappelle LJ, Koudstaal PJ; PISA Investigators. Effect of paracetamol (acetaminophen) and ibuprofen on body temperature in acute ischemic stroke PISA, a phase II double-blind, randomized, placebo-controlled trial [ISRCTN98608690]. *BMC Cardiovasc Disord*. 2003;3:2.
404. den Hertog HM, van der Worp HB, van Gemert HM, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ, Dippel DW; PAIS Investigators. The Paracetamol (Acetaminophen) In Stroke (PAIS) trial: a multicentre, randomised, placebo-controlled, phase III trial. *Lancet Neurol*. 2009;8:434–440.
405. Sulter G, Elting JW, Langedijk M, Maurits NM, De Keyser J. Admitting acute ischemic stroke patients to a stroke care monitoring unit versus a conventional stroke unit: a randomized pilot study. *Stroke*. 2003;34:101–104.
406. Cavallini A, Micieli G, Marcheselli S, Quaglini S. Role of monitoring in management of acute ischemic stroke patients. *Stroke*. 2003;34:2599–2603.
407. Qureshi AI, Ezzeddine MA, Nasar A, Suri MF, Kirmani JF, Hussein HM, Divani AA, Reddi AS. Prevalence of elevated blood pressure in 563,704 adult patients with stroke presenting to the ED in the United States. *Am J Emerg Med*. 2007;25:32–38.
408. Ahmed N, Näsman P, Wahlgren NG. Effect of intravenous nimodipine on blood pressure and outcome after acute stroke. *Stroke*. 2000;31:1250–1255.

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409. Broderick J, Brott T, Barsan W, Haley EC, Levy D, Marler J, Sheppard G, Blum C. Blood pressure during the first minutes of focal cerebral ischemia. *Ann Emerg Med*. 1993;22:1438–1443.
410. Christensen H, Meden P, Overgaard K, Boysen G. The course of blood pressure in acute stroke is related to the severity of the neurological deficits. *Acta Neurol Scand*. 2002;106:142–147.
411. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. *Lancet Neurol*. 2009;8:48–56.
412. Vemmos KN, Spengos K, Tsivgoulis G, Zakopoulos N, Manios E, Kotsis V, Daffertshofer M, Vassilopoulos D. Factors influencing acute blood pressure values in stroke subtypes. *J Hum Hypertens*. 2004;18:253–259.
413. Kaste M, Fogelholm R, Erilä T, Palomäki H, Murros K, Rissanen A, Sarna S. A randomized, double-blind, placebo-controlled trial of nimodipine in acute ischemic hemispheric stroke. *Stroke*. 1994;25:1348–1353.
414. Wallace JD, Levy LL. Blood pressure after stroke. *JAMA*. 1981;246:2177–2180.
415. Castillo J, Leira R, García MM, Serena J, Blanco M, Dávalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke*. 2004;35:520–526.
416. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke*. 2002;33:1315–1320.
417. Okumura K, Ohya Y, Maehara A, Wakugami K, Iseki K, Takishita S. Effects of blood pressure levels on case fatality after acute stroke. *J Hypertens*. 2005;23:1217–1223.
418. Vemmos KN, Tsivgoulis G, Spengos K, Zakopoulos N, Synetos A, Manios E, Konstantopoulou P, Mavrikakis M. U-shaped relationship between mortality and admission blood pressure in patients with acute stroke. *J Intern Med*. 2004;255:257–265.
419. Aslanyan S, Fazekas F, Weir CJ, Horner S, Lees KR; GAIN International Steering Committee and Investigators. Effect of blood pressure during the acute period of ischemic stroke on stroke outcome: a tertiary analysis of the GAIN International Trial. *Stroke*. 2003;34:2420–2425.
420. Aslanyan S, Weir CJ, Lees KR; GAIN International Steering Committee and Investigators. Elevated pulse pressure during the acute period of ischemic stroke is associated with poor stroke outcome. *Stroke*. 2004;35:e153–e155.
421. Boreas AM, Lodder J, Kessels F, de Leeuw PW, Troost J. Prognostic value of blood pressure in acute stroke. *J Hum Hypertens*. 2002;16:111–116.
422. Chamorro A, Vila N, Ascaso C, Elices E, Schonewille W, Blanc R. Blood pressure and functional recovery in acute ischemic stroke. *Stroke*. 1998;29:1850–1853.
423. Grabska K, Niewada M, Sarzynska-Dlugosz I, Kaminski B, Czlonkowska A. Pulse pressure: independent predictor of poor early outcome and mortality following ischemic stroke. *Cerebrovasc Dis*. 2009;27:187–192.
424. Jensen MB, Yoo B, Clarke WR, Davis PH, Adams HR Jr. Blood pressure as an independent prognostic factor in acute ischemic stroke. *Can J Neurol Sci*. 2006;33:34–38.
425. Rodríguez-García JL, Botia E, de La Sierra A, Villanueva MA, González-Spínola J. Significance of elevated blood pressure and its management on the short-term outcome of patients with acute ischemic stroke. *Am J Hypertens*. 2005;18:379–384.
426. Yong M, Diener HC, Kaste M, Mau J. Characteristics of blood pressure profiles as predictors of long-term outcome after acute ischemic stroke. *Stroke*. 2005;36:2619–2625.
427. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke*. 2008;39:366–372.
428. Oliveira-Filho J, Silva SC, Trabuco CC, Pedreira BB, Sousa EU, Bacellar A. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. *Neurology*. 2003;61:1047–1051.
429. Ritter MA, Kimmeyer P, Heuschmann PU, Dziewas R, Dittrich R, Nabavi DG, Ringelstein EB. Blood pressure threshold violations in the first 24 hours after admission for acute stroke: frequency, timing, predictors, and impact on clinical outcome. *Stroke*. 2009;40:462–468.
430. Wahlgren NG, MacMahon DG, DeKeyser J, Indredavik B, Ryman T. Intravenous Nimodipine West European Stroke Trial (INWEST) of nimodipine in the treatment of acute ischaemic stroke. *Cerebrovasc Dis*. 1994;4:204 –210.
431. Schrader J, Lüders S, Kulschewski A, Berger J, Zidek W, Treib J, Einhäupl K, Diener HC, Dominiak P; Acute Candesartan Cilexetil Therapy in Stroke Survivors Study Group. The ACCESS Study: evaluation of Acute Candesartan Cilexetil Therapy in Stroke Survivors. *Stroke*. 2003;34:1699–1703.
432. Sandset EC, Bath PM, Boysen G, Jatuzis D, Kõrv J, Lüders S, Murray GD, Richter PS, Roine RO, Terént A, Thijs V, Berge E; SCAST Study Group. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741–750.
433. Robinson TG, Potter JF, Ford GA, Bulpitt CJ, Chernova J, Jagger C, James MA, Knight J, Markus HS, Mistri AK, Poulter NR; COSSACS Investigators. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol*. 2010;9:767–775.
434. Ahmed N, Wahlgren N, Brainin M, Castillo J, Ford GA, Kaste M, Lees KR, Toni D; SITS Investigators. Relationship of blood pressure, antihypertensive therapy, and outcome in ischemic stroke treated with intravenous thrombolysis. retrospective analysis from Safe Implementation of Thrombolysis in Stroke-International Stroke Thrombolysis Register (SITS-ISTR). *Stroke*. 2009;40:2442–2449.
435. Karachalios GN, Charalabopoulos A, Papalimneou V, Kiortsis D, Dimicco P, Kostoula OK, Charalabopoulos K. Withdrawal syndrome following cessation of antihypertensive drug therapy. *Int J Clin Pract*. 2005;59:562–570.
436. Bhalla A, Sankaralingam S, Dundas R, Swaminathan R, Wolfe CD, Rudd AG. Influence of raised plasma osmolality on clinical outcome after acute stroke. *Stroke*. 2000;31:2043–2048.
437. Bistrain BB, Driscoll DF. Enteral and parenteral nutrition therapy. In: Fauci AS, Kasper DL, Longo Dl, Braunwald E, Hauser SL, Jameson JL, Loscalzo J, eds. *Harrison's Principals of Internal Medicine*. 17th ed. New York: McGraw-Hill; 2008:455–461.
438. Cryer PE, Davis SN, Shamoon H. Hypoglycemia in diabetes. *Diabetes Care*. 2003;26:1902–1912.
439. Service FJ. Hypoglycemic disorders. *N Engl J Med*. 1995;332:1144–1152.
440. Gentile NT, Seftchick MW, Huynh T, Kruus LK, Gaughan J. Decreased mortality by normalizing blood glucose after acute ischemic stroke. *Acad Emerg Med*. 2006;13:174–180.
441. Williams LS, Rotich J, Qi R, Fineberg N, Espay A, Bruno A, Fineberg SE, Tierney WR. Effects of admission hyperglycemia on mortality and costs in acute ischemic stroke. *Neurology*. 2002;59:67–71.
442. Capes SE, Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke*. 2001;32:2426–2432.
443. McCormick MT, Muir KW, Gray CS, Walters MR. Management of hyperglycemia in acute stroke: how, when, and for whom? *Stroke*. 2008;39:2177–2185.
444. Bruno A, Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE; NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology*. 2002;59:669–674.
445. Cucchiara B, Tanne D, Levine SR, Demchuk AM, Kasner S. A risk score to predict intracranial hemorrhage after recombinant tissue plasminogen activator for acute ischemic stroke. *J Stroke Cerebrovasc Dis*. 2008;17:331–333.
446. Demchuk AM, Tanne D, Hill MD, Kasner SE, Hanson S, Grond M, Levine SR; mMulticentre tPA Stroke Survey Group. Predictors of good outcome after intravenous tPA for acute ischemic stroke. *Neurology*. 2001;57:474–480.
447. Pundik S, McWilliams-Dunnigan L, Blackham KL, Kirchner HL, Sundararajan S, Sunshine JL, Tarr RW, Selman WR, Landis DM, Suarez JI. Older age does not increase risk of hemorrhagic complications after intravenous and/or intra-arterial thrombolysis for acute stroke. *J Stroke Cerebrovasc Dis*. 2008;17:266–272.
448. Baird TA, Parsons MW, Phanh T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM. Persistent poststroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke*. 2003;34:2208–2214.
449. Els T, Klisch J, Orszagh M, Hetzel A, Schulte-Mönting J, Schumacher M, Lücking CH. Hyperglycemia in patients with focal cerebral ischemia after intravenous thrombolysis: influence on clinical outcome and infarct size. *Cerebrovasc Dis*. 2002;13:89–94.
450. Parsons MW, Barber PA, Desmond PM, Baird TA, Darby DG, Byrnes G, Tress BM, Davis SM. Acute hyperglycemia adversely affects stroke outcome: a magnetic resonance imaging and spectroscopy study. *Ann Neurol*. 2002;52:20–28.
451. Ribo M, Molina CA, Delgado P, Rubiera M, Delgado-Mederos R, Rovira A, Munuera J, Alvarez-Sabin J. Hyperglycemia during ischemia rapidly accelerates brain damage in stroke patients treated with tPA. *J Cereb Blood Flow Metab*. 2007;27:1616–1622.

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452. Gray CS, Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol*. 2007;6:397–406.
453. Bruno A, Kent TA, Coull BM, Shankar RR, Saha C, Becker KJ, Kissela BM, Williams LS. Treatment of hyperglycemia in ischemic stroke (THIS): a randomized pilot trial. *Stroke*. 2008;39:384–389.
454. Johnston KC, Hall CE, Kissela BM, Bleck TP; for the GRASP Investigators. The Glucose Regulation in Acute Stroke Patients (GRASP) trial outcome results. Presented at: The International Stroke Conference; February 18, 2009; San Diego, CA.
455. Kreisel SH, Berschin UM, Hammes HP, Leweling H, Bertsch T, Hennerici MG, Schwarz S. Pragmatic management of hyperglycaemia in acute ischaemic stroke: safety and feasibility of intensive intravenous insulin treatment. *Cerebrovasc Dis*. 2009;27:167–175.
456. Walters MR, Weir CJ, Lees KR. A randomised, controlled pilot study to investigate the potential benefit of intervention with insulin in hyperglycaemic acute ischaemic stroke patients. *Cerebrovasc Dis*. 2006;22:116–122.
457. American Diabetes Association. Standards of medical care in diabetes: 2010 [published correction appears in *Diabetes Care*. 2010;33:692]. *Diabetes Care*. 2010;33(suppl 1):S11–S61.
458. Baker L, Juneja R, Bruno A. Management of hyperglycemia in acute ischemic stroke. *Curr Treat Options Neurol*. 2011;13:616–628.
459. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, Hennerici MG, Kaste M, Kuelkens S, Larrue V, Lees KR, Roine RO, Soinne L, Toni D, Vanhooren G; SITS-MOST Investigators. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet*. 2007;369:275–282.
460. Lyden PD, ed. *Thrombolytic Therapy for Acute Stroke.* 2nd ed. Totowa, NJ: Humana Press; 2005.
461. Wardlaw JM, Sandercock PA, Berge E. Thrombolytic therapy with recombinant tissue plasminogen activator for acute ischemic stroke: where do we go from here? A cumulative meta-analysis. *Stroke*. 2003;34:1437–1442.
462. Wardlaw JM, Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2003;(4):CD000213.
463. Sharma M, Clark H, Armour T, Stotts G, Coté R, Hill MD, et al. Acute stroke: evaluation and treatment. *Evid Rep Technol Assess (Summ)*. 2005;(127):1–7.
464. Hill MD, Buchan AM; Canadian Alteplase for Stroke Effectiveness Study (CASES) Investigators. Thrombolysis for acute ischemic stroke: results of the Canadian Alteplase for Stroke Effectiveness Study. *CMAJ*. 2005;172:1307–1312.
465. Chung H, Refoios Camejo R, Camejo RR, Barnett D. Alteplase for the treatment of acute ischaemic stroke: NICE technology appraisal guidance [published correction appears in *Heart*. 2008;94:229]. *Heart*. 2007;93:1616–1617.
466. Saver JL, Smith EE, Fonarow GC, Reeves MJ, Zhao X, Olson DM, Schwamm LH; GWTG-Stroke Steering Committee and Investigators. The "golden hour" and acute brain ischemia: presenting features and lytic therapy in >30,000 patients arriving within 60 minutes of stroke onset. *Stroke*. 2010;41:1431–1439.
467. Scott PA, Xu Z, Meurer WJ, Frederiksen SM, Haan MN, Westfall MW, Kothari SU, Morgenstern LB, Kalbfleisch JD. Attitudes and beliefs of Michigan emergency physicians toward tissue plasminogen activator use in stroke: baseline survey results from the INcreasing Stroke Treatment through INteractive behavioral Change Tactic (INSTINCT) trial hospitals. *Stroke*. 2010;41:2026–2032.
468. Deleted in proof.
469. Kwiatkowski TG, Libman RB, Frankel M, Tilley BC, Morgenstern LB, Lu M, Broderick JP, Lewandowski CA, Marler JR, Levine SR, Brott T. Effects of tissue plasminogen activator for acute ischemic stroke at one year. National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. *N Engl J Med*. 1999;340:1781–1787.
470. The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. *Stroke*. 1997;28:2109–2118.
471. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, Larrue V, Bluhmki E, Davis S, Donnan G, Schneider D, Diez-Tejedor E, Trouillas P. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II): Second European-Australasian Acute Stroke Study Investigators. *Lancet*. 1998;352:1245–1251.
472. Clark W, Ertag W, Orecchio E, Raps E. Cervene in acute ischemic stroke: results of a double-blind, placebo-controlled, dose-comparison study. *J Stroke Cerebrovasc Dis*. 1999;8:224–230.
473. Clark WM, Albers GW, Madden KP, Hamilton S;Thrombolytic Therapy in Acute Ischemic Stroke Study Investigators. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. *Stroke*. 2000;31:811–816.
474. Kwiatkowski T, Libman R, Tilley BC, Lewandowski C, Grotta JC, Lyden P, Levine SR, Brott T; National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study Group. The impact of imbalances in baseline stroke severity on outcome in the National Institute of Neurological Disorders and Stroke Recombinant Tissue Plasminogen Activator Stroke Study. *Ann Emerg Med*. 2005;45:377–384.
475. Wardlaw JM, Lindley RI, Lewis S. Thrombolysis for acute ischemic stroke: still a treatment for the few by the few. *West J Med*. 2002;176:198–199.
476. Saver JL, Yafeh B. Confirmation of tPA treatment effect by baseline severity-adjusted end point reanalysis of the NINDS-tPA stroke trials. *Stroke*. 2007;38:414–416.
477. Johnston KC, Connors AF Jr, Wagner DP, Haley EC Jr. Risk adjustment effect on stroke clinical trials. *Stroke*. 2004;35:e43–e45.
478. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA*. 2000;283:1145–1150.
479. Grond M, Stenzel C, Schmülling S, Rudolf J, Neveling M, Lechleuthner A, Schneweis S, Heiss WD. Early intravenous thrombolysis for acute ischemic stroke in a community-based approach. *Stroke*. 1998;29:1544–1549.
480. Derex L, Hermier M, Adeleine P, Pialat JB, Wiart M, Berthezène Y, Philippeau F, Honnorat J, Froment JC, Trouillas P, Nighoghossian N. Clinical and imaging predictors of intracerebral haemorrhage in stroke patients treated with intravenous tissue plasminogen activator. *J Neurol Neurosurg Psychiatr*. 2005;76:70–75.
481. Trouillas P, Nighoghossian N, Getenet JC, Riche G, Neuschwander P, Froment JC, Turjman F, Jin JX, Malicier D, Fournier G, Gabry AL, Ledoux X, Derex L, Berthezène Y, Adeleine P, Xie J, Ffrench P, Dechavanne M. Open trial of intravenous tissue plasminogen activator in acute carotid territory stroke: correlations of outcome with clinical and radiological data. *Stroke*. 1996;27:882–890.
482. Deleted in proof.
483. Katzan IL, Hammer MD, Hixson ED, Furlan AJ, Abou-Chebl A, Nadzam DM; Cleveland Clinic Health System Stroke Quality Improvement Team. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol*. 2004;61:346–350.
484. Graham GD. Tissue plasminogen activator for acute ischemic stroke in clinical practice: a meta-analysis of safety data. *Stroke*. 2003;34:2847–2850.
485. Hill MD, Lye T, Moss H, Barber PA, Demchuk AM, Newcommon NJ, Green TL, Kenney C, Cole-Haskayne A, Buchan AM. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology*. 2003;60:1525–1527.
486. Hill MD, Barber PA, Takahashi J, Demchuk AM, Feasby TE, Buchan AM. Anaphylactoid reactions and angioedema during alteplase treatment of acute ischemic stroke. *CMAJ*. 2000;162:1281–1284.
487. Aleu A, Mellado P, Lichy C, Köhrmann M, Schellinger PD. Hemorrhagic complications after off-label thrombolysis for ischemic stroke. *Stroke*. 2007;38:417–422.
488. Guillan M, Alonso-Canovas A, Garcia-Caldentey J, Sanchez-Gonzalez V, Hernandez-Medrano I, Defelipe-Mimbrera A, Matute MC, Alonso-Arias MA, Alonso de Leciñana M, Masjuan J. Off-label intravenous thrombolysis in acute stroke. *Eur J Neurol*. 2012;19:390–394.
489. Mishra NK, Ahmed N, Andersen G, Egido JA, Lindsberg PJ, Ringleb PA, Wahlgren NG, Lees KR; VISTA collaborators; SITS collaborators. Thrombolysis in very elderly people: controlled comparison of SITS International Stroke Thrombolysis Registry and Virtual International Stroke Trials Archive. *BMJ*. 2010;341:c6046.
490. Rubiera M, Ribo M, Santamarina E, Maisterra O, Delgado-Mederos R, Delgado P, Ortega G, Alvarez-Sabin J, Molina CA. Is it time to reassess the SITS-MOST criteria for thrombolysis? A comparison of patients with and without SITS-MOST exclusion criteria. *Stroke*. 2009;40:2568–2571.
491. Meretoja A, Roine RO, Kaste M, Linna M, Juntunen M, Erilä T, Hillbom M, Marttila R, Rissanen A, Sivenius J, Häkkinen U. Stroke monitoring

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on a national level: PERFECT Stroke, a comprehensive, registry-linkage stroke database in Finland. *Stroke*. 2010;41:2239–2246.
492. Breuer L, Blinzler C, Huttner HB, Kiphuth IC, Schwab S, Köhrmann M. Off-label thrombolysis for acute ischemic stroke: rate, clinical outcome and safety are influenced by the definition of "minor stroke." *Cerebrovasc Dis*. 2011;32:177–185.
493. De Silva DA, Manzano JJ, Chang HM, Wong MC. Reconsidering recent myocardial infarction as a contraindication for IV stroke thrombolysis. *Neurology*. 2011;76:1838–1840.
494. Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset: the ATLANTIS Study: a randomized controlled trial: Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. *JAMA*. 1999;282: 2019–2026.
495. Lansberg MG, Schrooten M, Bluhmki E, Thijs VN, Saver JL. Treatment time-specific number needed to treat estimates for tissue plasminogen activator therapy in acute stroke based on shifts over the entire range of the modified Rankin Scale. *Stroke*. 2009;40:2079–2084.
496. Mori E, Yoneda Y, Tabuchi M, Yoshida T, Ohkawa S, Ohsumi Y, Kitano K, Tsutsumi A, Yamadori A. Intravenous recombinant tissue plasminogen activator in acute carotid artery territory stroke. *Neurology*. 1992;42:976–982.
497. Yamaguchi, T, Hayakawa T, Kikuchi H; for the Japanese Thrombolysis Study Group. Intravenous tissue plasminogen activator in acute thromboembolic stroke: a placebo-controlled, double blind trial. In: del Zoppo GJ, Mori E, Hacke W, eds. *Thrombolytic Therapy in Acute Ischemic Stroke II*. Heidelberg, Germany: Springer Verlag; 1993:59–65.
498. Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G, Innes K, Venables G, Czlonkowska A, Kobayashi A, Ricci S, Murray V, Berge E, Slot KB, Hankey GJ, Correia M, Peeters A, Matz K, Lyrer P, Gubitz G, Phillips SJ, Arauz A. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the Third International Stroke Trial [IST-3]): a randomised controlled trial [published correction appears in *Lancet*. 2012;380:730]. *Lancet*. 2012;379:2352–2363.
499. Antman EM, Hand M, Armstrong PW, Bates ER, Green LA, Halasyamani LK, Hochman JS, Krumholz HM, Lamas GA, Mullany CJ, Pearle DL, Sloan MA, Smith SC Jr. 2007 Focused update of the ACC/AHA 2004 guidelines for the management of patients with ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Group to Review New Evidence and Update the ACC/AHA 2004 Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction) [published correction appears in *Circulation*. 2008;117:e162]. *Circulation*. 2008;117:296–329.
500. Mehta R, Ward RP, Chandra S, Agarwal R, Williams KA; American College of Cardiology Foundation; American Society of Nuclear Cardiology. Evaluation of the American College of Cardiology Foundation/American Society of Nuclear Cardiology appropriateness criteria for SPECT myocardial perfusion imaging. *J Nucl Cardiol*. 2008;15:337–344.
501. Szoeke CE, Parsons MW, Butcher KS, Baird TA, Mitchell PJ, Fox SE, Davis SM. Acute stroke thrombolysis with intravenous tissue plasminogen activator in an Australian tertiary hospital. *Med J Aust*. 2003; 178:324–328.
502. Grotta J. Lubeluzole treatment of acute ischemic stroke: the US and Canadian Lubeluzole Ischemic Stroke Study Group. *Stroke*. 1997;28:2338–2346.
503. De Keyser J, Gdovinová Z, Uyttenboogaart M, Vroomen PC, Luijckx GJ. Intravenous alteplase for stroke: beyond the guidelines and in particular clinical situations. *Stroke*. 2007;38:2612–2618.
504. Smith EE, Abdullah AR, Petkovska I, Rosenthal E, Koroshetz WJ, Schwamm LH. Poor outcomes in patients who do not receive intravenous tissue plasminogen activator because of mild or improving ischemic stroke. *Stroke*. 2005;36:2497–2499.
505. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from TPA therapy? An analysis of patient eligibility. *Neurology*. 2001;56:1015–1020.
506. García-Moncó JC, Pinedo A, Escalza I, Ferreira E, Foncea N, Gómez-Beldarrain M, Ruiz-Ojeda J, Mateo I, Mediavilla J, Basterretxea JM. Analysis of the reasons for exclusion from tPA therapy after early arrival in acute stroke patients. *Clin Neurol Neurosurg*. 2007;109:50–53.
507. Laloux P, Thijs V, Peeters A, Desfontaines P. Obstacles to the use of intravenous tissue plasminogen activator for acute ischemic stroke: is time the only barrier? *Acta Neurol Belg*. 2007;107:103–107.
508. Rajajee V, Kidwell C, Starkman S, Ovbiagele B, Alger JR, Villablanca P, Vinuela F, Duckwiler G, Jahan R, Fredieu A, Suzuki S, Saver JL. Early MRI and outcomes of untreated patients with mild or improving ischemic stroke. *Neurology*. 2006;67:980–984.
509. Alberts MJ, Bernstein RA, Naccarelli GV, Garcia DA. Using dabigatran in patients with stroke: a practical guide for clinicians. *Stroke*. 2012;43:271–279.
510. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H,Diener HC, Joyner CD, Wallentin L; RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation [published correction appears in *N Engl J Med*. 2010;363:1877]. *N Engl J Med*. 2009;361:1139–1151.
511. Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, Turan TN, Wood KA; on behalf of the American Heart Association Stroke Council, Council on Quality of Care and Outcomes Research, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/ American Stroke Association. *Stroke*. 2012;43:3442–3453.
512. Kazmi RS, Lwaleed BA. New anticoagulants: how to deal with treatment failure and bleeding complications. *Br J Clin Pharmacol*. 2011; 72:593–603.
513. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, Zhu J, Wallentin L; ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2011;365:981–992.
514. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM; ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med*. 2011;365:883–891.
515. Donnan GA, Hommel M, Davis SM, McNeil JJ. Streptokinase in acute ischaemic stroke: Steering Committees of the ASK and MAST-E trials: Australian Streptokinase Trial. *Lancet*. 1995;346:56.
516. Hommel M, Boissel JP, Cornu C, Boutitie F, Lees KR, Besson G, Leys D, Amarenco P, Bogaert M. Termination of trial of streptokinase in severe acute ischaemic stroke: MAST Study Group. *Lancet*. 1995;345:57.
517. The Multicenter Acute Stroke Trial--Europe Study Group. Thrombolytic therapy with streptokinase in acute ischemic stroke. *N Engl J Med*. 1996;335:145–150.
518. Multicentre Acute Stroke Trial—Italy (MAST-I) Group. Randomised controlled trial of streptokinase, aspirin, and combination of both in treatment of acute ischaemic stroke. *Lancet*. 1995;346:1509–1514.
519. Haley EC Jr, Lyden PD, Johnston KC, Hemmen TM; TNK in Stroke Investigators. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. *Stroke*. 2005;36:607–612.
520. Parsons MW, Miteff F, Bateman GA, Spratt N, Loiselle A, Attia J, Levi CR. Acute ischemic stroke: imaging-guided tenecteplase treatment in an extended time window. *Neurology*. 2009;72:915–921.
521. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, O'Brien B, Bladin C, McElduff P, Allen C, Bateman G, Donnan G, Davis S, Levi C. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med*. 2012;366:1099–1107.
522. Sherman DG. Antithrombotic and hypofibrinogenetic therapy in acute ischemic stroke: what is the next step? *Cerebrovasc Dis*. 2004;17(suppl 1):138–143.
523. Sherman DG, Atkinson RP, Chippendale T, Levin KA, Ng K, Futrell N, Hsu CY, Levy DE. Intravenous ancrod for treatment of acute ischemic stroke: the STAT study: a randomized controlled trial: Stroke Treatment with Ancrod Trial. *JAMA*. 2000;283:2395–2403.
524. The Ancrod Stroke Study Investigators. Ancrod for the treatment of acute ischemic brain infarction. *Stroke*. 1994;25:1755–1759.
525. Liu M, Counsell C, Zhao XL, Wardlaw J. Fibrinogen depleting agents for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2003;3:CD000091.
526. Hennerici MG, Kay R, Bogousslavsky J, Lenzi GL, Verstraete M, Orgogozo JM; ESTAT Investigators. Intravenous ancrod for acute ischaemic stroke in the European Stroke Treatment with Ancrod Trial: a randomised controlled trial. *Lancet*. 2006;368:1871–1878.

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527. Levy DE, del Zoppo GJ, Demaerschalk BM, Demchuk AM, Diener HC, Howard G, Kaste M, Pancioli AM, Ringelstein EB, Spatareanu C, Wasiewski WW. Ancrod in acute ischemic stroke: results of 500 subjects beginning treatment within 6 hours of stroke onset in the ancrod stroke program [published correction appears in *Stroke*. 2010;41:e61]. *Stroke*. 2009;40:3796–3803.
528. Eggers J, Koch B, Meyer K, König I, Seidel G. Effect of ultrasound on thrombolysis of middle cerebral artery occlusion. *Ann Neurol*. 2003;53:797–800.
529. Cintas P, Le Traon AP, Larrue V. High rate of recanalization of middle cerebral artery occlusion during 2-MHz transcranial color-coded Doppler continuous monitoring without thrombolytic drug. *Stroke*. 2002;33:626–628.
530. Tomsick T, Broderick J, Carrozella J, Khatri P, Hill M, Palesch Y, Khoury J; Interventional Management of Stroke II Investigators. Revascularization results in the Interventional Management of Stroke II trial. *AJNR Am J Neuroradiol*. 2008;29:582–587.
531. Alexandrov AV. Ultrasound enhancement of fibrinolysis. *Stroke*. 2009; 40(suppl):S107–S110.
532. Pancioli AM, Broderick J, Brott T, Tomsick T, Khoury J, Bean J, del Zoppo G, Kleindorfer D, Woo D, Khatri P, Castaldo J, Frey J, Gebel J Jr, Kasner S, Kidwell C, Kwiatkowski T, Libman R, Mackenzie R, Scott P,Starkman S, Thurman RJ; CLEAR Trial Investigators. The combined approach to lysis utilizing eptifibatide and rt-PA in acute ischemic stroke: the CLEAR stroke trial. *Stroke*. 2008;39:3268–3276.
533. American Academy of Neurology. Consent issues in the management of cerebrovascular diseases: a position paper of the American Academy of Neurology Ethics and Humanities Subcommittee. *Neurology*. 1999;53:9–11.
534. White-Bateman SR, Schumacher HC, Sacco RL, Appelbaum PS. Consent for intravenous thrombolysis in acute stroke: review and future directions. *Arch Neurol*. 2007;64:785–792.
535. Moskop JC. Informed consent in the emergency department. *Emerg Med Clin North Am*. 1999;17:327–340, ix.
536. Qureshi AI, Kirmani JF, Sayed MA, Safdar A, Ahmed S, Ferguson R, Hershey LA, Qazi KJ; Buffalo Metropolitan Area and Erie County Stroke Study Group. Time to hospital arrival, use of thrombolytics, and in-hospital outcomes in ischemic stroke. *Neurology*. 2005;64:2115–2120.
536a. Morgenstern LB, Hemphill JC 3rd, Anderson C, Becker K, Broderick JP, Connolly ES Jr, Greenberg SM, Huang JN, MacDonald RL, Messé SR, Mitchell PH, Selim M, Tamargo RJ. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2010;41:2108–2129.
537. Sylaja PN, Dzialowski I, Krol A, Roy J, Federico P, Demchuk AM; Calgary Stroke Program. Role of CT angiography in thrombolysis decision-making for patients with presumed seizure at stroke onset. *Stroke*. 2006;37:915–917.
538. Selim M, Kumar S, Fink J, Schlaug G, Caplan LR, Linfante I. Seizure at stroke onset: should it be an absolute contraindication to thrombolysis? *Cerebrovasc Dis*. 2002;14:54–57.
539. Macleod MR, Davis SM, Mitchell PJ, Gerraty RP, Fitt G, Hankey GJ, Stewart-Wynne EG, Rosen D, McNeil JJ, Bladin CF, Chambers BR, Herkes GK, Young D, Donnan GA. Results of a multicentre, randomised controlled trial of intra-arterial urokinase in the treatment of acute posterior circulation ischaemic stroke. *Cerebrovasc Dis*. 2005;20:12–17.
540. Saver JL. Intra-arterial fibrinolysis for acute ischemic stroke: the message of melt. *Stroke*. 2007;38:2627–2628.
541. Lee M, Hong KS, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials. *Stroke*. 2010;41:932–937.
542. Tountopoulou A, Ahl B, Weissenborn K, Becker H, Goetz F. Intra-arterial thrombolysis using rt-PA in patients with acute stroke due to vessel occlusion of anterior and/or posterior cerebral circulation. *Neuroradiology*. 2008;50:75–83.
543. Jahan R, Duckwiler GR, Kidwell CS, Sayre JW, Gobin YP, Villablanca JP, Saver J, Starkman S, Martin N, Vinuela F. Intraarterial thrombolysis for treatment of acute stroke: experience in 26 patients with long-term follow-up. *AJNR Am J Neuroradiol*. 1999;20:1291–1299.
544. Ducrocq X, Bracard S, Taillandier L, Anxionnat R, Lacour JC, Guillemin F, Debouverie M, Bollaert PE. Comparison of intravenous and intra-arterial urokinase thrombolysis for acute ischaemic stroke. *J Neuroradiol*. 2005;32:26–32.
545. Nagel S, Schellinger PD, Hartmann M, Juettler E, Huttner HB, Ringleb P, Schwab S, Köhrmann M. Therapy of acute basilar artery occlusion: intraarterial thrombolysis alone vs bridging therapy. *Stroke*. 2009;40:140–146.
546. Arnold M, Nedeltchev K, Mattle HP, Loher TJ, Stepper F, Schroth G, Brekenfeld C, Sturzenegger M,Remonda L. Intra-arterial thrombolysis in 24 consecutive patients with internal carotid artery T occlusions. *J Neurol Neurosurg Psychiatr*. 2003;74:739–742.
547. Ezaki Y, Tsutsumi K, Onizuka M, Kawakubo J, Yagi N, Shibayama A, Toba T, Koga H, Miyazaki H. Retrospective analysis of neurological outcome after intra-arterial thrombolysis in basilar artery occlusion. *Surg Neurol*. 2003;60:423–429.
548. Casto L, Moschini L, Camerlingo M, Gazzaniga G, Partziguain T, Belloni G, Mamoli A. Local intraarterial thrombolysis for acute stroke in the carotid artery territories. *Acta Neurol Scand*. 1992;86:308–311.
549. Sen S, Huang DY, Akhavan O, Wilson S, Verro P, Solander S. IV vs. IA TPA in acute ischemic stroke with CT angiographic evidence of major vessel occlusion: a feasibility study. *Neurocrit Care*. 2009;11:76–81.
550. Saver JL, Albers GW, Dunn B, Johnston KC, Fisher M; STAIR VI Consortium. Stroke Therapy Academic Industry Roundtable (STAIR) recommendations for extended window acute stroke therapy trials. *Stroke*. 2009;40:2594–2600.
551. Fukuda I, Imazuru T, Osaka M, Watanabe K, Meguro K, Wada M. Thrombolytic therapy for delayed, in-hospital stroke after cardiac surgery. *Ann Thorac Surg*. 2003;76:1293–1295.
552. Katzan IL, Masaryk TJ, Furlan AJ, Sila CA, Perl J 2nd, Andrefsky JC, Cosgrove DM, Sabik JF, McCarthy PM. Intra-arterial thrombolysis for perioperative stroke after open heart surgery. *Neurology*. 1999;52:1081–1084.
553. Moazami N, Smedira NG, McCarthy PM, Katzan I, Sila CA, Lytle BW, Cosgrove DM 3rd. Safety and efficacy of intraarterial thrombolysis for perioperative stroke after cardiac operation. *Ann Thorac Surg*. 2001;72:1933–1937.
554. Chalela JA, Katzan I, Liebeskind DS, Rasmussen P, Zaidat O, Suarez JI, Chiu D, Klucznick RP, Jauch E, Cucchiara BL, Saver J, Kasner SE. Safety of intra-arterial thrombolysis in the postoperative period. *Stroke*. 2001;32:1365–1369.
555. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA; IMS I and II Investigators. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology*. 2009;73:1066–1072.
556. IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke*. 2004;35:904–9-1-1.
557. IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. *Stroke*. 2007;38:2127–2135.
558. Ernst R, Pancioli A, Tomsick T, Kissela B, Woo D, Kanter D, Jauch E, Carrozzella J, Spilker J, Broderick J. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. *Stroke*. 2000;31:2552–2557.
559. Higashida R, Furlan A, Roberts H, Tomsick T, Connors B, Barr J, Dillon W, Warach S, Broderick J, Tilley B, Sacks D; Technology Assessment Committees of the American Society of Interventional and Therapeutic Neuroradiology and the Society of Interventional Radiology. Trial design and reporting standards for intraarterial cerebral thrombolysis for acute ischemic stroke. *J Vasc Interv Radiol*. 2003;14(pt 2):S493–S494.
560. Khatri P, Hill MD, Palesch YY, Spilker J, Jauch EC, Carrozzella JA, Demchuk AM, Martin R, Mauldin P, Dillon C, Ryckborst KJ, Janis S, Tomsick TA, Broderick JP; Interventional Management of Stroke III Investigators. Methodology of the Interventional Management of Stroke III Trial. *Int J Stroke*. 2008;3:130–137.
561. Shaltoni HM, Albright KC, Gonzales NR, Weir RU, Khaja AM, Sugg RM, Campbell MS 3rd, Cacayorin ED, Grotta JC, Noser EA. Is intra-arterial thrombolysis safe after full-dose intravenous recombinant tissue plasminogen activator for acute ischemic stroke? *Stroke*. 2007;38:80–84.
562. Qureshi AI. Endovascular treatment of cerebrovascular diseases and intracranial neoplasms. *Lancet*. 2004;363:804–813.
563. Smith WS, Sung G, Starkman S, Saver JL, Kidwell CS, Gobin YP, Lutsep HL, Nesbit GM, Grobelny T, Rymer MM, Silverman IE, Higashida RT, Budzik RF, Marks MP; MERCI Trial Investigators. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke*. 2005;36:1432–1438.
564. Smith WS, Sung G, Saver J, Budzik R, Duckwiler G, Liebeskind DS, Lutsep HL, Rymer MM, Higashida RT, Starkman S, Gobin YP; Multi MERCI Investigators. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke*. 2008;39:1205–1212.

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565. Smith WS. Safety of mechanical thrombectomy and intravenous tissue plasminogen activator in acute ischemic stroke: results of the multi Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial, part I. *AJNR Am J Neuroradiol*. 2006;27:1177–1182.
566. Flint AC, Duckwiler GR, Budzik RF, Liebeskind DS, Smith WS; MERCI and Multi MERCI Writing Committee. Mechanical thrombectomy of intracranial internal carotid occlusion: pooled results of the MERCI and Multi MERCI Part I trials. *Stroke*. 2007;38:1274–1280.
567. Lutsep HL, Rymer MM, Nesbit GM. Vertebrobasilar revascularization rates and outcomes in the MERCI and multi-MERCI trials. *J Stroke Cerebrovasc Dis*. 2008;17:55–57.
568. Nogueira RG, Smith WS; MERCI and Multi MERCI Writing Committee. Safety and efficacy of endovascular thrombectomy in patients with abnormal hemostasis: pooled analysis of the MERCI and multi MERCI trials. *Stroke*. 2009;40:516–522.
569. Josephson SA, Saver JL, Smith WS; Merci and Multi Merci Investigators. Comparison of mechanical embolectomy and intraarterial thrombolysis in acute ischemic stroke within the MCA: MERCI and Multi MERCI compared to PROACT II. *Neurocrit Care*. 2009;10:43–49.
570. The Penumbra Pivotal Stroke Trial Investigators. The Penumbra Pivotal Stroke Trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke* 2009;40:2761–2768.
571. Tarr R, Hsu D, Kulcsar Z, Bonvin C, Rufenacht D, Alfke K, Stingele R, Jansen O, Frei D, Bellon R, Madison M, Struffert T, Dorfler A, Grunwald IQ, Reith W, Haass A. The POST trial: initial post-market experience of the Penumbra system: revascularization of large vessel occlusion in acute ischemic stroke in the United States and Europe [published correction appears in *J Neurointerv Surg*. 2011;3:97]. *J Neurointerv Surg*. 2010;2:341–344.
572. Saver JL, Jahan R, Levy EI, Jovin TG, Baxter B, Nogueira RG, Clark W, Budzik R, Zaidat OO; SWIFT Trialists. Solitaire flow restoration device versus the Merci Retriever in patients with acute ischaemic stroke (SWIFT): a randomised, parallel-group, non-inferiority trial. *Lancet*. 2012;380:1241–1249.
573. Nogueira RG, Lutsep HL, Gupta R, Jovin TG, Albers GW, Walker GA, Liebeskind DS, Smith WS; TREVO 2 Trialists. Trevo versus Merci retrievers for thrombectomy revascularisation of large vessel occlusions in acute ischaemic stroke (TREVO 2): a randomised trial [published correction appears in *Lancet*. 2012;380:1230]. *Lancet*. 2012;380:1231–1240.
574. National Institute of Neurological Disorders and Stroke. Interventional Management of Stroke III Trial (IMS III). http://www.ninds.nih.gov/disorders/clinical_trials/NCT00359424.htm. Accessed September 12, 2012.
575. Levy EI, Siddiqui AH, Crumlish A, Snyder KV, Hauck EF, Fiorella DJ, Hopkins LN, Mocco J. First Food and Drug Administration-approved prospective trial of primary intracranial stenting for acute stroke: SARIS (stent-assisted recanalization in acute ischemic stroke). *Stroke*. 2009;40:3552–3556.
575. Costalat V, Machi P, Lobotesis K, Maldonado I, Vendrell JF, Riquelme C, Mourand I, Milhaud D, Héroum C, Perrigault PF, Arquizan C, Bonafé A. Rescue, combined, and stand-alone thrombectomy in the management of large vessel occlusion stroke using the Solitaire device: a prospective 50-patient single-center study: timing, safety, and efficacy. *Stroke*. 2011;42:1929–1935.
577. Rohde S, Haehnel S, Herweh C, Pham M, Stampfl S, Ringleb PA, Bendszus M. Mechanical thrombectomy in acute embolic stroke: preliminary results with the Revive device. *Stroke*. 2011;42:2954–2956.
578. Nikas D, Reimers B, Elisabetta M, Saccá S, Cernetti C, Pasquetto G, Favero L, Fattorello C, Pascotto P. Percutaneous interventions in patients with acute ischemic stroke related to obstructive atherosclerotic disease or dissection of the extracranial carotid artery. *J Endovasc Ther*. 2007;14:279–288.
579. Hayashi K, Kitagawa N, Takahata H, Morikawa M, Yoshioka T, Shabani HK, Kitange G, Ochi M, Kaminogo M, Shibata S. Endovascular treatment for cervical carotid artery stenosis presenting with progressing stroke: three case reports. *Surg Neurol*. 2002;58:148–154.
580. Imai K, Mori T, Izumoto H, Watanabe M, Majima K. Emergency carotid artery stent placement in patients with acute ischemic stroke. *AJNR Am J Neuroradiol*. 2005;26:1249–1258.
581. Jovin TG, Gupta R, Uchino K, Jungreis CA, Wechsler LR, Hammer MD, Tayal A, Horowitz MB. Emergent stenting of extracranial internal carotid artery occlusion in acute stroke has a high revascularization rate. *Stroke*. 2005;36:2426–2430.
582. Nedeltchev K, Brekenfeld C, Remonda L, Ozdoba C, Do DD, Arnold M, Mattle HP, Schroth G. Internal carotid artery stent implantation in 25 patients with acute stroke: preliminary results. *Radiology*. 2005;237:1029–1037.
583. Wang H, Wang D, Fraser K, Swischuk J, Elwood P. Emergent combined intracranial thrombolysis and carotid stenting in the hyperacute management of stroke patients with severe cervical carotid stenosis. *AJNR Am J Neuroradiol*. 2007;28:1162–1166.
584. Dabitz R, Triebe S, Leppmeier U, Ochs G, Vorwerk D. Percutaneous recanalization of acute internal carotid artery occlusions in patients with severe stroke. *Cardiovasc Intervent Radiol*. 2007;30:34–41.
585. Lin DD, Gailloud P, Beauchamp NJ, Aldrich EM, Wityk RJ, Murphy KJ. Combined stent placement and thrombolysis in acute vertebrobasilar ischemic stroke. *AJNR Am J Neuroradiol*. 2003;24:1827–1833.
586. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial: phase I findings. *N Engl J Med*. 1985;312:932–936.
587. Soares BP, Chien JD, Wintermark M. MR and CT monitoring of recanalization, reperfusion, and penumbra salvage: everything that recanalizes does not necessarily reperfuse! *Stroke*. 2009;40(suppl):S24–S27.
588. Qureshi AI. New grading system for angiographic evaluation of arterial occlusions and recanalization response to intra-arterial thrombolysis in acute ischemic stroke. *Neurosurgery*. 2002;50:1405–1414.
589. Mohammad YM, Christoforidis GA, Bourekas EC, Slivka AP. Qureshi grading scheme predicts subsequent volume of brain infarction following intra-arterial thrombolysis in patients with acute anterior circulation ischemic stroke. *J Neuroimaging*. 2008;18:262–267.
590. Mohammad Y, Xavier AR, Christoforidis G, Bourekas E, Slivka A. Qureshi grading scheme for angiographic occlusions strongly correlates with the initial severity and in-hospital outcome of acute ischemic stroke. *J Neuroimaging*. 2004;14:235–241.
591. Khatri P, Neff J, Broderick JP, Khoury JC, Carrozzella J, Tomsick T; IMS-I Investigators. Revascularization end points in stroke interventional trials: recanalization versus reperfusion in IMS-I. *Stroke*. 2005;36:2400–2403.
592. The NeuroVascular Research Foundation. INterventional Stroke Therapy Outcomes Registry (INSTOR). http://www.strokeregistry.org. Accessed August 25, 2011.
593. Janjua N, Alkawi A, Suri MF, Qureshi AI. Impact of arterial reocclusion and distal fragmentation during thrombolysis among patients with acute ischemic stroke. *AJNR Am J Neuroradiol*. 2008;29:253–258.
594. Qureshi AI, Hussein HM, Abdelmoula M, Georgiadis AL, Janjua N. Subacute recanalization and reocclusion in patients with acute ischemic stroke following endovascular treatment. *Neurocrit Care*. 2009;10:195–203.
595. Qureshi AI, Abou-Chebl A, Jovin TG. Qualification requirements for performing neurointerventional procedures: a report of the Practice Guidelines Committee of the American Society of Neuroimaging and the Society of Vascular and Interventional Neurology. *J Neuroimaging*. 2008;18:433–447.
596. Al-Sadat A, Sunbulli M, Chaturvedi S. Use of intravenous heparin by North American neurologists: do the data matter? *Stroke*. 2002;33:1574–1577.
597. Schmidt WP, Heuschmann P, Taeger D, Henningsen H, Buecker-Nott HJ, Berger K. Determinants of IV heparin treatment in patients with ischemic stroke. *Neurology*. 2004;63:2407–2409.
598. Adams HP Jr, Adams RJ, Brott T, del Zoppo GJ, Furlan A, Goldstein LB, Grubb RL, Higashida R, Kidwell C, Kwiatkowski TG, Marler JR, Hademenos GJ; Stroke Council of the American Stroke Association. Guidelines for the early management of patients with ischemic stroke: a scientific statement from the Stroke Council of the American Stroke Association. *Stroke*. 2003;34:1056–1083.
599. Adams HP Jr, Brott TG, Crowell RM, Furlan AJ, Gomez CR, Grotta J, Helgason CM, Marler JR, Woolson RF, Zivin JA, et al. Guidelines for the management of patients with acute ischemic stroke: a statement for healthcare professionals from a special writing group of the Stroke Council, American Heart Association. *Circulation*. 1994;90:1588–1601.
600. Coull BM, Williams LS, Goldstein LB, Meschia JF, Heitzman D, Chaturvedi S, Johnston KC, Starkman S, Morgenstern LB, Wilterdink JL, Levine SR, Saver JL; American Academy of Neurology; American Stroke Association. Anticoagulants and antiplatelet agents in acute ischemic stroke: report of the Joint Stroke Guideline Development Committee of the American Academy of Neurology and the American Stroke Association (a division of the American Heart Association). *Neurology*. 2002;59:13–22.
601. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P; American College of Chest Physicians. Antithrombotic and thrombolytic therapy for ischemic stroke: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). *Chest*. 2008;133(suppl):630S–669S.

Downloaded from http://stroke.ahajournals.org/ at Wayne State University on February 18, 2013

602. Cerebral Embolism Study Group. Immediate anticoagulation of embolic stroke: brain hemorrhage and management options. *Stroke*. 1984;15:779–789.
603. Cerebral Embolism Study Group. Cardioembolic stroke, early anticoagulation, and brain hemorrhage. *Arch Intern Med*. 1987;147:636–640.
604. Berge E, Abdelnoor M, Nakstad PH, Sandset PM. Low molecular-weight heparin versus aspirin in patients with acute ischaemic stroke and atrial fibrillation: a double-blind randomised study: HAEST Study Group: Heparin in Acute Embolic Stroke Trial. *Lancet*. 2000;355:1205–1210.
605. CAST (Chinese Acute Stroke Trial) Collaborative Group. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. *Lancet*. 1997;349:1641–1649.
606. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. *Lancet*. 1997;349:1569–1581.
607. The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA*. 1998;279:1265–1272.
608. Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke*. 2001;32:2333–2337.
609. Rödén-Jüllig A, Britton M. Effectiveness of heparin treatment for progressing ischaemic stroke: before and after study. *J Intern Med*. 2000;248:287–291.
610. Camerlingo M, Salvi P, Belloni G, Gamba T, Cesana BM, Mamoli A. Intravenous heparin started within the first 3 hours after onset of symptoms as a treatment for acute nonlacunar hemispheric cerebral infarctions. *Stroke*. 2005;36:2415–2420.
611. Micheli S, Agnelli G, Caso V, Paciaroni M. Clinical benefit of early anticoagulation in cardioembolic stroke. *Cerebrovasc Dis*. 2008;25:289–296.
612. Chamorro A, Busse O, Obach V, Toni D, Sandercock P, Reverter JC, Cervera A, Torres F, Dávalos A; RAPID Investigators. The rapid Anticoagulation Prevents Ischemic Damage Study in Acute Stroke: final results from the writing committee. *Cerebrovasc Dis*. 2005;19:402–404.
613. Sandercock PA, Counsell C, Kamal AK. Anticoagulants for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2008;(4):CD000024.
614. Paciaroni M, Agnelli G, Micheli S, Caso V. Efficacy and safety of anticoagulant treatment in acute cardioembolic stroke: a meta-analysis of randomized controlled trials. *Stroke*. 2007;38:423–430.
615. Audebert HJ, Schenk B, Tietz V, Schenkel J, Heuschmann PU. Initiation of oral anticoagulation after acute ischaemic stroke or transient ischaemic attack: timing and complications of overlapping heparin or conventional treatment. *Cerebrovasc Dis*. 2008;26:171–177.
616. Kawano H, Toyoda K, Miyata S, Yamamoto H, Okamoto A, Kakutani I, Walenga JM, Naritomi H, Minematsu K. Heparin-induced thrombocytopenia: a serious complication of heparin therapy for acute stroke. *Cerebrovasc Dis*. 2008;26:641–649.
617. Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, Chan FL, Fong KY, Law CB, Wong A. Low-molecular-weight heparin for the treatment of acute ischemic stroke. *N Engl J Med*. 1995;333:1588–1593.
618. Chamorro A. Heparin in acute ischemic stroke: the case for a new clinical trial. *Cerebrovasc Dis*. 1999;9(suppl 3):16–23.
619. O'Donnell MJ, Berge E, Sandset PM. Are there patients with acute ischemic stroke and atrial fibrillation that benefit from low molecular weight heparin? *Stroke*. 2006;37:452–455.
620. Diener HC, Ringelstein EB, von Kummer R, Langohr HD, Bewermeyer H, Landgraf H, Hennerici M, Welzel D, Gräve M, Brom J, Weidinger G. Treatment of acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the TOPAS trial: Therapy of Patients With Acute Stroke (TOPAS) Investigators. *Stroke*. 2001;32:22–29.
621. Bath PM, Lindenstrom E, Boysen G, De Deyn P, Friis P, Leys D, Marttila R, Olsson J, O'Neill D, Orgogozo J, Ringelstein B, van der Sande J, Turpie AG. Tinzaparin in Acute Ischaemic Stroke (TAIST): a randomised aspirin-controlled trial. *Lancet*. 2001;358:702–710.
622. Adams HP Jr, Bendixen BH, Leira E, Chang KC, Davis PH, Woolson RF, Clarke WR, Hansen MD. Antithrombotic treatment of ischemic stroke among patients with occlusion or severe stenosis of the internal carotid artery: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53:122–125.
623. Lovett JK, Coull AJ, Rothwell PM. Early risk of recurrence by subtype of ischemic stroke in population-based incidence studies. *Neurology*. 2004;62:569–573.
624. Wong KS, Chen C, Ng PW, Tsoi TH, Li HL, Fong WC, Yeung J, Wong CK, Yip KK, Gao H, Wong HB; FISS-tris Study Investigators. Low-molecular-weight heparin compared with aspirin for the treatment of acute ischaemic stroke in Asian patients with large artery occlusive disease: a randomised study. *Lancet Neurol*. 2007;6:407–413.
625. Woessner R, Grauer M, Bianchi O, Mueller M, Moersdorf S, Berlit P, Goertler M, Grotemeyer KH, Sliwka U, Stoll M, Treib J. Treatment with anticoagulants in cerebral events (TRACE). *Thromb Haemost*. 2004;91:690–693.
626. Bath P, Leonardi-Bee J, Bath F. Low molecular weight heparin versus aspirin for acute ischemic stroke: a systematic review. *J Stroke Cerebrovasc Dis*. 2002;11:55–62.
627. Hillbom M, Erilä T, Sotaniemi K, Tatlisumak T, Sarna S, Kaste M. Enoxaparin vs heparin for prevention of deep-vein thrombosis in acute ischaemic stroke: a randomized, double-blind study. *Acta Neurol Scand*. 2002;106:84–92.
628. Diener HC, Ringelstein EB, von Kummer R, Landgraf H, Koppenhagen K, Harenberg J, Rektor I, Csányi A, Schneider D, Klingelhöfer J, Brom J, Weidinger G; PROTECT Trial Group. Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT Trial. *Stroke*. 2006;37:139–144.
629. Sherman DG, Albers GW, Bladin C, Fieschi C, Gabbai AA, Kase CS, O'Riordan W, Pineo GF; PREVAIL Investigators. The efficacy and safety of enoxaparin versus unfractionated heparin for the prevention of venous thromboembolism after acute ischaemic stroke (PREVAIL Study): an open-label randomised comparison. *Lancet*. 2007;369:1347–1355.
630. Sandercock PA, Counsell C, Tseng MC. Low-molecular-weight heparins or heparinoids versus standard unfractionated heparin for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2008;(3):CD000119.
631. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke: PROACT Investigators: Prolyse in Acute Cerebral Thromboembolism. *Stroke*. 1998;29:4–11.
632. Furlan AJ, Kanoti G. When is thrombolysis justified in patients with acute ischemic stroke? A bioethical perspective. *Stroke*. 1997;28:214–218.
633. Schmülling S, Rudolf J, Strotmann-Tack T, Grond M, Schneweis S, Sobesky J, Thiel A, Heiss WD. Acetylsalicylic acid pretreatment, concomitant heparin therapy and the risk of early intracranial hemorrhage following systemic thrombolysis for acute ischemic stroke. *Cerebrovasc Dis*. 2003;16:183–190.
634. Grond M, Rudolf, J, Neveling M, Stenzel C, Heiss WD. Risk of immediate heparin after rt-PA therapy in acute ischemic stroke. *Cerebrovasc Dis*. 1997;7:318–323.
635. Mandava P, Lick SD, Rahman MA, Langsjoen H, Reddy KV, Nelson J, Kent TA. Initial safety experience of abciximab and heparin for acute ischemic stroke. *Cerebrovasc Dis*. 2005;19:276–278.
636. Wallentin L, Yusuf S, Ezekowitz MD, Alings M, Flather M, Franzosi MG, Pais P, Dans A, Eikelboom J, Oldgren J, Pogue J, Reilly PA, Yang S, Connolly SJ; RE-LY investigators. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. *Lancet*. 2010;376:975–983.
637. LaMonte MP, Stallmeyer MJ. Acute ischemic stroke successfully treated using sequenced intravenous and intra-arterial thrombolysis and argatroban anticoagulation: a case study. *J Thromb Thrombolysis*. 2004;17:151–156.
638. Hosomi N, Naya T, Kohno M, Kobayashi S, Koziol JA; Japan Standard Stroke Registry Study Group. Efficacy of anti-coagulant treatment with argatroban on cardioembolic stroke. *J Neurol*. 2007;254:605–612.
639. Qureshi AI, Luft AR, Sharma M, Guterman LR, Hopkins LN. Prevention and treatment of thromboembolic and ischemic complications associated with endovascular procedures: part I: pathophysiological and pharmacological features. *Neurosurgery*. 2000;46:1344–1359.
640. Suri MF, Hussein HM, Abdelmoula MM, Divani AA, Qureshi AI. Safety and tolerability of 600 mg clopidogrel bolus in patients with acute ischemic stroke: preliminary experience. *Med Sci Monit*. 2008;14:PI39–PI44.
641. Meyer DM, Albright KC, Allison TA, Grotta JC. LOAD: a pilot study of the safety of loading of aspirin and clopidogrel in acute ischemic stroke and transient ischemic attack. *J Stroke Cerebrovasc Dis*. 2008;17:26–29.
642. Chairangsarit P, Sithinamsuwan P, Niyasom S, Udommongkol C, Nidhinandana S, Suwantamee J. Comparison between aspirin combined with dipyridamole versus aspirin alone within 48 hours after ischemic

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stroke event for prevention of recurrent stroke and improvement of neurological function: a preliminary study. *J Med Assoc Thai*. 2005;88(suppl 3):S148–S154.
643. Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T, Eschenfelder CC, Leonard J, Weissenborn K, Kastrup A, Haberl R; EARLY Investigators. Early treatment with aspirin plus extended-release dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. *Lancet Neurol*. 2010;9:159–166.
644. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomised controlled pilot trial. *Lancet Neurol*. 2007;6:961–969.
645. Lapchak PA, Araujo DM. Therapeutic potential of platelet glycoprotein IIb/IIIa receptor antagonists in the management of ischemic stroke. *Am J Cardiovasc Drugs*. 2003;3:87–94.
646. Seitz RJ, Siebler M. Platelet GPIIb/IIIa receptor antagonists in human ischemic brain disease. *Curr Vasc Pharmacol*. 2008;6:29–36.
647. Abou-Chebl A, Bajzer CT, Krieger DW, Furlan AJ, Yadav JS. Multimodal therapy for the treatment of severe ischemic stroke combining GPIIb/IIIa antagonists and angioplasty after failure of thrombolysis. *Stroke*. 2005;36:2286–2288.
648. Qureshi AI, Suri MF, Ali Z, Ringer AJ, Boulos AS, Nakada MT, Alberico RA, Martin LB, Guterman LR, Hopkins LN. Intraarterial reteplase and intravenous abciximab for treatment of acute ischemic stroke: a preliminary feasibility and safety study in a non-human primate model. *Neuroradiology*. 2005;47:845–854.
649. Zaidat OO, Wolfe T, Hussain SI, Lynch JR, Gupta R, Delap J, Torbey MT, Fitzsimmons BF. Interventional acute ischemic stroke therapy with intracranial self-expanding stent. *Stroke*. 2008;39:2392–2395.
650. Lee JY, Kim SH, Lee MS, Park SH, Lee SS. Prediction of clinical outcome with baseline and 24-hour perfusion CT in acute middle cerebral artery territory ischemic stroke treated with intravenous recanalization therapy. *Neuroradiology*. 2008;50:391–396.
651. Mitsias PD, Lu M, Silver B, Morris D, Ewing JR, Daley S, Lewandowski C, Katramados A, Papamitsakis NI, Ebadian HB, Zhao Q, Soltanian-Zadeh H, Hearshen D, Patel SC, Chopp M. MRI-guided, open trial of abciximab for ischemic stroke within a 3- to 24-hour window. *Neurology*. 2005;65:612–615.
652. Deshmukh VR, Fiorella DJ, Albuquerque FC, Frey J, Flaster M, Wallace RC, Spetzler RF, McDougall CG. Intra-arterial thrombolysis for acute ischemic stroke: preliminary experience with platelet glycoprotein IIb/IIIa inhibitors as adjunctive therapy. *Neurosurgery*. 2005;56:46–54.
653. Morris DC, Silver B, Mitsias P, Lewandowski C, Patel S, Daley S, Zhang ZG, Lu M. Treatment of acute stroke with recombinant tissue plasminogen activator and abciximab. *Acad Emerg Med*. 2003;10:1396–1399.
654. The Abciximab in Ischemic Stroke Investigators. Abciximab in acute ischemic stroke: a randomized, double-blind, placebo-controlled, dose-escalation study. *Stroke*. 2000;31:601–609.
655. Abciximab Emergency Stroke Treatment Trial (AbESTT) Investigators. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of a randomized phase 2 trial. *Stroke*. 2005;36:880–890.
656. Adams HP Jr, Effron MB, Torner J, Dávalos A, Frayne J, Teal P, Leclerc J, Oemar B, Padgett L, Barnathan ES, Hacke W; AbESTT-II Investigators. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). *Stroke*. 2008;39:87–99.
657. Adams HP Jr, Leira EC, Torner JC, Barnathan E, Padgett L, Effron MB, Hacke W; AbESTT-II Investigators. Treating patients with "wake-up" stroke: the experience of the AbESTT-II trial. *Stroke*. 2008;39:3277–3282.
658. Bukow SC, Daffertshofer M, Hennerici MG. Tirofiban for the treatment of ischaemic stroke. *Expert Opin Pharmacother*. 2006;7:73–79.
659. Del Pace S, Scheggi V. Acute ischaemic stroke treated with combined intra-arterial thrombolysis and intravenous tirofiban despite oral anticoagulant therapy at an international normalised ratio > or = 2.0. *Intern Emerg Med*. 2006;1:250–252.
660. Mangiafico S, Cellerini M, Nencini P, Gensini G, Inzitari D. Intravenous glycoprotein IIb/IIIa inhibitor (tirofiban) followed by intra-arterial urokinase and mechanical thrombolysis in stroke. *AJNR Am J Neuroradiol*. 2005;26:2595–2601.
661. Mangiafico S, Cellerini M, Nencini P, Gensini G, Inzitari D. Intravenous tirofiban with intra-arterial urokinase and mechanical thrombolysis in stroke: preliminary experience in 11 cases. *Stroke*. 2005;36:2154–2158.
662. Seitz RJ, Meisel S, Moll M, Wittsack HJ, Junghans U, Siebler M. The effect of combined thrombolysis with rtPA and tirofiban on ischemic brain lesions. *Neurology*. 2004;62:2110–2112.
663. Song TJ, Lee KO, Kim DJ, Lee KY. Rescue treatment with intra-arterial tirofiban infusion and emergent carotid stenting. *Yonsei Med J*. 2008;49:857–859.
664. Siebler M, Hennerici MG, Schneider D, von Reutern GM, Seitz RJ, Röther J, Witte OW, Hamann G, Junghans U, Villringer A, Fiebach JB. Safety of Tirofiban in acute Ischemic Stroke: the SaTIS trial. *Stroke*. 2011;42:2388–2392.
665. Zinkstok SM, Roos YB; ARTIS investigators. Early administration of aspirin in patients treated with alteplase for acute ischaemic stroke: a randomised controlled trial. *Lancet*. 2012;380:731–737.
666. Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB, Gorelick P, Halperin J, Harbaugh R, Johnston SC, Katzan I, Kelly-Hayes M, Kenton EJ, Marks M, Schwamm LH, Tomsick T; American Heart Association; American Stroke Association Council on Stroke; Council on Cardiovascular Radiology and Intervention; American Academy of Neurology. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:577–617.
667. Astrup J, Siesjö BK, Symon L. Thresholds in cerebral ischemia: the ischemic penumbra. *Stroke*. 1981;12:723–725.
668. Heiss WD, Sobesky J, Hesselmann V. Identifying thresholds for penumbra and irreversible tissue damage. *Stroke*. 2004;35(suppl 1):2671–2674.
669. Qureshi AI. Acute hypertensive response in patients with stroke: pathophysiology and management. *Circulation*. 2008;118:176–187.
670. Hartmann A, Dettmers C, Lagreze H, Tsuda Y. Blood flow and clinical course in patients with ischemic stroke without cerebrospecific therapy. *Acta Neurochir Suppl (Wien)*. 1993;57:130–135.
671. Allport LE, Parsons MW, Butcher KS, MacGregor L, Desmond PM, Tress BM, Davis SM. Elevated hematocrit is associated with reduced reperfusion and tissue survival in acute stroke. *Neurology*. 2005;65:1382–1387.
672. Belayev L, Busto R, Zhao W, Clemens JA, Ginsberg MD. Effect of delayed albumin hemodilution on infarction volume and brain edema after transient middle cerebral artery occlusion in rats. *J Neurosurg*. 1997;87:595–601.
673. Rodriguez GJ, Cordina SM, Vazquez G, Suri MF, Kirmani JF, Ezzeddine MA, Qureshi AI. The Hydration Influence on the Risk of Stroke (THIRST) study. *Neurocrit Care*. 2009;10:187–194.
674. Sacco S, Marini C, Olivieri L, Pistoia F, Carolei A. Contribution of hematocrit to early mortality after ischemic stroke. *Eur Neurol*. 2007;58:233–238.
675. Tanne D, Macko RF, Lin Y, Tilley BC, Levine SR; NINDS rtPA Stroke Study Group. Hemostatic activation and outcome after recombinant tissue plasminogen activator therapy for acute ischemic stroke. *Stroke*. 2006;37:1798–1804.
676. Hartmann A, Dettmers C, Beyenburg S. Effect of hemodilution on regional cerebral blood flow. *Acta Neurol Scand Suppl*. 1989;127:36–48.
677. Hartmann A, Rommel T, Dettmers C, Tsuda Y, Lagrèze H, Broich K. Hemodilution in cerebral infarcts. *Arzneimittelforschung*. 1991;41(3A):348–351.
678. Hartmann A, Tsuda Y, Lagrèze H. Effect of hypervolaemic haemodilution of regional cerebral blood flow in patients with acute ischaemic stroke: a controlled study with hydroxyethylstarch. *J Neurol*. 1987;235:34–38.
679. Vorstrup S, Andersen A, Juhler M, Brun B, Boysen G. Hemodilution increases cerebral blood flow in acute ischemic stroke. *Stroke*. 1989;20:884–889.
680. Wood JH, Polyzoidis KS, Kee DB Jr, Prats AR, Gibby GL, Tindall GT. Augmentation of cerebral blood flow induced by hemodilution in stroke patients after superficial temporal-middle cerebral arterial bypass operation. *Neurosurgery*. 1984;15:535–539.
681. Rudolf J; HES in Acute Stroke Study Group. Hydroxyethyl starch for hypervolemic hemodilution in patients with acute ischemic stroke: a randomized, placebo-controlled phase II safety study. *Cerebrovasc Dis*. 2002;14:33–41.
682. Woessner R, Grauer MT, Dieterich HJ, Bepperling F, Baus D, Kahles T, Georgi S, Bianchi O, Morgenthaler M, Treib J. Influence of a long-term, high-dose volume therapy with 6% hydroxyethyl starch 130/0.4 or crystalloid solution on hemodynamics, rheology and hemostasis in patients with acute ischemic stroke: results of a randomized, placebo-controlled, double-blind study. *Pathophysiol Haemost Thromb*. 2003;33:121–126.

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683. Asplund K. Haemodilution for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2002;(4):CD000103.
684. Chan YW, Kay CS. Pentoxifylline in the treatment of acute ischaemic stroke: a reappraisal in Chinese stroke patients. *Clin Exp Neurol*. 1993;30:110–116.
685. Bath PM, Bath-Hextall FJ. Pentoxifylline, propentofylline and pentifylline for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2004;(3):CD000162.
686. Chalela JA, Dunn B, Todd JW, Warach S. Induced hypertension improves cerebral blood flow in acute ischemic stroke. *Neurology*. 2005;64:1979.
687. Georgiadis AL, Al-Kawi A, Janjua N, Kirmani JF, Ezzeddine MA, Qureshi AI. Cerebral angiography can demonstrate changes in collateral flow during induced hypertension. *Radiol Case Rep*. 2007;2:1–3.
688. Hillis AE, Barker PB, Beauchamp NJ, Winters BD, Mirski M, Wityk RJ. Restoring blood pressure reperfused Wernicke's area and improved language. *Neurology*. 2001;56:670–672.
689. Qureshi AI, El-Gengaihi A, Hussein HM, Suri MF, Liebeskind DS. Occurrence and variability in acute formation of leptomeningeal collaterals in proximal middle cerebral artery occlusion. *J Vasc Interv Neurol*. 2008;1:70–72.
690. Tariq N, Khatri R. Leptomeningeal collaterals in acute ischemic stroke. *J Vasc Interv Neurol*. 2008;1:91–95.
691. Rordorf G, Cramer SC, Efird JT, Schwamm LH, Buonanno F, Koroshetz WJ. Pharmacological elevation of blood pressure in acute stroke: clinical effects and safety. *Stroke*. 1997;28:2133–2138.
692. Rordorf G, Koroshetz WJ, Ezzeddine MA, Segal AZ, Buonanno FS. A pilot study of drug-induced hypertension for treatment of acute stroke. *Neurology*. 2001;56:1210–1213.
693. Marzan AS, Hungerbühler HJ, Studer A, Baumgartner RW, Georgiadis D. Feasibility and safety of norepinephrine-induced arterial hypertension in acute ischemic stroke. *Neurology*. 2004;62:1193–1195.
694. Hillis AE, Ulatowski JA, Barker PB, Torbey M, Ziai W, Beauchamp NJ, Oh S, Wityk RJ. A pilot randomized trial of induced blood pressure elevation: effects on function and focal perfusion in acute and subacute stroke. *Cerebrovasc Dis*. 2003;16:236–246.
695. Koenig MA, Geocadin RG, de Grouchy M, Glasgow J, Vimal S, Restrepo L, Wityk RJ. Safety of induced hypertension therapy in patients with acute ischemic stroke. *Neurocrit Care*. 2006;4:3–7.
696. Shah QA, Patel S, Qureshi AI. Induced hypertension in patients with partial recanalization after intra-arterial thrombolysis for acute ischemic stroke. *J Neurosurg Anesthesiol*. 2008;20:154–155.
697. Ginsberg MD. Neuroprotection for ischemic stroke: past, present and future. *Neuropharmacology*. 2008;55:363–389.
698. Belayev L, Pinard E, Nallet H, Seylaz J, Liu Y, Riyamongkol P, Zhao W, Busto R, Ginsberg MD. Albumin therapy of transient focal cerebral ischemia: in vivo analysis of dynamic microvascular responses. *Stroke*. 2002;33:1077–1084.
699. Belayev L, Zhao W, Pattany PM, Weaver RG, Huh PW, Lin B,Busto R, Ginsberg MD. Diffusion-weighted magnetic resonance imaging confirms marked neuroprotective efficacy of albumin therapy in focal cerebral ischemia. *Stroke*. 1998;29:2587–2599.
700. Cho YM, Choi IS, Bian RX, Kim JH, Han JY, Lee SG. Serum albumin at admission for prediction of functional outcome in ischaemic stroke patients. *Neurol Sci*. 2008;29:445–449.
701. Dziedzic T, Slowik A, Szczudlik A. Serum albumin level as a predictor of ischemic stroke outcome [published correction appears in *Stroke*. 2005;36:689]. *Stroke*. 2004;35:e156–e158.
702. Ginsberg MD, Hill MD, Palesch YY, Ryckborst KJ, Tamariz D. The ALIAS Pilot Trial: a dose-escalation and safety study of albumin therapy for acute ischemic stroke, I: physiological responses and safety results. *Stroke*. 2006;37:2100–2106.
703. Palesch YY, Hill MD, Ryckborst KJ, Tamariz D, Ginsberg MD. The ALIAS Pilot Trial: a dose-escalation and safety study of albumin therapy for acute ischemic stroke, II: neurologic outcome and efficacy analysis. *Stroke*. 2006;37:2107–2114.
704. Ginsberg MD, Palesch YY, Hill MD. The ALIAS (ALbumin In Acute Stroke) Phase III randomized multicentre clinical trial: design and progress report. *Biochem Soc Trans*. 2006;34(pt 6):1323–1326.
705. Ginsberg MD, Palesch YY, Martin RH, Hill MD, Moy CS, Waldman BD, Yeatts SD, Tamariz D, Ryckborst K; ALIAS Investigators. The Albumin in Acute Stroke (ALIAS) multicenter clinical trial: safety analysis of part 1 and rationale and design of part 2. *Stroke*. 2011;42:119–127.
706. Hill MD, Martin RH, Palesch YY, Tamariz D, Waldman BD, Ryckborst KJ, Moy CS, Barsan WG, Ginsberg MD; ALIAS Investigators; Neurological Emergencies Treatment Trials Network. The Albumin in Acute Stroke Part 1 Trial: an exploratory efficacy analysis. *Stroke*. 2011;42:1621–1625.
707. Stokland O, Molaug M, Thorvaldson J, Ilebekk A, Kiil F. Cardiac effects of splanchnic and non-splanchnic blood volume redistribution during aortic occlusions in dogs. *Acta Physiol Scand*. 1981;113:139–146.
708. Stokland O, Thorvaldson J, Ilebekk A, Kiil F. Contributions of blood drainage from the liver, spleen and intestines to cardiac effects of aortic occlusion in the dog. *Acta Physiol Scand*. 1982;114:351–362.
709. Strømholm T, Dale LG, Saether OD, Aadahl P, Myhre HO. Selective carotid angiography during cross-clamping of the descending thoracic aorta in pigs. *Int Angiol*. 1996;15:263–267.
710. Simeone FA. Enhancement of cerebral flood flow by intermittent aortic occlusion. *Eur Neurol*. 1972;8:142–144.
711. Simeone FA, Laurent JP, Trepper PJ, Brown DJ, Cotter J. Experimental augmentation of cerebral blood flow by intermittent aortic occlusion. *J Neurosurg*. 1972;36:700–713.
712. Stokland O, Miller MM, Ilebekk A, Kiil F. Mechanism of hemodynamic responses to occlusion of the descending thoracic aorta. *Am J Physiol*. 1980;238:H423–H429.
713. Gelman S, Khazaeli MB, Orr R, Henderson T. Blood volume redistribution during cross-clamping of the descending aorta. *Anesth Analg*. 1994;78:219–224.
714. Saether OD, Juul R, Aadahl P, Strømholm T, Myhre HO. Cerebral haemodynamics during thoracic- and thoracoabdominal aortic aneurysm repair. *Eur J Vasc Endovasc Surg*. 1996;12:81–85.
715. Strømholm T, Saether OD, Aadahl P, Nilsen G, Kvaerness J, Myhre HO. Alterations in intracranial volume following cross-clamping of the descending thoracic aorta in pigs: an experimental study using MRI. *Eur J Vasc Endovasc Surg*. 1995;10:36–39.
716. Liebeskind DS. Aortic occlusion for cerebral ischemia: from theory to practice. *Curr Cardiol Rep*. 2008;10:31–36.
717. Campbell MIG, JC; Gomez, CR; Ozdemir, G. Perfusion augmentation in stroke using controlled aortic obstruction: pilot study results. *Stroke*. 2004;35:291. Abstract.
718. Deleted in proof.
719. Shuaib A, Bornstein NM, Diener HC, Dillon W, Fisher M, Hammer MD, Molina CA, Rutledge JN, Saver JL, Schellinger PD, Shownkeen H; SENTIS Trial Investigators. Partial aortic occlusion for cerebral perfusion augmentation: safety and efficacy of NeuroFlo in Acute Ischemic Stroke trial. *Stroke*. 2011;42:1680–1690.
720. Bonetti PO, Holmes DR Jr, Lerman A, Barsness GW. Enhanced external counterpulsation for ischemic heart disease: what's behind the curtain? *J Am Coll Cardiol*. 2003;41:1918–1925.
721. Masuda D, Nohara R, Hirai T, Kataoka K, Chen LG, Hosokawa R, Inubushi M, Tadamura E, Fujita M, Sasayama S. Enhanced external counterpulsation improved myocardial perfusion and coronary flow reserve in patients with chronic stable angina; evaluation by ^{13}N-ammonia positron emission tomography. *Eur Heart J*. 2001;22:1451–1458.
722. Applebaum RM, Kasliwal R, Tunick PA, Konecky N, Katz ES, Trehan N, Kronzon I. Sequential external counterpulsation increases cerebral and renal blood flow. *Am Heart J*. 1997;133:611–615.
723. Alexandrov AW, Ribo M, Wong KS, Sugg RM, Garami Z, Jesurum JT, Montgomery B, Alexandrov AV. Perfusion augmentation in acute stroke using mechanical counter-pulsation: phase IIa: effect of external counterpulsation on middle cerebral artery mean flow velocity in five healthy subjects. *Stroke*. 2008;39:2760–2764.
724. Han JH, Leung TW, Lam WW, Soo YO, Alexandrov AW, Mok V, Leung YF, Lo R, Wong KS. Preliminary findings of external counterpulsation for ischemic stroke patient with large artery occlusive disease. *Stroke*. 2008;39:1340–1343.
725. O'Collins VE, Macleod MR, Donnan GA, Horky LL, van der Worp BH, Howells DW. 1,026 Experimental treatments in acute stroke. *Ann Neurol*. 2006;59:467–477.
726. Kidwell CS, Liebeskind DS, Starkman S, Saver JL. Trends in acute ischemic stroke trials through the 20th century. *Stroke*. 2001;32:1349–1359.
727. Lutsep HL, Clark WM. Neuroprotection in acute ischaemic stroke: current status and future potential. *Drugs R D*. 1999;1:3–8.
728. Wahlgren NG, Ahmed N. Neuroprotection in cerebral ischaemia: facts and fancies: the need for new approaches. *Cerebrovasc Dis*. 2004;17(suppl 1):153–166.
729. Bederson JB, Connolly ES Jr, Batjer HH, Dacey RG, Dion JE, Diringer MN, Duldner JE Jr, Harbaugh RE, Patel AB, Rosenwasser RH.; American Heart Association. Guidelines for the management of aneurysmal subarachnoid hemorrhage: a statement for healthcare professionals

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from a special writing group of the Stroke Council, American Heart Association [published correction appears in *Stroke*. 2009;40:e518]. *Stroke*. 2009;40:994–1025.
730. Bogousslavsky J, Regli F, Zumstein V, Köbberling W. Double-blind study of nimodipine in non-severe stroke. *Eur Neurol*. 1990;30:23–26.
731. The American Nimodipine Study Group. Clinical trial of nimodipine in acute ischemic stroke [published correction appears in *Stroke*. 1992;23:615]. *Stroke*. 1992;23:3–8.
732. Horn J, de Haan RJ, Vermeulen M, Limburg M. Very Early Nimodipine Use in Stroke (VENUS): a randomized, double-blind, placebo-controlled trial. *Stroke*. 2001;32:461–465.
733. Franke CL, Palm R, Dalby M, Schoonderwaldt HC, Hantson L, Eriksson B, Lang-Jenssen L,Smakman J. Flunarizine in stroke treatment (FIST): a double-blind, placebo-controlled trial in Scandinavia and the Netherlands. *Acta Neurol Scand*. 1996;93:56–60.
734. Azcona A, Lataste X. Isradipine in patients with acute ischaemic cerebral infarction: an overview of the ASCLEPIOS Programme. *Drugs*. 1990;40(suppl 2):52–57.
735. Oczkowski WJ, Hachinski VC, Bogousslavsky J, Barnett HJ, Carruthers SG. A double-blind, randomized trial of PY108-068 in acute ischemic cerebral infarction. *Stroke*. 1989;20:604–608.
736. Rosenbaum D, Zabramski J, Frey J, Yatsu F, Marler J, Spetzler R, Grotta J. Early treatment of ischemic stroke with a calcium antagonist. *Stroke*. 1991;22:437–441.
737. Shah QA, Georgiadis A, Suri MF, Rodriguez G, Qureshi AI. Preliminary experience with intra-arterial nicardipine in patients with acute ischemic stroke. *Neurocrit Care*. 2007;7:53–57.
738. Horn J, Limburg M. Calcium antagonists for acute ischemic stroke. *Cochrane Database Syst Rev*. 2000;5:CD001928.
739. Davis SM, Lees KR, Albers GW, Diener HC, Markabi S, Karlsson G, Norris J. Selfotel in acute ischemic stroke: possible neurotoxic effects of an NMDA antagonist. *Stroke*. 2000;31:347–354.
740. Grotta J, Clark W, Coull B, Pettigrew LC, Mackay B, Goldstein LB, Meissner I, Murphy D, LaRue L. Safety and tolerability of the glutamate antagonist CGS 19755 (Selfotel) in patients with acute ischemic stroke: results of a phase IIa randomized trial. *Stroke*. 1995;26:602–605.
741. Morris GF, Bullock R, Marshall SB, Marmarou A, Maas A, Marshall LF. Failure of the competitive *N*-methyl-D-aspartate antagonist Selfotel (CGS 19755) in the treatment of severe head injury: results of two phase III clinical trials: the Selfotel Investigators. *J Neurosurg*. 1999;91:737–743.
742. Albers GW, Goldstein LB, Hall D, Lesko LM; Aptiganel Acute Stroke Investigators. Aptiganel hydrochloride in acute ischemic stroke: a randomized controlled trial. *JAMA*. 2001;286:2673–2682.
743. Dyker AG, Edwards KR, Fayad PB, Hormes JT, Lees KR. Safety and tolerability study of aptiganel hydrochloride in patients with an acute ischemic stroke. *Stroke*. 1999;30:2038–2042.
744. Albers GW, Atkinson RP, Kelley RE, Rosenbaum DM; Dextrorphan Study Group. Safety, tolerability, and pharmacokinetics of the *N*-methyl-D-aspartate antagonist dextrorphan in patients with acute stroke. *Stroke*. 1995;26:254–258.
745. Diener HC, AlKhedr A, Busse O, Hacke W, Zingmark PH, Jonsson N, Basun H. Treatment of acute ischaemic stroke with the low-affinity, use-dependent NMDA antagonist AR-R15896AR: a safety and tolerability study. *J Neurol*. 2002;249:561–568.
746. Lees KR, Asplund K, Carolei A, Davis SM, Diener HC, Kaste M, Orgogozo JM, Whitehead J. Glycine antagonist (gavestinel) in neuroprotection (GAIN International) in patients with acute stroke: a randomised controlled trial: GAIN International Investigators. *Lancet*. 2000;355:1949–1954.
747. Lees KR, Lavelle JF, Cunha L, Diener HC, Sanders EA, Tack P, Wester P; GAIN Phase II European Study Group. Glycine antagonist (GV150526) in acute stroke: a multicentre, double-blind placebo-controlled phase II trial. *Cerebrovasc Dis*. 2001;11:20–29.
748. Sacco RL, DeRosa JT, Haley EC Jr, Levin B, Ordronneau P, Phillips SJ, Rundek T, Snipes RG, Thompson JL; Glycine Antagonist in Neuroprotection Americas Investigators. Glycine antagonist in neuroprotection for patients with acute stroke: GAIN Americas: a randomized controlled trial. *JAMA*. 2001;285:1719–1728.
749. Haley EC Jr, Thompson JL, Levin B, Davis S, Lees KR, Pittman JG, DeRosa JT, Ordronneau P, Brown DL, Sacco RL; GAIN Americas and GAIN International Investigators. Gavestinel does not improve outcome after acute intracerebral hemorrhage: an analysis from the GAIN International and GAIN Americas studies. *Stroke*. 2005;36:1006–1010.
750. Albers GW, Clark WM, Atkinson RP, Madden K, Data JL, Whitehouse MJ. Dose escalation study of the NMDA glycine-site antagonist licostinel in acute ischemic stroke. *Stroke*. 1999;30:508–513.
751. Dyker AG, Lees KR. Safety and tolerability of GV150526 (a glycine site antagonist at the *N*-methyl-D-aspartate receptor) in patients with acute stroke. *Stroke*. 1999;30:986–992.
752. Lees KR. Cerestat and other NMDA antagonists in ischemic stroke. *Neurology*. 1997;49(suppl 4):S66–S69.
753. Muir KW, Lees KR. Excitatory amino acid antagonists for acute stroke. *Cochrane Database Syst Rev*. 2003;(3):CD001244.
754. Grotta J; Combination Therapy Stroke Trial Investigators. Combination Therapy Stroke Trial: recombinant tissue-type plasminogen activator with/without lubeluzole. *Cerebrovasc Dis*. 2001;12:258–263.
755. Diener HC, Cortens M, Ford G, Grotta J, Hacke W, Kaste M, Koudstaal PJ, Wessel T. Lubeluzole in acute ischemic stroke treatment: a double-blind study with an 8-hour inclusion window comparing a 10-mg daily dose of lubeluzole with placebo. *Stroke*. 2000;31:2543–2551.
756. Diener HC, Hacke W, Hennerici M, Rådberg J, Hantson L, De Keyser J; Lubeluzole International Study Group. Lubeluzole in acute ischemic stroke: a double-blind, placebo-controlled phase II trial. *Stroke*. 1996;27:76–81.
757. Gandolfo C, Sandercock P, Conti M. Lubeluzole for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2002;(1):CD001924.
758. Lyden P, Shuaib A, Ng K, Levin K, Atkinson RP, Rajput A, Wechsler L, Ashwood T, Claesson L, Odergren T, Salazar-Grueso E; CLASS-I/H/T Investigators. Clomethiazole Acute Stroke Study in ischemic stroke (CLASS-I): final results. *Stroke*. 2002;33:122–128.
759. Wahlgren NG, Bornhov S, Sharma A, Cederin B, Rosolacci T, Ashwood T, Claesson L; CLASS Study Group. The Clomethiazole Acute Stroke Study (CLASS): efficacy results in 545 patients classified as total anterior circulation syndrome (TACS). *J Stroke Cerebrovasc Dis*. 1999;8:231–239.
760. Wahlgren NG, Díez-Tejedor E, Teitelbaum J, Arboix A, Leys D, Ashwood T, Grossman E. Results in 95 hemorrhagic stroke patients included in CLASS, a controlled trial of clomethiazole versus placebo in acute stroke patients. *Stroke*. 2000;31:82–85.
761. Wahlgren NG, Ranasinha KW, Rosolacci T, Franke CL, van Erven PM, Ashwood T, Claesson L. Clomethiazole Acute Stroke Study (CLASS): results of a randomized, controlled trial of clomethiazole versus placebo in 1360 acute stroke patients. *Stroke*. 1999;30:21–28.
762. Zingmark PH, Ekblom M, Odergren T, Ashwood T, Lyden P, Karlsson MO, Jonsson EN. Population pharmacokinetics of clomethiazole and its effect on the natural course of sedation in acute stroke patients. *Br J Clin Pharmacol*. 2003;56:173–183.
763. Wester P, Strand T, Wahlgren NG, Ashwood T, Osswald G. An open study of clomethiazole in patients with acute cerebral infarction. *Cerebrovasc Dis*. 1998;8:188–190.
764. Lodder J, van Raak L, Hilton A, Hardy E, Kessels A; EGASIS Study Group. Diazepam to improve acute stroke outcome: results of the early GABA-Ergic activation study in stroke trial. a randomized double-blind placebo-controlled trial. *Cerebrovasc Dis*. 2006;21:120–127.
765. Olinger CP, Adams HP Jr, Brott TG, Biller J, Barsan WG, Toffol GJ, Eberle RW, Marler JR. High-dose intravenous naloxone for the treatment of acute ischemic stroke. *Stroke*. 1990;21:721–725.
766. Clark WM, Raps EC, Tong DC, Kelly RE; Cervene Stroke Study Investigators. Cervene (Nalmefene) in acute ischemic stroke: final results of a phase III efficacy study. *Stroke*. 2000;31:1234–1239.
767. Lees KR, Sharma AK, Barer D, Ford GA, Kostulas V, Cheng YF, Odergren T. Tolerability and pharmacokinetics of the nitrone NXY-059 in patients with acute stroke. *Stroke*. 2001;32:675–680.
768. Lees KR, Zivin JA, Ashwood T, Davalos A, Davis SM, Diener HC, Grotta J,Lyden P,Shuaib A, Hårdemark HG, Wasiewski WW; Stroke-Acute Ischemic NXY Treatment (SAINT I) Trial Investigators. NXY-059 for acute ischemic stroke. *N Engl J Med*. 2006;354:588–600.
769. Shuaib A, Lees KR, Lyden P, Grotta J, Davalos A, Davis SM, Diener HC, Ashwood T, Wasiewski WW, Emeribe U; SAINT II Trial Investigators. NXY-059 for the treatment of acute ischemic stroke. *N Engl J Med*. 2007;357:562–571.
770. The RANTTAS Investigators. A randomized trial of tirilazad mesylate in patients with acute stroke (RANTTAS). *Stroke*. 1996;27:1453–1458.
771. Haley EC Jr. High-dose tirilazad for acute stroke (RANTTAS II): RANTTAS II Investigators. *Stroke*. 1998;29:1256–1257.
772. Bath PM, Iddenden R, Bath FJ, Orgogozo JM; Tirilazad International Steering Committee. Tirilazad for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2001;(4):CD002087.

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773. Yamaguchi T, Sano K, Takakura K, Saito I, Shinohara Y, Asano T, Yasuhara H; Ebselen Study Group. Ebselen in acute ischemic stroke: a placebo-controlled, double-blind clinical trial. *Stroke*. 1998;29:12–17.
774. The Internet Stroke Center. Stroke Trials Registry. Ebselen Trial: Phase III. http://www.strokecenter.org/trials/clinicalstudies/298. Accessed January 21, 2013.
775. Edaravone Acute Infarction Study Group. Effect of a novel free radical scavenger, edaravone (MCI-186), on acute brain infarction: randomized, placebo-controlled, double-blind study at multicenters. *Cerebrovasc Dis*. 2003;15:222–229.
776. Piriyawat P, Labiche LA, Burgin WS, Aronowski JA, Grotta JC. Pilot dose-escalation study of caffeine plus ethanol (caffeinol) in acute ischemic stroke. *Stroke*. 2003;34:1242–1245.
777. Lampl Y, Gilad R, Geva D, Eshel Y, Sadeh M. Intravenous administration of magnesium sulfate in acute stroke: a randomized double-blind study. *Clin Neuropharmacol*. 2001;24:11–15.
778. Muir KW, Lees KR. A randomized, double-blind, placebo-controlled pilot trial of intravenous magnesium sulfate in acute stroke. *Stroke*. 1995;26:1183–1188.
779. Muir KW, Lees KR. Dose optimization of intravenous magnesium sulfate after acute stroke. *Stroke*. 1998;29:918–923.
780. Muir KW, Lees KR, Ford I, Davis S; Intravenous Magnesium Efficacy in Stroke (IMAGES) Study Investigators. Magnesium for acute stroke (Intravenous Magnesium Efficacy in Stroke trial): randomised controlled trial. *Lancet*. 2004;363:439–445.
781. Saver JL, Kidwell C, Eckstein M, Starkman S; FAST-MAG Pilot Trial Investigators. Prehospital neuroprotective therapy for acute stroke: results of the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) pilot trial. *Stroke*. 2004;35:e106–e108.
782. Clark WM, Warach SJ, Pettigrew LC, Gammans RE, Sabounjian LA. A randomized dose-response trial of citicoline in acute ischemic stroke patients: Citicoline Stroke Study Group. *Neurology*. 1997;49:671–678.
783. Clark WM, Wechsler LR, Sabounjian LA, Schwiderski UE; Citicoline Stroke Study Group. A phase III randomized efficacy trial of 2000 mg citicoline in acute ischemic stroke patients. *Neurology*. 2001;57:1595–1602.
784. Clark WM, Williams BJ, Selzer KA, Zweifler RM, Sabounjian LA, Gammans RE. A randomized efficacy trial of citicoline in patients with acute ischemic stroke. *Stroke*. 1999;30:2592–2597.
785. Saver JL. Citicoline: update on a promising and widely available agent for neuroprotection and neurorepair. *Rev Neurol Dis*. 2008;5:167–177.
786. Dávalos A, Castillo J, Alvarez-Sabín J, Secades JJ, Mercadal J, López S, Cobo E, Warach S, Sherman D, Clark WM, Lozano R. Oral citicoline in acute ischemic stroke: an individual patient data pooling analysis of clinical trials. *Stroke*. 2002;33:2850–2857.
787. Bolland K, Whitehead J, Cobo E, Secades JJ. Evaluation of a sequential global test of improved recovery following stroke as applied to the ICTUS trial of citicoline. *Pharm Stat*. 2009;8:136–149.
788. Dávalos A, Alvarez-Sabín J, Castillo J, Díez-Tejedor E, Ferro J, Martínez-Vila E, Serena J, Segura T, Cruz VT, Masjuan J, Cobo E, Secades JJ; International Citicoline Trial on acUte Stroke (ICTUS) Trial Investigators. Citicoline in the treatment of acute ischaemic stroke: an international, randomised, multicentre, placebo-controlled study (ICTUS trial). *Lancet*. 2012;380:349–357.
789. Lenzi GL, Grigoletto F, Gent M, Roberts RS, Walker MD, Easton JD, Carolei A, Dorsey FC, Rocca WA, Bruno R. Early treatment of stroke with monosialoganglioside GM-1: efficacy and safety results of the Early Stroke Trial. *Stroke*. 1994;25:1552–1558.
790. Ganglioside GM1 in acute ischemic stroke: the SASS Trial. *Stroke*. 1994;25:1141–1148.
791. Bassi S, Albizzati MG, Sbacchi M, Frattola L, Massarotti M. Double-blind evaluation of monosialoganglioside (GM1) therapy in stroke. *J Neurosci Res*. 1984;12:493–498.
792. Argentino C, Sacchetti ML, Toni D, Savoini G, D'Arcangelo E, Erminio F, Federico F, Milone FF, Gallai V, Gambi D. GM1 ganglioside therapy in acute ischemic stroke: Italian Acute Stroke Study–Hemodilution + Drug. *Stroke*. 1989;20:1143–1149.
793. Candelise L, Ciccone A. Gangliosides for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2001;(4):CD000094.
794. Elkind MS, Sacco RL, MacArthur RB, Fink DJ, Peerschke E, Andrews H, Neils G, Stillman J, Corporan T, Leifer D, Cheung K. The Neuroprotection with Statin Therapy for Acute Recovery Trial (NeuSTART): an adaptive design phase I dose-escalation study of high-dose lovastatin in acute ischemic stroke. *Int J Stroke*. 2008;3:210–218.
795. Blanco M, Nombela F, Castellanos M, Rodriguez-Yáñez M, García-Gil M, Leira R, Lizasoain I, Serena J, Vivancos J, Moro MA, Dávalos A, Castillo J. Statin treatment withdrawal in ischemic stroke: a controlled randomized study. *Neurology*. 2007;69:904–910.
796. Ehrenreich H, Hasselblatt M, Dembowski C, Cepek L, Lewczuk P, Stiefel M, Rustenbeck HH, Breiter N, Jacob S, Knerlich F, Bohn M, Poser W, Rüther E, Kochen M, Gefeller O, Gleiter C, Wessel TC, De Ryck M, Itri L, Prange H, Cerami A, Brines M, Sirén AL. Erythropoietin therapy for acute stroke is both safe and beneficial. *Mol Med*. 2002;8:495–505.
797. Ehrenreich H, Weissenborn K, Prange H, Schneider D, Weimar C, Wartenberg K, Schellinger PD, Bohn M, Becker H, Wegrzyn M, Jähnig P, Herrmann M, Knauth M, Bähr M, Heide W, Wagner A, Schwab S, Reichmann H, Schwendemann G, Dengler R, Kastrup A, Bartels C; EPO Stroke Trial Group. Recombinant human erythropoietin in the treatment of acute ischemic stroke. *Stroke*. 2009;40:e647–e656.
798. Bath PM, Sprigg N. Colony stimulating factors (including erythropoietin, granulocyte colony stimulating factor and analogues) for stroke. *Cochrane Database Syst Rev*. 2007;(2):CD005207.
799. Enlimomab Acute Stroke Trial Investigators. Use of anti-ICAM-1 therapy in ischemic stroke: results of the Enlimomab Acute Stroke Trial. *Neurology*. 2001;57:1428–1434.
800. Krams M, Lees KR, Hacke W, Grieve AP, Orgogozo JM, Ford GA; ASTIN Study Investigators. Acute Stroke Therapy by Inhibition of Neutrophils (ASTIN): an adaptive dose-response study of UK-279,276 in acute ischemic stroke. *Stroke*. 2003;34:2543–2548.
801. Ladurner G, Kalvach P, Moessler H; Cerebrolysin Study Group. Neuroprotective treatment with cerebrolysin in patients with acute stroke: a randomised controlled trial. *J Neural Transm*. 2005;112:415–428.
802. Bogousslavsky J, Victor SJ, Salinas EO, Pallay A, Donnan GA, Fieschi C, Kaste M,Orgogozo JM, Chamorro A, Desmet A; European-Australian Fiblast (Trafermin) in Acute Stroke Group. Fiblast (trafermin) in acute stroke: results of the European-Australian phase II/III safety and efficacy trial. *Cerebrovasc Dis*. 2002;14:239–251.
803. Donnan GA. The 2007 Feinberg lecture: a new road map for neuroprotection. *Stroke*. 2008;39:242.
804. Savitz SI, Fisher M. Future of neuroprotection for acute stroke: in the aftermath of the SAINT trials. *Ann Neurol*. 2007;61:396–402.
805. Hammer MD, Krieger DW. Hypothermia for acute ischemic stroke: not just another neuroprotectant. *Neurologist*. 2003;9:280–289.
806. Linares G, Mayer SA. Hypothermia for the treatment of ischemic and hemorrhagic stroke. *Crit Care Med*. 2009;37(suppl):S243–S249.
807. Nolan JP, Neumar RW, Adrie C, Aibiki M, Berg RA, Böttiger BW, Callaway C, Clark RS, Geocadin RG, Jauch EC, Kern KB, Laurent I, Longstreth WT, Merchant RM, Morley P, Morrison LJ, Nadkarni V, Peberdy MA, Rivers EP, Rodriguez-Nunez A, Sellke FW, Spaulding C, Sunde K, Hoek TV. Post-cardiac arrest syndrome: epidemiology, pathophysiology, treatment, and prognostication: a scientific statement from the International Liaison Committee on Resuscitation; the American Heart Association Emergency Cardiovascular Care Committee; the Council on Cardiovascular Surgery and Anesthesia; the Council on Cardiopulmonary, Perioperative, and Critical Care; the Council on Clinical Cardiology; the Council on Stroke. *Resuscitation*. 2008;79:350–379.
808. Hypothermia After Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest [published correction appears in *N Engl J Med*. 2002;346:1756]. *N Engl J Med*. 2002;346:549–556.
809. Bernard SA, Buist M. Induced hypothermia in critical care medicine: a review. *Crit Care Med*. 2003;31:2041–2051.
810. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002;346:557–563.
811. Todd MM, Hindman BJ, Clarke WR, Torner JC; Intraoperative Hypothermia for Aneurysm Surgery Trial (IHAST) Investigators. Mild intraoperative hypothermia during surgery for intracranial aneurysm. *N Engl J Med*. 2005;352:135–145.
812. Georgiadis D, Schwarz S, Kollmar R, Schwab S. Endovascular cooling for moderate hypothermia in patients with acute stroke: first results of a novel approach. *Stroke*. 2001;32:2550–2553.
813. Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: a case-control study: the Copenhagen Stroke Study. *Stroke*. 2000;31:2251–2256.
815. Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, Mayberg MR, Furlan AJ. Cooling for acute ischemic brain damage (COOL AID): an open pilot study of induced hypothermia in acute ischemic stroke. *Stroke*. 2001;32:1847–1854.

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816. Schwab S, Schwarz S, Aschoff A, Keller E, Hacke W. Moderate hypothermia and brain temperature in patients with severe middle cerebral artery infarction. *Acta Neurochir Suppl*. 1998;71:131–134.
816. Schwab S, Schwarz S, Spranger M, Keller E, Bertram M, Hacke W. Moderate hypothermia in the treatment of patients with severe middle cerebral artery infarction. *Stroke*. 1998;29:2461–2466.
817. Slotboom J, Kiefer C, Brekenfeld C, Ozdoba C, Remonda L, Nedeltchev K, Arnold M, Mattle H, Schroth G. Locally induced hypothermia for treatment of acute ischaemic stroke: a physical feasibility study. *Neuroradiology*. 2004;46:923–934.
818. Wang H, Olivero W, Lanzino G, Elkins W, Rose J, Honings D, Rodde M, Burnham J, Wang D. Rapid and selective cerebral hypothermia achieved using a cooling helmet. *J Neurosurg*. 2004;100:272–277.
819. Georgiadis D, Schwarz S, Aschoff A, Schwab S. Hemicraniectomy and moderate hypothermia in patients with severe ischemic stroke. *Stroke*. 2002;33:1584–1588.
820. Milhaud D, Thouvenot E, Heroum C, Escuret E. Prolonged moderate hypothermia in massive hemispheric infarction: clinical experience. *J Neurosurg Anesthesiol*. 2005;17:49–53.
821. Olsen TS, Weber UJ, Kammersgaard LP. Therapeutic hypothermia for acute stroke. *Lancet Neurol*. 2003;2:410–416.
822. Den Hertog HM, van der Worp HB, Tseng MC, Dippel DW. Cooling therapy for acute stroke. *Cochrane Database Syst Rev*. 2009;(1):CD001247.
823. Meloni BP, Campbell K, Zhu H, Knuckey NW. In search of clinical neuroprotection after brain ischemia: the case for mild hypothermia (35 degrees C) and magnesium. *Stroke*. 2009;40:2236–2240.
824. Martin-Schild S, Hallevi H, Shaltoni H, Barreto AD, Gonzales NR, Aronowski J, Savitz SI, Grotta JC. Combined neuroprotective modalities coupled with thrombolysis in acute ischemic stroke: a pilot study of caffeinol and mild hypothermia. *J Stroke Cerebrovasc Dis*. 2009;18:86–96.
825. Tibbles PM, Edelsberg JS. Hyperbaric-oxygen therapy. *N Engl J Med*. 1996;334:1642–1648.
826. Fukaya E, Hopf HW. HBO and gas embolism. *Neurol Res*. 2007;29:142–145.
827. Bitterman H, Melamed Y. Delayed hyperbaric treatment of cerebral air embolism. *Isr J Med Sci*. 1993;29:22–26.
828. Sukoff MH, Ragatz RE. Hyperbaric oxygenation for the treatment of acute cerebral edema. *Neurosurgery*. 1982;10:29–38.
829. Thom SR. Functional inhibition of leukocyte B2 integrins by hyperbaric oxygen in carbon monoxide-mediated brain injury in rats. *Toxicol Appl Pharmacol*. 1993;123:248–256.
830. Mink RB, Dutka AJ. Hyperbaric oxygen after global cerebral ischemia in rabbits reduces brain vascular permeability and blood flow. *Stroke*. 1995;26:2307–2312.
831. Hills BA. A role for oxygen-induced osmosis in hyperbaric oxygen therapy. *Med Hypotheses*. 1999;52:259–263.
832. Helms AK, Whelan HT, Torbey MT. Hyperbaric oxygen therapy of cerebral ischemia. *Cerebrovasc Dis*. 2005;20:417–426.
833. Zhang JH, Lo T, Mychaskiw G, Colohan A. Mechanisms of hyperbaric oxygen and neuroprotection in stroke. *Pathophysiology*. 2005;12:63–77.
834. Anderson DC, Bottini AG, Jagiella WM, Westphal B, Ford S, Rockswold GL, Loewenson RB. A pilot study of hyperbaric oxygen in the treatment of human stroke. *Stroke*. 1991;22:1137–1142.
835. Nighoghossian N, Trouillas P. Hyperbaric oxygen in the treatment of acute ischemic stroke: an unsettled issue. *J Neurol Sci*. 1997;150:27–31.
836. Nighoghossian N, Trouillas P, Adeleine P, Salord F. Hyperbaric oxygen in the treatment of acute ischemic stroke: a double-blind pilot study. *Stroke*. 1995;26:1369–1372.
837. Rusyniak DE, Kirk MA, May JD, Kao LW, Brizendine EJ, Welch JL, Cordell WH, Alonso RJ; Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study. Hyperbaric oxygen therapy in acute ischemic stroke: results of the Hyperbaric Oxygen in Acute Ischemic Stroke Trial Pilot Study. *Stroke*. 2003;34:571–574.
838. Bennett MH, Wasiak J, Schnabel A, Kranke P, French C. Hyperbaric oxygen therapy for acute ischaemic stroke. *Cochrane Database Syst Rev*. 2005;(3):CD004954.
839. Yip S, Zivin J. Laser therapy in acute stroke treatment. *Int J Stroke*. 2008;3:88–91.
840. Conlan MJ, Rapley JW, Cobb CM. Biostimulation of wound healing by low-energy laser irradiation: a review. *J Clin Periodontol*. 1996;23:492–496.
841. Mochizuki-Oda N, Kataoka Y, Cui Y, Yamada H, Heya M, Awazu K. Effects of near-infra-red laser irradiation on adenosine triphosphate and adenosine diphosphate contents of rat brain tissue. *Neurosci Lett*. 2002;323:207–210.
842. Streeter J, De Taboada L, Oron U. Mechanisms of action of light therapy for stroke and acute myocardial infarction. *Mitochondrion*. 2004;4:569–576.
843. Detaboada L, Ilic S, Leichliter-Martha S, Oron U, Oron A, Streeter J. Transcranial application of low-energy laser irradiation improves neurological deficits in rats following acute stroke. *Lasers Surg Med*. 2006;38:70–73.
844. Lapchak PA, Salgado KF, Chao CH, Zivin JA. Transcranial near-infrared light therapy improves motor function following embolic strokes in rabbits: an extended therapeutic window study using continuous and pulse frequency delivery modes. *Neuroscience*. 2007;148:907–914.
845. Lapchak PA, Wei J, Zivin JA. Transcranial infrared laser therapy improves clinical rating scores after embolic strokes in rabbits. *Stroke*. 2004;35:1985–1988.
846. Oron A, Oron U, Chen J, Eilam A, Zhang C, Sadeh M, Lampl Y, Streeter J, DeTaboada L, Chopp M. Low-level laser therapy applied transcranially to rats after induction of stroke significantly reduces long-term neurological deficits. *Stroke*. 2006;37:2620–2624.
847. Lampl Y, Zivin JA, Fisher M, Lew R, Welin L, Dahlof B, Borenstein P, Andersson B, Perez J, Caparo C, Ilic S, Oron U. Infrared laser therapy for ischemic stroke: a new treatment strategy: results of the NeuroThera Effectiveness and Safety Trial-1 (NEST-1). *Stroke*. 2007;38:1843–1849.
848. NEST-1 and -2 investigators. Transcranial laser therapy for acute ischemic stroke: a pooled analysis of NEST-1 and NEST-2. *Int J Stroke*. 2012 Feb 2.
849. Fairhead JF, Mehta Z, Rothwell PM. Population-based study of delays in carotid imaging and surgery and the risk of recurrent stroke. *Neurology*. 2005;65:371–375.
850. Johansson EP, Wester P. Delay from symptoms to carotid endarterectomy. *J Intern Med*. 2008;263:404–411.
850a. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. *N Engl J Med*. 1991;325:445–453.
851. Sbarigia E, Toni D, Speziale F, Acconcia MC, Fiorani P. Early carotid endarterectomy after ischemic stroke: the results of a prospective multicenter Italian study. *Eur J Vasc Endovasc Surg*. 2006;32:229–235.
852. Ballotta E, Meneghetti G, Da Giau G, Manara R, Saladini M, Baracchini C. Carotid endarterectomy within 2 weeks of minor ischemic stroke: a prospective study. *J Vasc Surg*. 2008;48:595–600.
853. Huber R, Müller BT, Seitz RJ, Siebler M, Mödder U, Sandmann W. Carotid surgery in acute symptomatic patients. *Eur J Vasc Endovasc Surg*. 2003;25:60–67.
854. Welsh S, Mead G, Chant H, Picton A, O'Neill PA, McCollum CN. Early carotid surgery in acute stroke: a multicentre randomised pilot study. *Cerebrovasc Dis*. 2004;18:200–205.
855. Paty PS, Darling RC 3rd, Feustel PJ, Bernardini GL, Mehta M, Ozsvath KJ, Choi D, Roddy SP, Chang BB, Kreienberg PB, Shah DM. Early carotid endarterectomy after acute stroke. *J Vasc Surg*. 2004;39:148–154.
856. Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke*. 2009;40:e564–e572.
857. Sundt TM, Sandok BA, Whisnant JP. Carotid endarterectomy: complications and preoperative assessment of risk. *Mayo Clin Proc*. 1975;50:301–306.
858. Biller J, Adams HP Jr, Boarini D, Godersky JC, Smoker WR, Kongable G. Intraluminal clot of the carotid artery: a clinical-angiographic correlation of nine patients and literature review. *Surg Neurol*. 1986;25:467–477.
859. Heros RC. Carotid endarterectomy in patients with intraluminal thrombus. *Stroke*. 1988;19:667–668.
860. Buchan A, Gates P, Pelz D, Barnett HJ. Intraluminal thrombus in the cerebral circulation: implications for surgical management. *Stroke*. 1988;19:681–687.
861. Kakinuma K, Ezuka I, Takai N, Yamamoto K, Sasaki O. The simple indicator for revascularization of acute middle cerebral artery occlusion using angiogram and ultra-early embolectomy. *Surg Neurol*. 1999;51:332–341.
862. Yoshimoto Y, Kwak S. Superficial temporal artery–middle cerebral artery anastomosis for acute cerebral ischemia: the effect of small augmentation of blood flow. *Acta Neurochir (Wien)*. 1995;137:128–137.
863. Heros RC, Nelson PB. Intracerebral hemorrhage after microsurgical cerebral revascularization. *Neurosurgery*. 1980;6:371–375.
864. Meyer FB. Emergency embolectomy for treatment of acute middle cerebral artery occlusion. *J Neurosurg*. 2007;106:255–256.
865. Meyer FB, Piepgras DG, Sundt TM Jr, Yanagihara T. Emergency embolectomy for acute occlusion of the middle cerebral artery. *J Neurosurg*. 1985;62:639–647.

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866. Harrigan MR, Guterman LR. Endovascular treatment of acute stroke. *Neurosurg Clin N Am*. 2005;16:433–444, xi.
867. Nesbit GM, Luh G, Tien R, Barnwell SL. New and future endovascular treatment strategies for acute ischemic stroke. *J Vasc Interv Radiol*. 2004;15(pt 2):S103–S110.
868. Castillo J. Deteriorating stroke: diagnostic criteria, predictors, mechanisms and treatment. *Cerebrovasc Dis*. 1999;9(suppl 3):1–8.
869. Davalos A, Castillo J. Potential mechanisms of worsening. *Cerebrovasc Dis*. 1997;7 (suppl 5):19–24.
870. Dávalos A, Cendra E, Teruel J, Martinez M, Genís D. Deteriorating ischemic stroke: risk factors and prognosis. *Neurology*. 1990;40:1865–1869.
871. Rödén-Jüllig A. Progressing stroke: epidemiology. *Cerebrovasc Dis*. 1997;7(suppl 5):2–5.
872. Yamamoto H, Bogousslavsky J, van Melle G. Different predictors of neurological worsening in different causes of stroke. *Arch Neurol*. 1998;55:481–486.
873. Johnston KC, Li JY, Lyden PD, Hanson SK, Feasby TE, Adams RJ, Faught RE Jr, Haley EC Jr; RANTTAS Investigators. Medical and neurological complications of ischemic stroke: experience from the RANTTAS trial. *Stroke*. 1998;29:447–453.
874. Langhorne P, Stott DJ, Robertson L, MacDonald J, Jones L, McAlpine C, Dick F, Taylor GS, Murray G. Medical complications after stroke: a multicenter study. *Stroke*. 2000;31:1223–1229.
875. European Stroke Initiative Executive Committee; EUSI Writing Committee; Olsen TS, Langhorne P, Diener HC, Hennerici M, Ferro J, Sivenius J, Wahlgren NG, Bath P. European Stroke Initiative recommendations for stroke management: update 2003. *Cerebrovasc Dis*. 2003;16:311–337.
876. van der Worp HB, Kappelle LJ. Complications of acute ischaemic stroke. *Cerebrovasc Dis*. 1998;8:124–132.
877. Zorowitz RD, Tietjen GE. Medical complications after stroke. *J Stroke Cerebrovasc Dis*. 1999;8:192–196.
878. Summers D, Leonard A, Wentworth D, Saver JL, Simpson J, Spilker JA, Hock N, Miller E, Mitchell PH; American Heart Association Council on Cardiovascular Nursing and the Stroke Council. Comprehensive overview of nursing and interdisciplinary care of the acute ischemic stroke patient: a scientific statement from the American Heart Association [published corrections appear in *Stroke*. 2011;42:e357 and *Stroke*. 2010;41:e563]. *Stroke*. 2009;40:29-1-1–2944.
879. Stroke Unit Trialists Collaboration. How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. *Stroke*. 1997;28:2139–2144.
880. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *BMJ*. 1997;314:1151–1159.
881. Stroke Unit Trialists' Collaboration. Organised inpatient (stroke unit) care for stroke. *Cochrane Database Syst Rev*. 2007;(4):CD000197.
882. Indredavik B. Stroke units: the Norwegian experience. *Cerebrovasc Dis*. 2003;15(suppl 1):19–20.
883. Indredavik B, Bakke F, Slørdahl SA, Rokseth R, Håheim LL. Stroke unit treatment improves long-term quality of life: a randomized controlled trial. *Stroke*. 1998;29:895–899.
884. Indredavik B, Bakke F, Slordahl SA, Rokseth R, Hâheim LL. Stroke unit treatment: 10-year follow-up. *Stroke*. 1999;30:1524–1527.
885. Indredavik B, Bakke F, Solberg R, Rokseth R, Haaheim LL, Holme I. Benefit of a stroke unit: a randomized controlled trial. *Stroke*. 1991;22:1026–1031.
886. Indredavik B, Slørdahl SA, Bakke F, Rokseth R, Håheim LL. Stroke unit treatment: long-term effects. *Stroke*. 1997;28:1861–1866.
887. Koton S, Tanne D, Bornstein NM, Green MS. Triggering risk factors for ischemic stroke: a case-crossover study. *Neurology*. 2004;63:2006–2010.
888. Rønning OM, Guldvog B. Stroke units versus general medical wards, I: twelve- and eighteen-month survival: a randomized, controlled trial. *Stroke*. 1998;29:58–62.
889. Rønning OM, Guldvog B. Stroke unit versus general medical wards, II: neurological deficits and activities of daily living: a quasi-randomized controlled trial. *Stroke*. 1998;29:586–590.
890. Rudd AG, Hoffman A, Irwin P, Lowe D, Pearson MG. Stroke unit care and outcome: results from the 2001 National Sentinel Audit of Stroke (England, Wales, and Northern Ireland). *Stroke*. 2005;36:103–106.
891. Stegmayr B, Asplund K, Hulter-Asberg K, Norrving B, Peltonen M, Terént A, Wester PO. Stroke units in their natural habitat: can results of randomized trials be reproduced in routine clinical practice? Riks-Stroke Collaboration. *Stroke*. 1999;30:709–714.
892. Zhu HF, Newcommon NN, Cooper ME, Green TL, Seal B, Klein G, Weir NU, Coutts SB, Watson T, Barber PA, Demchuk AM, Hill MD; Calgary Stroke Program. Impact of a stroke unit on length of hospital stay and in-hospital case fatality. *Stroke*. 2009;40:18–23.
893. Gilligan AK, Thrift AG, Sturm JW, Dewey HM, Macdonell RA, Donnan GA. Stroke units, tissue plasminogen activator, aspirin and neuroprotection: which stroke intervention could provide the greatest community benefit? *Cerebrovasc Dis*. 2005;20:239–244.
894. California Acute Stroke Pilot Registry Investigators. The impact of standardized stroke orders on adherence to best practices. *Neurology*. 2005;65:360–365.
895. Hinchey JA, Shephard T, Tonn ST, Ruthazer R, Selker HP, Kent DM. Benchmarks and determinants of adherence to stroke performance measures. *Stroke*. 2008;39:1619–1620.
896. Kwan J, Sandercock P. In-hospital care pathways for stroke. *Cochrane Database Syst Rev*. 2004;(4):CD002924.
897. Minkman MM, Schouten LM, Huijsman R, van Splunteren PT. Integrated care for patients with a stroke in the Netherlands: results and experiences from a national Breakthrough Collaborative Improvement project. *Int J Integr Care*. 2005;5:e14.
898. Read SJ, Levy J. Effects of care pathways on stroke care practices at regional hospitals. *Intern Med J*. 2006;36:638–642.
899. Albright KC, Raman R, Ernstrom K, Hallevi H, Martin-Schild S, Meyer BC, Meyer DM, Morales MM, Grotta JC, Lyden PD, Savitz SI.Can comprehensive stroke centers erase the "weekend effect"? *Cerebrovasc Dis*. 2009;27:107–113.
900. Hacke W, Krieger D, Hirschberg M. General principles in the treatment of acute ischemic stroke. *Cerebrovasc Dis*. 1991;1(suppl 1):93–99.
901. Langhorne P. Measures to improve recovery in the acute phase of stroke. *Cerebrovasc Dis*. 1999;9:2–5.
902. Indredavik B, Rohweder G, Naalsund E, Lydersen S. Medical complications in a comprehensive stroke unit and an early supported discharge service. *Stroke*. 2008;39:414–420.
903. Bernhardt J, Dewey H, Thrift A, Collier J, Donnan G. A Very Early Rehabilitation Trial for Stroke (AVERT): phase II safety and feasibility. *Stroke*. 2008;39:390–396.
904. Linn SL, Granat MH, Lees KR. Prevention of shoulder subluxation after stroke with electrical stimulation. *Stroke*. 1999;30:963–968.
905. Zorowitz RD, Hughes MB, Idank D, Ikai T, Johnston MV. Shoulder pain and subluxation after stroke: correlation or coincidence? *Am J Occup Ther*. 1996;50:194–201.
906. Tutuarima JA, van der Meulen JH, de Haan RJ, van Straten A, Limburg M. Risk factors for falls of hospitalized stroke patients. *Stroke*. 1997;28:297–301.
907. Choi-Kwon S, Yang YH, Kim EK, Jeon MY, Kim JS. Nutritional status in acute stroke: undernutrition versus overnutrition in different stroke subtypes. *Acta Neurol Scand*. 1998;98:187–192.
908. Gariballa SE, Parker SG, Taub N, Castleden CM. Influence of nutritional status on clinical outcome after acute stroke. *Am J Clin Nutr*. 1998;68:275–281.
909. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke*. 2005;36:2756–2763.
910. Mann G, Hankey GJ, Cameron D. Swallowing function after stroke: prognosis and prognostic factors at 6 months. *Stroke*. 1999;30:744–748.
911. Daniels SK, Ballo LA, Mahoney MC, Foundas AL. Clinical predictors of dysphagia and aspiration risk: outcome measures in acute stroke patients. *Arch Phys Med Rehabil*. 2000;81:1030–1033.
912. Daniels SK, Brailey K, Foundas AL. Lingual discoordination and dysphagia following acute stroke: analyses of lesion localization. *Dysphagia*. 1999;14:85–92.
913. Elmståhl S, Bülow M, Ekberg O, Petersson M, Tegner H. Treatment of dysphagia improves nutritional conditions in stroke patients. *Dysphagia*. 1999;14:61–66.
914. Addington WR, Stephens RE, Gilliland KA. Assessing the laryngeal cough reflex and the risk of developing pneumonia after stroke: an interhospital comparison. *Stroke*. 1999;30:1203–1207.
915. Turner-Lawrence DE, Peebles M, Price MF, Singh SJ, Asimos AW. A feasibility study of the sensitivity of emergency physician dysphagia screening in acute stroke patients. *Ann Emerg Med*. 2009;54:344–348, 348.e1.
916. Weinhardt J, Hazelett S, Barrett D, Lada R, Enos T, Keleman R. Accuracy of a bedside dysphagia screening: a comparison of registered nurses and speech therapists. *Rehabil Nurs*. 2008;33:247–252.
917. Hinchey JA, Shephard T, Furie K, Smith D, Wang D, Tonn S; Stroke Practice Improvement Network Investigators. Formal dysphagia screening protocols prevent pneumonia. *Stroke*. 2005;36:1972–1976.

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918. Martino R, Silver F, Teasell R, Bayley M, Nicholson G, Streiner DL, Diamant NE. The Toronto Bedside Swallowing Screening Test (TOR-BSST): development and validation of a dysphagia screening tool for patients with stroke. *Stroke*. 2009;40:555–561.
919. Smith Hammond CA, Goldstein LB, Horner RD, Ying J, Gray L, Gonzalez-Rothi L, Bolser DC. Predicting aspiration in patients with ischemic stroke: comparison of clinical signs and aerodynamic measures of voluntary cough. *Chest*. 2009;135:769–777.
920. Warnecke T, Teismann I, Oelenberg S, Hamacher C, Ringelstein EB, Schäbitz WR, Dziewas R. Towards a basic endoscopic evaluation of swallowing in acute stroke: identification of salient findings by the inexperienced examiner. *BMC Med Educ*. 2009;9:13.
921. Warnecke T, Teismann I, Oelenberg S, Hamacher C, Ringelstein EB, Schäbitz WR, Dziewas R. The safety of fiberoptic endoscopic evaluation of swallowing in acute stroke patients. *Stroke*. 2009;40:482–486.
922. O'Mahony D, McIntyre AS. Artificial feeding for elderly patients after stroke. *Age Ageing*. 1995;24:533–535.
923. James A, Kapur K, Hawthorne AB. Long-term outcome of percutaneous endoscopic gastrostomy feeding in patients with dysphagic stroke. *Age Ageing*. 1998;27:671–676.
924. Wijdicks EF, McMahon MM. Percutaneous endoscopic gastrostomy after acute stroke: complications and outcome. *Cerebrovasc Dis*. 1999;9:109–111.
925. Dennis M, Lewis S, Cranswick G, Forbes J; FOOD Trial Collaboration. FOOD: a multicentre randomised trial evaluating feeding policies in patients admitted to hospital with a recent stroke. *Health Technol Assess*. 2006;10:iii-iv, ix-x, 1–120.
926. Dennis MS, Lewis SC, Warlow C; FOOD Trial Collaboration. Effect of timing and method of enteral tube feeding for dysphagic stroke patients (FOOD): a multicentre randomised controlled trial. *Lancet*. 2005;365:764–772.
927. Dennis MS, Lewis SC, Warlow C; FOOD Trial Collaboration. Routine oral nutritional supplementation for stroke patients in hospital (FOOD): a multicentre randomised controlled trial. *Lancet*. 2005;365:755–763.
928. Prosser-Loose EJ, Paterson PG. The FOOD Trial Collaboration: nutritional supplementation strategies and acute stroke outcome. *Nutr Rev*. 2006;64:289–294.
929. Harari D, Norton C, Lockwood L, Swift C. Treatment of constipation and fecal incontinence in stroke patients: randomized controlled trial. *Stroke*. 2004;35:2549–2555.
930. Su Y, Zhang X, Zeng J, Pei Z, Cheung RT, Zhou QP, Ling L, Yu J, Tan J, Zhang Z. New-onset constipation at acute stage after first stroke: incidence, risk factors, and impact on the stroke outcome. *Stroke*. 2009;40:1304–1309.
931. Aslanyan S, Weir CJ, Diener HC, Kaste M, Lees KR; GAIN International Steering Committee and Investigators. Pneumonia and urinary tract infection after acute ischaemic stroke: a tertiary analysis of the GAIN International trial. *Eur J Neurol*. 2004;11:49–53.
932. Field TS, Green TL, Roy K, Pedersen J, Hill MD. Trends in hospital admission for stroke in Calgary. *Can J Neurol Sci*. 2004;31:387–393.
933. Nakagawa T, Sekizawa K, Arai H, Kikuchi R, Manabe K, Sasaki H. High incidence of pneumonia in elderly patients with basal ganglia infarction. *Arch Intern Med*. 1997;157:321–324.
934. Hilker R, Poetter C, Findeisen N, Sobesky J, Jacobs A, Neveling M, Heiss WD. Nosocomial pneumonia after acute stroke: implications for neurological intensive care medicine. *Stroke*. 2003;34:975–981.
935. Upadya A, Thorevska N, Sena KN, Manthous C, Amoateng-Adjepong Y. Predictors and consequences of pneumonia in critically ill patients with stroke. *J Crit Care*. 2004;19:16–22.
936. Chamorro A, Horcajada JP, Obach V, Vargas M, Revilla M, Torres F, Cervera A, Planas AM, Mensa J. The Early Systemic Prophylaxis of Infection After Stroke study: a randomized clinical trial. *Stroke*. 2005;36:1495–1500.
937. Roth EJ, Lovell L, Harvey RL, Heinemann AW, Semik P, Diaz S. Incidence of and risk factors for medical complications during stroke rehabilitation. *Stroke*. 2001;32:523–529.
938. Kong KH, Young S. Incidence and outcome of poststroke urinary retention: a prospective study. *Arch Phys Med Rehabil*. 2000;81:1464–1467.
939. McLean DE. Medical complications experienced by a cohort of stroke survivors during inpatient, tertiary-level stroke rehabilitation. *Arch Phys Med Rehabil*. 2004;85:466–469.
940. Ween JE, Alexander MP, D'Esposito M, Roberts M. Incontinence after stroke in a rehabilitation setting: outcome associations and predictive factors. *Neurology*. 1996;47:659–663.
941. Wijdicks EF, Scott JP. Pulmonary embolism associated with acute stroke. *Mayo Clin Proc*. 1997;72:297–300.
942. Desmukh M, Bisignani M, Landau P, Orchard TJ. Deep vein thrombosis in rehabilitating stroke patients: incidence, risk factors and prophylaxis. *Am J Phys Med Rehabil*. 1991;70:313–316.
943. Kelly J, Rudd A, Lewis R, Hunt BJ. Venous thromboembolism after acute stroke. *Stroke*. 2001;32:262–267.
944. Kelly J, Rudd A, Lewis RR, Coshall C, Moody A, Hunt BJ. Venous thromboembolism after acute ischemic stroke: a prospective study using magnetic resonance direct thrombus imaging. *Stroke*. 2004;35:2320–2325.
945. Sun KK, Wang C, Guli XT, Luo Q. Risk factors and clinical features of deep venous thrombosis: a report of 388 cases [in Chinese]. *Zhonghua Jie He He Hu Xi Za Zhi*. 2004;27:727–730.
946. Warlow C, Ogston D, Douglas AS. Deep venous thrombosis of the legs after strokes: part I: incidence and predisposing factors. *Br Med J*. 1976;1:1178–1181.
947. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis: a meta-analysis of randomized, controlled trials. *Ann Intern Med*. 1999;130:800–809.
948. Hyers TM, Agnelli G, Hull RD, Weg JG, Morris TA, Samama M, Tapson V. Antithrombotic therapy for venous thromboembolic disease. *Chest*. 1998;114(suppl):561S–578S.
949. Sandercock PA, van den Belt AG, Lindley RI, Slattery J. Antithrombotic therapy in acute ischaemic stroke: an overview of the completed randomised trials. *J Neurol Neurosurg Psychiatr*. 1993;56:17–25.
950. Geerts WH, Pineo GF, Heit JA, Bergqvist D, Lassen MR, Colwell CW, Ray JG. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest*. 2004;126(suppl):338S–400S.
951. Kamphuisen PW, Agnelli G, Sebastianelli M. Prevention of venous thromboembolism after acute ischemic stroke. *J Thromb Haemost*. 2005;3:1187–1194.
952. Ridker PM, Goldhaber SZ, Glynn RJ. Low-intensity versus conventional-intensity warfarin for prevention of recurrent venous thromboembolism. *N Engl J Med*. 2003;349:2164–2167.
953. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy, III: reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. *BMJ*. 1994;308:235–246.
954. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;355:1295–1302.
955. Black PM, Crowell RM, Abbott WM. External pneumatic calf compression reduces deep venous thrombosis in patients with ruptured intracranial aneurysms. *Neurosurgery*. 1986;18:25–28.
956. Kamran SI, Downey D, Ruff RL. Pneumatic sequential compression reduces the risk of deep vein thrombosis in stroke patients. *Neurology*. 1998;50:1683–1688.
957. Mazzone C, Chiodo GF, Sandercock P, Miccio M, Salvi R. Physical methods for preventing deep vein thrombosis in stroke. *Cochrane Database Syst Rev*. 2004;(4):CD001922.
958. Britton M, de Faire U, Helmers C, Miah K, Ryding C, Wester PO. Arrhythmias in patients with acute cerebrovascular disease. *Acta Med Scand*. 1979;205:425–428.
959. Jabaudon D, Sztajzel J, Sievert K, Landis T, Sztajzel R. Usefulness of ambulatory 7-day ECG monitoring for the detection of atrial fibrillation and flutter after acute stroke and transient ischemic attack. *Stroke*. 2004;35:1647–1651.
960. Yung D, Kapral MK, Asllani E, Fang J, Lee DS; Investigators of the Registry of the Canadian Stroke Network. Reinitiation of anticoagulation after warfarin-associated intracranial hemorrhage and mortality risk: the Best Practice for Reinitiating Anticoagulation Therapy After Intracranial Bleeding (BRAIN) study. *Can J Cardiol*. 2012;28:33–39.
961. Furie KL, Kasner SE, Adams RJ, Albers GW, Bush RL, Fagan SC, Halperin JL, Johnston SC, Katzan I, Kernan WN, Mitchell PH, Ovbiagele B, Palesch YY, Sacco RL, Schwamm LH, Wassertheil-Smoller S, Turan TN, Wentworth D; American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from

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the American Heart Association/American Stroke Association. *Stroke*. 2011;42:227–276.
962. Miller EL, Murray L, Richards L, Zorowitz RD, Bakas T, Clark P, Billinger SA; American Heart Association Council on Cardiovascular Nursing and the Stroke Council. Comprehensive overview of nursing and interdisciplinary rehabilitation care of the stroke patient: a scientific statement from the American Heart Association. *Stroke*. 2010;41:2402–2448.
963. Maramattom BV, Bahn MM, Wijdicks EF. Which patient fares worse after early deterioration due to swelling from hemispheric stroke? *Neurology*. 2004;63:2142–2145.
964. Heinsius T, Bogousslavsky J, Van Melle G. Large infarcts in the middle cerebral artery territory: etiology and outcome patterns [published correction appears in *Neurology*. 1998;50:1940–1943]. *Neurology*. 1998;50:341–350.
965. Qureshi AI, Suarez JI, Yahia AM, Mohammad Y, Uzun G, Suri MF, Zaidat OO, Ayata C, Ali Z, Wityk RJ. Timing of neurologic deterioration in massive middle cerebral artery infarction: a multicenter review. *Crit Care Med*. 2003;31:272–277.
966. Ropper AH, Shafran B. Brain edema after stroke: clinical syndrome and intracranial pressure. *Arch Neurol*. 1984;41:26–29.
967. Heo JH, Han SW, Lee SK. Free radicals as triggers of brain edema formation after stroke. *Free Radic Biol Med*. 2005;39:51–70.
968. Berrouschot J, Barthel H, von Kummer R, Knapp WH, Hesse S, Schneider D. ^{99m}Technetium-ethyl-cysteinate-dimer single-photon emission CT can predict fatal ischemic brain edema. *Stroke*. 1998;29:2556–2562.
969. Bratton SL, Chestnut RM, Ghajar J, McConnell Hammond FF, Harris OA, Hartl R, Manley GT, Nemecek A, Newell DW, Rosenthal G, Schouten J, Shutter L, Timmons SD, Ullman JS, Videtta W, Wilberger JE, Wright DW. Guidelines for the management of severe traumatic brain injury, VI: indications for intracranial pressure monitoring [published correction appears in *J Neurotrauma*. 2008;25:276–278]. *J Neurotrauma*. 2007;24(suppl 1):S37–S44.
970. Steiner T, Kaste M, Forsting M, Mendelow D, Kwiecinski H, Szikora I, Juvela S, Marchel A, Chapot R, Cognard C, Unterberg A, Hacke W. Recommendations for the management of intracranial haemorrhage, part I: spontaneous intracerebral haemorrhage: the European Stroke Initiative Writing Committee and the Writing Committee for the EUSI Executive Committee [published correction appears in *Cerebrovasc Dis*. 2006;22:461]. *Cerebrovasc Dis*. 2006;22:294–316.
971. Wagner I, Hauer EM, Staykov D, Volbers B, Dörfler A, Schwab S, Bardutzky J. Effects of continuous hypertonic saline infusion on perihemorrhagic edema evolution. *Stroke*. 2011;42:1540–1545.
972. Koenig MA, Bryan M, Lewin JL 3rd, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. *Neurology*. 2008;70:1023–1029.
973. Wijdicks EF, Diringer MN. Middle cerebral artery territory infarction and early brain swelling: progression and effect of age on outcome. *Mayo Clin Proc*. 1998;73:829–836.
974. Thomalla GJ, Kucinski T, Schoder V, Fiehler J, Knab R, Zeumer H, Weiller C, Röther J. Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. *Stroke*. 2003;34:1892–1899.
975. Cho DY, Chen TC, Lee HC. Ultra-early decompressive craniectomy for malignant middle cerebral artery infarction. *Surg Neurol*. 2003;60:227–232.
976. Toni D, Fiorelli M, Gentile M, Bastianello S, Sacchetti ML, Argentino C, Pozzilli C, Fieschi C. Progressing neurological deficit secondary to acute ischemic stroke: a study on predictability, pathogenesis, and prognosis. *Arch Neurol*. 1995;52:670–675.
977. Abe M, Udono H, Tabuchi K, Uchino A, Yoshikai T, Taki K. Analysis of ischemic brain damage in cases of acute subdural hematomas. *Surg Neurol*. 2003;59:464–472.
978. Hussain SI, Cordero-Tumangday C, Goldenberg FD, Wollman R, Frank JI, Rosengart AJ. Brainstem ischemia in acute herniation syndrome. *J Neurol Sci*. 2008;268:190–192.
979. Robertson SC, Lennarson P, Hasan DM, Traynelis VC. Clinical course and surgical management of massive cerebral infarction. *Neurosurgery*. 2004;55:55–61.
980. Schwab S, Steiner T, Aschoff A, Schwarz S, Steiner HH, Jansen O, Hacke W. Early hemicraniectomy in patients with complete middle cerebral artery infarction. *Stroke*. 1998;29:1888–1893.
981. Fandino J, Keller E, Barth A, Landolt H, Yonekawa Y, Seiler RW. Decompressive craniotomy after middle cerebral artery infarction: retrospective analysis of patients treated in three centres in Switzerland. *Swiss Med Wkly*. 2004;134:423–429.
982. Curry WT Jr, Sethi MK, Ogilvy CS, Carter BS. Factors associated with outcome after hemicraniectomy for large middle cerebral artery territory infarction. *Neurosurgery*. 2005;56:681–692.
983. Cockroft KM. Hemicraniectomy after massive hemispheric cerebral infarction: are we ready for a prospective randomised controlled trial? *J Neurol Neurosurg Psychiatr*. 2004;75:179–180.
984. Gupta R, Connolly ES, Mayer S, Elkind MS. Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. *Stroke*. 2004;35:539–543.
985. Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W; DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol*. 2007;6:215–222.
986. Foerch C, Lang JM, Krause J, Raabe A, Sitzer M, Seifert V, Steinmetz H, Kessler KR. Functional impairment, disability, and quality of life outcome after decompressive hemicraniectomy in malignant middle cerebral artery infarction. *J Neurosurg*. 2004;101:248–254.
987. Carter BS, Ogilvy CS, Candia GJ, Rosas HD, Buonanno F. One-year outcome after decompressive surgery for massive nondominant hemispheric infarction. *Neurosurgery*. 1997;40:1168–1175.
988. Hacke W, Schwab S, Horn M, Spranger M, De Georgia M, von Kummer R. "Malignant" middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol*. 1996;53:309–315.
989. Kalia KK, Yonas H. An aggressive approach to massive middle cerebral artery infarction. *Arch Neurol*. 1993;50:1293–1297.
990. Horwitz NH, Ludolph C. Acute obstructive hydrocephalus caused by cerebellar infarction: treatment alternatives. *Surg Neurol*. 1983;20:13–19.
991. Hornig CR, Rust DS, Busse O, Jauss M, Laun A. Space-occupying cerebellar infarction: clinical course and prognosis. *Stroke*. 1994;25:372–374.
992. Chen HJ, Lee TC, Wei CP. Treatment of cerebellar infarction by decompressive suboccipital craniectomy. *Stroke*. 1992;23:957–961.
993. Motto C, Aritzu E, Boccardi E, De Grandi C, Piana A, Candelise L. Reliability of hemorrhagic transformation diagnosis in acute ischemic stroke. *Stroke*. 1997;28:302–306.
994. Motto C, Ciccone A, Aritzu E, Boccardi E, De Grandi C, Piana A, Candelise L. Hemorrhage after an acute ischemic stroke. MAST-I Collaborative Group. *Stroke*. 1999;30:761–764.
995. Leigh R, Zaidat OO, Suri MF, Lynch G, Sundararajan S, Sunshine JL, Tarr R, Selman W, Landis DM, Suarez JI. Predictors of hyperacute clinical worsening in ischemic stroke patients receiving thrombolytic therapy. *Stroke*. 2004;35:1903–1907.
996. Bogousslavsky J, Regli F. Anticoagulant-induced intracerebral bleeding in brain ischemia: evaluation in 200 patients with TIAs, emboli from the heart, and progressing stroke. *Acta Neurol Scand*. 1985;71:464–471.
997. Warach S, Latour LL. Evidence of reperfusion injury, exacerbated by thrombolytic therapy, in human focal brain ischemia using a novel imaging marker of early blood-brain barrier disruption. *Stroke*. 2004;35(suppl 1):2659–2661.
998. French KF, White J, Hoesch RE. Treatment of intracerebral hemorrhage with tranexamic acid after thrombolysis with tissue plasminogen activator. *Neurocrit Care*. 2012;17:107–111.
999. Bayramoglu M, Karatas M, Leblebici B, Cetin N, Sözay S, Turhan N. Hemorrhagic transformation in stroke patients. *Am J Phys Med Rehabil*. 2003;82:48–52.
1000. Koh MG, Phan TG, Atkinson JL, Wijdicks EF. Neuroimaging in deteriorating patients with cerebellar infarcts and mass effect. *Stroke*. 2000;31:2062–2067.
1001. Kilincer C, Asil T, Utku U, Hamamcioglu MK, Turgut N, Hicdonmez T, Simsek O, Ekuklu G, Cobanoglu S. Factors affecting the outcome of decompressive craniectomy for large hemispheric infarctions: a prospective cohort study. *Acta Neurochir (Wien)*. 2005;147:587–594.
1002. Burn J, Dennis M, Bamford J, Sandercock P, Wade D, Warlow C. Epileptic seizures after a first stroke: the Oxfordshire Community Stroke Project. *BMJ*. 1997;315:1582–1587.
1003. Alberti A, Paciaroni M, Caso V, Venti M, Palmerini F, Agnelli G. Early seizures in patients with acute stroke: frequency, predictive factors, and effect on clinical outcome. *Vasc Health Risk Manag*. 2008;4:715–720.
1004. Awada A, Omojola MF, Obeid T. Late epileptic seizures after cerebral infarction. *Acta Neurol Scand*. 1999;99:265–268.
1005. Camilo O, Goldstein LB. Seizures and epilepsy after ischemic stroke. *Stroke*. 2004;35:1769–1775.
1006. Chahine LM, Malik B, Davis M. Palliative care needs of patients with neurologic or neurosurgical conditions. *Eur J Neurol*. 2008;15:1265–1272.

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Guidelines for the Early Management of Patients With Acute Ischemic Stroke: Executive Summary

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

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

Endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons

Edward C. Jauch, MD, MS, FAHA, Chair; Jeffrey L. Saver, MD, FAHA, Vice Chair; Harold P. Adams, Jr, MD, FAHA; Askiel Bruno, MD, MS; J.J. (Buddy) Connors, MD; Bart M. Demaerschalk, MD, MSc; Pooja Khatri, MD, MSc, FAHA; Paul W. McMullan, Jr, MD, FAHA; Adnan I. Qureshi, MD, FAHA; Kenneth Rosenfield, MD, FAHA; Phillip A. Scott, MD, FAHA; Debbie R. Summers, RN, MSN, FAHA; David Z. Wang, DO, FAHA; Max Wintermark, MD; Howard Yonas, MD; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology

This publication, "Guidelines for the Early Management of Patients With Acute Ischemic Stroke," from the American Heart Association/American Stroke Association (AHA/ASA) is an overview of the current evidence and management recommendations for evaluation and treatment of adults with acute ischemic stroke. The intended audiences are prehospital care providers, physicians, allied health professionals, and hospital administrators responsible for the care of acute ischemic stroke patients within the first 48 hours from stroke onset. These guidelines supersede the prior 2007 guidelines and the 2009 update on the extended time window for administration of fibrinolytic agents.

These guidelines take on increased relevance as the global burden of stroke continues to increase, and yet the impact of our focused attention on stroke is encouraging. In 2008, after years of being the third-leading cause of death in the United States, stroke dropped to fourth. In part, this may reflect the results of a commitment made by the AHA/ASA more than a decade ago to reduce stroke, coronary heart disease, and cardiovascular risk by 25% by the year 2010. The reasons for the success were multifactorial and included improved prevention and improved care within the first hours of acute stroke. To continue these encouraging trends, the public and healthcare professionals must remain vigilant and committed to improving overall stroke care. This document addresses opportunities for optimal stroke care in the acute phase of the acute ischemic stroke.

The goal of these guidelines is to further reduce the morbidity and mortality associated with stroke. The guidelines support the overarching concept of stroke systems of care and detail aspects of stroke care from patient recognition; emergency medical services (EMS) activation, transport, and triage; through the initial hours in the emergency department and stroke unit. These guidelines specifically deal with the acute diagnosis, stabilization, and medical and surgical treatments of acute ischemic stroke, as well as early inpatient management, secondary prevention, and complication management. Over the past several years, several new guidelines, policy statements, and recommendations on implementation strategies for EMS within stroke systems of care, imaging in acute ischemic stroke, management of stroke in infants and children, nursing and interdisciplinary care in acute stroke, primary prevention of ischemic stroke, stroke systems of care, and management of transient ischemic attack (TIA) related to acute ischemic stroke have been published by the AHA/ASA. To minimize redundancy, the reader will be referred to these publications where appropriate.

The Stroke Council of the AHA/ASA commissioned the assembled authors, representing the fields of cardiology,

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emergency medicine, neurosurgery, nursing, radiology, rehabilitation, neurocritical care, endovascular neurosurgical radiology, and vascular neurology, from several AHA/ASA councils to completely revise and update the guidelines for the management of acute ischemic stroke. Because of the wide scope of the guidelines, individual members of the panel were assigned as primary and secondary authors for individual sections, then the panel assessed the complete guidelines. If the panel concluded that data supported or did not support the use of a specific intervention, appropriate recommendations were made. In some instances, supporting evidence based on clinical trial research was not available for a specific intervention, but the panel has made a specific recommendation on the basis of pathophysiological reasoning and expert practice experience. In summary, in writing these guidelines, the panel applied the well-described rules of evidence and the formulation of strength of recommendations used by other panels of the AHA/ASA.

This guideline document is a testament to the incredible commitment of AHA/ASA expert volunteers and reviewers to produce a contemporary document that summarizes the current state of science regarding acute stroke care. Adherence to these guidelines will certainly contribute to the decreased morbidity and mortality of patients with acute stroke.

Recommendations

Prehospital Stroke Management

1. 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 (*Class I; Level of Evidence B*). (Unchanged from the previous guideline)
2. Activation of the 911 system by patients or other members of the public is strongly recommended (*Class I; Level of Evidence B*). 911 Dispatchers should make stroke a priority dispatch, and transport times should be minimized. (Unchanged from the previous guideline)
3. Prehospital care providers should use prehospital stroke assessment tools, such as the Los Angeles Prehospital Stroke Screen or Cincinnati Prehospital Stroke Scale *(Class I; Level of Evidence B)*. (Unchanged from the previous guideline)
4. EMS personnel should begin the initial management of stroke in the field, as outlined in Table 4 in the full text of the guideline *(Class I; Level of Evidence B)*. Development of a stroke protocol to be used by EMS personnel is strongly encouraged. (Unchanged from the previous guideline)
5. Patients should be transported rapidly to the closest available certified primary stroke center or comprehensive stroke center or, if no such centers exist, the most appropriate institution that provides emergency stroke care as described in the statement *(Class I; Level of Evidence A)*. In some instances, this may involve air medical transport and hospital bypass. (Revised from the previous guideline)
6. 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 *(Class I; Level of Evidence B)*. (Revised from the previous guideline)

Designation of Stroke Centers and Stroke Care Quality Improvement Process

1. The creation of primary stroke centers is recommended *(Class I; Level of Evidence B)*. The organization of such resources will depend on local resources. The stroke system design of regional acute stroke-ready hospitals and primary stroke centers that provide emergency care and that are closely associated with a comprehensive stroke center, which provides more extensive care, has considerable appeal. (Unchanged from the previous guideline)
2. Certification of stroke centers by an independent external body, such as The Joint Commission or state health department, is recommended *(Class I; Level of Evidence B)*. Additional medical centers should seek such certification. (Revised from the previous guideline)
3. Healthcare institutions should organize a multidisciplinary quality improvement committee to review and monitor stroke care quality benchmarks, indicators, evidence-based practices, and outcomes (*Class I; Level of Evidence B*). 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. (New recommendation)
4. For patients with suspected stroke, EMS should bypass hospitals that do not have resources to treat stroke and go to the closest facility most capable of treating acute stroke (*Class I; Level of Evidence B*). (Unchanged from the previous guideline)
5. For sites without in-house imaging interpretation expertise, teleradiology systems approved by the Food and Drug Administration (or equivalent organization) are recommended for timely review of brain computed tomography (CT) and magnetic resonance imaging (MRI) scans in patients with suspected acute stroke (*Class I; Level of Evidence B*). (New recommendation)
6. 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 *(Class I; Level of Evidence B)*. (New recommendation)
7. The development of comprehensive stroke centers is recommended *(Class I; Level of Evidence C)*. (Unchanged from the previous guideline)
8. Implementation of telestroke consultation in conjunction with stroke education and training for healthcare providers can be useful in increasing the use of intravenous recombinant tissue-type plasminogen activator (rtPA) at community hospitals without access to adequate onsite stroke expertise (*Class IIa; Level of Evidence B*). (New recommendation)
9. The creation of acute stroke-ready hospitals can be useful (*Class IIa; Level of Evidence C*). As with primary stroke centers, the organization of such resources will

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depend on local resources. The stroke system design of regional acute stroke-ready hospitals and primary stroke centers that provide emergency care and that are closely associated with a comprehensive stroke center, which provides more extensive care, has considerable appeal. (New recommendation)

Emergency Evaluation and Diagnosis of Acute Ischemic Stroke

1. An organized protocol for the emergency evaluation of patients with suspected stroke is recommended *(Class I; Level of Evidence B)*. The goal is to complete an evaluation and to begin fibrinolytic treatment within 60 minutes of the patient's arrival in an emergency department. Designation of an acute stroke team that includes physicians, nurses, and laboratory/radiology personnel is encouraged. Patients with stroke should have a careful clinical assessment, including neurological examination. (Unchanged from the previous guideline)
2. The use of a stroke rating scale, preferably the National Institutes of Health Stroke Scale (NIHSS), is recommended *(Class I; Level of Evidence B)*. (Unchanged from the previous guideline)
3. A limited number of hematologic, coagulation, and biochemistry tests are recommended during the initial emergency evaluation, and only the assessment of blood glucose must precede the initiation of intravenous rtPA (Table 8 in the full text of the guideline) *(Class I; Level of Evidence B)*. (Revised from the previous guideline)
4. Baseline electrocardiogram assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA *(Class I; Level of Evidence B)*. (Revised from the previous guideline)
5. Baseline troponin assessment is recommended in patients presenting with acute ischemic stroke but should not delay initiation of intravenous rtPA *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
6. 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 *(Class IIb; Level of Evidence B)*. (Revised from the previous guideline)

Early Diagnosis: Brain and Vascular Imaging

For patients with acute cerebral ischemic symptoms that have not yet resolved:

1. Emergency imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke *(Class I; Level of Evidence A)*. In most instances, non–contrast-enhanced CT will provide the necessary information to make decisions about emergency management. (Unchanged from the previous guideline)
2. Either non–contrast-enhanced CT or MRI is recommended before intravenous rtPA administration to exclude intracerebral hemorrhage (absolute contraindication) and to determine whether CT hypodensity or MRI hyperintensity of ischemia is present *(Class I; Level of Evidence A)*. (Revised from the 2009 imaging scientific statement)
3. Intravenous fibrinolytic therapy is recommended in the setting of early ischemic changes (other than frank hypodensity) on CT, regardless of their extent *(Class I; Level of Evidence A)*. (Revised from the 2009 imaging scientific statement)
4. A noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation of the acute stroke patient if either intra-arterial fibrinolysis or mechanical thrombectomy is contemplated for management but should not delay intravenous rtPA if indicated *(Class I; Level of Evidence A)*. (Revised from the 2009 imaging scientific statement)
5. In intravenous fibrinolysis candidates, the brain imaging study should be interpreted within 45 minutes of patient arrival in the emergency department by a physician with expertise in reading CT and MRI studies of the brain parenchyma *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
6. CT perfusion and MRI perfusion and diffusion imaging, including measures of infarct core and penumbra, may be considered for the selection of patients for acute reperfusion therapy beyond the time windows for intravenous fibrinolysis. These techniques provide additional information that may improve diagnosis, mechanism, and severity of ischemic stroke and allow more informed clinical decision making *(Class IIb; Level of Evidence B)*. (Revised from the 2009 imaging scientific statement)
7. Frank hypodensity on non–contrast-enhanced CT may increase the risk of hemorrhage with fibrinolysis and should be considered in treatment decisions. If frank hypodensity involves more than one third of the middle cerebral artery territory, intravenous rtPA treatment should be withheld *(Class III; Level of Evidence A)*. (Revised from the 2009 imaging scientific statement)

For patients with cerebral ischemic symptoms that have resolved:

1. Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIAs *(Class I; Level of Evidence A)*. (Unchanged from the 2009 TIA scientific statement)
2. Noninvasive imaging by means of CT angiography or magnetic resonance angiography of the intracranial vasculature is recommended to exclude the presence of proximal intracranial stenosis and/or occlusion *(Class I; Level of Evidence A)* and should be obtained when knowledge of intracranial steno-occlusive disease will alter management. Reliable diagnosis of the presence and degree of intracranial stenosis requires the performance of catheter angiography to confirm abnormalities detected with noninvasive testing. (Revised from the 2009 TIA scientific statement)
3. Patients with transient ischemic neurological symptoms should undergo neuroimaging evaluation within 24 hours of symptom onset or as soon as possible in patients with delayed presentations. MRI, including diffusion-weighted imaging, is the preferred brain diagnostic imaging modality. If MRI is not available, head CT should be performed *(Class I; Level of Evidence B)*. (Unchanged from the 2009 TIA scientific statement)

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General Supportive Care and Treatment of Acute Complications

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 *(Class I; Level of Evidence B)*. (Revised from the previous guideline)
2. Patients who have elevated blood pressure and are otherwise eligible for treatment with intravenous rtPA should have their blood pressure carefully lowered (Table 9 in the full text of the guideline) so that their systolic blood pressure is <185 mm Hg and their diastolic blood pressure is <110 mm Hg *(Class I; Level of Evidence B)* 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. (Unchanged from the previous guideline)
3. 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 (*Class I; Level of Evidence C*). (Unchanged from the previous guideline)
4. Supplemental oxygen should be provided to maintain oxygen saturation >94% *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
5. 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 *(Class I; Level of Evidence C)*. (Unchanged from the previous guideline)
6. Until other data become available, consensus exists that the previously described blood pressure recommendations should be followed in patients undergoing other acute interventions to recanalize occluded vessels, including intra-arterial fibrinolysis *(Class I; Level of Evidence C)*. (Unchanged from the previous guideline)
7. In patients with markedly elevated blood pressure who do not receive fibrinolysis, a reasonable goal is to lower blood pressure by 15% during the first 24 hours after onset of stroke. The level of blood pressure that would mandate such treatment is not known, but consensus exists that medications should be withheld unless the systolic blood pressure is >220 mm Hg or the diastolic blood pressure is >120 mm Hg *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
8. Hypovolemia should be corrected with intravenous normal saline, and cardiac arrhythmias that might be reducing cardiac output should be corrected *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
9. Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with acute ischemic stroke *(Class I; Level of Evidence C)*. The goal is to achieve normoglycemia. (Revised from the previous guideline)
10. Evidence from one clinical trial indicates that initiation of antihypertensive therapy within 24 hours of stroke is relatively safe. Restarting antihypertensive medications is reasonable after the first 24 hours for patients who have preexisting hypertension and are neurologically stable unless a specific contraindication to restarting treatment is known *(Class IIa; Level of Evidence B)*. (Revised from the previous guideline)
11. No data are available to guide selection of medications for the lowering of blood pressure in the setting of acute ischemic stroke. The antihypertensive medications and doses included in Table 9 in the full text of the guideline are reasonable choices based on general consensus *(Class IIa; Level of Evidence C)*. (Revised from the previous guideline)
12. Evidence indicates that persistent in-hospital hyperglycemia during the first 24 hours after stroke 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 acute ischemic stroke *(Class IIa; Level of Evidence C)*. (Revised from the previous guideline)
13. The management of arterial hypertension in patients not undergoing reperfusion strategies remains challenging. Data to guide recommendations for treatment are inconclusive or conflicting. Many patients have spontaneous declines in blood pressure during the first 24 hours after onset of stroke. Until more definitive data are available, the benefit of treating arterial hypertension in the setting of acute ischemic stroke is not well established *(Class IIb; Level of Evidence C)*. Patients who have malignant hypertension or other medical indications for aggressive treatment of blood pressure should be treated accordingly. (Revised from the previous guideline)
14. Supplemental oxygen is not recommended in nonhypoxic patients with acute ischemic stroke *(Class III; Level of Evidence B)*. (Unchanged from the previous guideline)

Intravenous Fibrinolysis

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 *(Class I; Level of Evidence A)*. Physicians should review the criteria outlined in Tables 10 and 11 in the full text of the guideline (which are modeled on those used in the National Institute of Neurologic Disorders and Stroke rt-PA Stroke Study) to determine the eligibility of the patient. A recommended regimen for observation and treatment of patients who receive intravenous rtPA is described in Table 12 in the full text of the guideline. (Unchanged from the previous guideline)
2. 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 *(Class I; Level of Evidence A)*. (New recommendation)
3. 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 *(Class I; Level of Evidence B)*. The eligibility criteria for treatment in this time period are similar to

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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 international normalized ratio, those with a baseline NIHSS score >25, those with imaging evidence of ischemic injury involving more than one third of the middle cerebral artery territory, or those with a history of both stroke and diabetes mellitus. (Revised from the 2009 IV rtPA Science Advisory)

4. Intravenous rtPA is reasonable in patients whose blood pressure can be lowered safely (to below 185/110 mm Hg) with antihypertensive agents, with the physician assessing the stability of the blood pressure before starting intravenous rtPA *(Class I; Level of Evidence B)*. (Unchanged from the previous guideline)
5. 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 *(Class I; Level of Evidence B)*. (Revised from the previous guideline)
6. Intravenous rtPA is reasonable in patients with a seizure at the time of onset of stroke if evidence suggests that residual impairments are secondary to stroke and not a postictal phenomenon *(Class IIa; Level of Evidence C)*. (Unchanged from the previous guideline)
7. The effectiveness of sonothrombolysis for treatment of patients with acute stroke is not well established *(Class IIb; Level of Evidence B)*. (New recommendation)
8. The usefulness of intravenous administration of tenecteplase, reteplase, desmoteplase, urokinase, or other fibrinolytic agents and the intravenous administration of ancrod or other defibrinogenating agents is not well established, and they should only be used in the setting of a clinical trial *(Class IIb; Level of Evidence B)*. (Revised from the previous guideline)
9. For patients who can be treated in the time period of 3 to 4.5 hours after stroke but have 1 or more of the following exclusion criteria: (1) patients >80 years old, (2) those taking oral anticoagulants, even with international normalized ratio ≤1.7, (3) those with a baseline NIHSS score >25, or (4) those with a history of both stroke and diabetes mellitus, the effectiveness of intravenous treatment with rtPA is not well-established, *(Class IIb, Level of Evidence C)*, and requires further study.
10. Use of intravenous fibrinolysis in patients with conditions of mild stroke deficits, rapidly improving stroke symptoms, major surgery in the preceding 3 months, and recent myocardial infarction may be considered, and potential increased risk should be weighed against the anticipated benefits *(Class IIb; Level of Evidence C)*. These circumstances require further study. (New recommendation)
11. The intravenous administration of streptokinase for treatment of stroke is not recommended *(Class III; Level of Evidence A)*. (Revised from the previous guideline)
12. The use of intravenous rtPA in patients taking direct thrombin inhibitors or direct factor Xa inhibitors may be harmful and is not recommended unless sensitive laboratory tests such as activated partial thromboplastin time, international normalized ratio, platelet count, and 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 >2 days (assuming normal renal metabolizing function). Similar consideration should be given to patients being considered for intra-arterial rtPA *(Class III; Level of Evidence C)*. (New recommendation) Further study is required.

Endovascular Interventions

1. Patients eligible for intravenous rtPA should receive intravenous rtPA even if intra-arterial treatments are being considered (*Class I; Level of Evidence A*). (Unchanged from the previous guideline)
2. Intra-arterial fibrinolysis is beneficial for treatment of carefully selected patients with major ischemic strokes of <6 hours' duration caused by occlusions of the middle cerebral artery who are not otherwise candidates for intravenous rtPA (*Class I; Level of Evidence B*). The optimal dose of intra-arterial rtPA is not well established, and rtPA does not have Food and Drug Administration approval for intra-arterial use. (Revised from the previous guideline)
3. As with intravenous fibrinolytic therapy, reduced time from symptom onset to reperfusion with intra-arterial therapies is highly correlated with better clinical outcomes, and all efforts must be undertaken to minimize delays to definitive therapy *(Class I; Level of Evidence B)*. (New recommendation)
4. Intra-arterial treatment requires the patient to be at an experienced stroke center with rapid access to cerebral angiography and qualified interventionalists. An emphasis on expeditious assessment and treatment should be made. Facilities are encouraged to define criteria that can be used to credential individuals who can perform intra-arterial revascularization procedures. Outcomes on all patients should be tracked *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
5. When mechanical thrombectomy is pursued, stent retrievers such as Solitaire FR and Trevo are generally preferred to coil retrievers such as Merci *(Class I; Level of Evidence A)*. The relative effectiveness of the Penumbra System versus stent retrievers is not yet characterized. (New recommendation)
6. The Merci, Penumbra System, Solitaire FR, and Trevo thrombectomy devices can be useful in achieving recanalization alone or in combination with pharmacological fibrinolysis in carefully selected patients *(Class IIa; Level of Evidence B)*. Their ability to improve patient outcomes has not yet been established. These devices should continue to be studied in randomized controlled trials to determine the efficacy of such treatments in improving patient outcomes. (Revised from the previous guideline)
7. Intra-arterial fibrinolysis or mechanical thrombectomy is reasonable in patients who have contraindications to the use of intravenous fibrinolysis *(Class IIa; Level of Evidence C)*. (Revised from the previous guideline)
8. Rescue intra-arterial fibrinolysis or mechanical thrombectomy may be reasonable approaches to recanalization in patients with large-artery occlusion who have

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not responded to intravenous fibrinolysis. Additional randomized trial data are needed *(Class IIb; Level of Evidence B)*. (New recommendation)
9. The usefulness of mechanical thrombectomy devices other than the Merci retriever, the Penumbra System, Solitaire FR, and Trevo is not well established *(Class IIb; Level of Evidence C)*. These devices should be used in the setting of clinical trials. (Revised from the previous guideline)
10. The usefulness of emergent intracranial angioplasty and/or stenting is not well established. These procedures should be used in the setting of clinical trials *(Class IIb; Level of Evidence C)*. (New recommendation)
11. The usefulness of emergent angioplasty and/or stenting of the extracranial carotid or vertebral arteries in unselected patients is not well established *(Class IIb; Level of Evidence C)*. Use of these techniques may be considered in certain circumstances, such as in the treatment of acute ischemic stroke resulting from cervical atherosclerosis or dissection *(Class IIb; Level of Evidence C)*. Additional randomized trial data are needed. (New recommendation)

Anticoagulants

1. At present, the usefulness of argatroban or other thrombin inhibitors for treatment of patients with acute ischemic stroke is not well established *(Class IIb; Level of Evidence B)*. These agents should be used in the setting of clinical trials. (New recommendation)
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 (*Class IIb; Level of Evidence B*). (New recommendation)
3. Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke, is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence A)*. (Unchanged from the previous guideline)
4. Urgent anticoagulation for the management of noncerebrovascular conditions is not recommended for patients with moderate-to-severe strokes because of an increased risk of serious intracranial hemorrhagic complications *(Class III; Level of Evidence A)*. (Unchanged from the previous guideline)
5. Initiation of anticoagulant therapy within 24 hours of treatment with intravenous rtPA is not recommended *(Class III; Level of Evidence B)*. (Unchanged from the previous guideline)

Antiplatelet Agents

1. Oral administration of aspirin (initial dose is 325 mg) within 24 to 48 hours after stroke onset is recommended for treatment of most patients *(Class I; Level of Evidence A)*. (Unchanged from the previous guideline)
2. The usefulness of clopidogrel for the treatment of acute ischemic stroke is not well established *(Class IIb; Level of Evidence C)*. Further research testing the usefulness of the emergency administration of clopidogrel in the treatment of patients with acute stroke is required. (Revised from the previous guideline)
3. The efficacy of intravenous tirofiban and eptifibatide is not well established, and these agents should be used only in the setting of clinical trials (*Class IIb; Level of Evidence C*). (New recommendation)
4. Aspirin is not recommended as a substitute for other acute interventions for treatment of stroke, including intravenous rtPA *(Class III; Level of Evidence B)*. (Unchanged from the previous guideline)
5. The administration of other intravenous antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended *(Class III; Level of Evidence B)*. (Revised from the previous guideline) Further research testing the usefulness of emergency administration of these medications as a treatment option in patients with acute ischemic stroke is required.
6. The administration of aspirin (or other antiplatelet agents) as an adjunctive therapy within 24 hours of intravenous fibrinolysis is not recommended *(Class III; Level of Evidence C)*. (Revised from the previous guideline)

Volume Expansion, Vasodilators, and Induced Hypertension

1. In exceptional cases with systemic hypotension producing neurological sequelae, a physician may prescribe vasopressors to improve cerebral blood flow. If drug-induced hypertension is used, close neurological and cardiac monitoring is recommended *(Class I; Level of Evidence C)*. (Revised from the previous guideline)
2. The administration of high-dose albumin is not well established as a treatment for most patients with acute ischemic stroke until further definitive evidence regarding efficacy becomes available *(Class IIb; Level of Evidence B)*. (New recommendation)
3. At present, use of devices to augment cerebral blood flow for the treatment of patients with acute ischemic stroke is not well established *(Class IIb; Level of Evidence B)*. These devices should be used in the setting of clinical trials. (New recommendation)
4. The usefulness of drug-induced hypertension in patients with acute ischemic stroke is not well established *(Class IIb; Level of Evidence B)*. (Revised from the previous guideline) Induced hypertension should be performed in the setting of clinical trials.
5. Hemodilution by volume expansion is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence A)*. (Revised from the previous guideline)
6. The administration of vasodilatory agents, such as pentoxifylline, is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence A)*. (Unchanged from the previous guideline)

Neuroprotective Agents

1. Among patients already taking statins at the time of onset of ischemic stroke, continuation of statin therapy during the acute period is reasonable *(Class IIa; Level of Evidence B)*. (New recommendation)
2. The utility of induced hypothermia for the treatment of patients with ischemic stroke is not well established,

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and further trials are recommended *(Class IIb; Level of Evidence B)*. (Revised from the previous guideline)
3. At present, transcranial near-infrared laser therapy is not well established for the treatment of acute ischemic stroke *(Class IIb; Level of Evidence B)*, and further trials are recommended. (New recommendation)
4. 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 *(Class III; Level of Evidence A)*. (Revised from the previous guideline)
5. Data on the utility of hyperbaric oxygen are inconclusive, and some data imply that the intervention may be harmful. Thus, with the exception of stroke secondary to air embolization, this intervention is not recommended for treatment of patients with acute ischemic stroke *(Class III; Level of Evidence B)*. (Unchanged from the previous guideline)

Surgical Interventions

1. The usefulness of emergent or urgent carotid endarterectomy 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 carotid endarterectomy, in which acute thrombosis of the surgical site is suspected, is not well established *(Class IIb; Level of Evidence B)*. (New recommendation)
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 *(Class IIb; Level of Evidence B)*. (New recommendation)

Admission to the Hospital and General Acute Treatment (After Hospitalization)

1. The use of comprehensive specialized stroke care (stroke units) that incorporates rehabilitation is recommended *(Class I; Level of Evidence A)*. (Unchanged from the previous guideline)
2. Patients with suspected pneumonia or urinary tract infections should be treated with appropriate antibiotics *(Class I; Level of Evidence A)*. (Revised from the previous guideline)
3. Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent deep vein thrombosis *(Class I; Level of Evidence A)*. (Unchanged from the previous guideline)
4. The use of standardized stroke care order sets is recommended to improve general management *(Class I; Level of Evidence B)*. (Unchanged from the previous guideline)
5. Assessment of swallowing before the patient begins eating, drinking, or receiving oral medications is recommended (*Class I; Level of Evidence B*). (Unchanged from the previous guideline)
6. Patients who cannot take solid food and liquids orally should receive nasogastric, nasoduodenal, or percutaneous endoscopic gastrostomy tube feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing *(Class I; Level of Evidence B)*. (Revised from the previous guideline)
7. Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended *(Class I; Level of Evidence C)*. (Unchanged from the previous guideline)
8. Treatment of concomitant medical diseases is recommended *(Class I; Level of Evidence C*). (Unchanged from the previous guideline)
9. Early institution of interventions to prevent recurrent stroke is recommended *(Class I; Level of Evidence C)*. (Unchanged from the previous guideline)
10. The use of aspirin is reasonable for treatment of patients who cannot receive anticoagulants for prophylaxis of deep vein thrombosis *(Class IIa; Level of Evidence A)*. (Revised from the previous guideline)
11. In selecting between nasogastric and percutaneous endoscopic gastrostomy tube routes of feeding in patients who cannot take solid food or liquids orally, it is reasonable to prefer nasogastric tube feeding until 2 to 3 weeks after stroke onset *(Class IIa; Level of Evidence B)*. (Revised from the previous guideline)
12. The use of intermittent external compression devices is reasonable for treatment of patients who cannot receive anticoagulants *(Class IIa; Level of Evidence B)*. (Revised from the previous guideline)
13. Routine use of nutritional supplements has not been shown to be beneficial *(Class III; Level of Evidence B)*. (Revised from the previous guideline)
14. Routine use of prophylactic antibiotics has not been shown to be beneficial *(Class III; Level of Evidence B)*. (Revised from the previous guideline)
15. Routine placement of indwelling bladder catheters is not recommended because of the associated risk of catheter-associated urinary tract infections *(Class III; Level of Evidence C)*. (Unchanged from the previous guideline)

Treatment of Acute Neurological Complications

1. Patients with major infarctions are at high risk for complicating brain edema and increased intracranial pressure. 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 *(Class I; Level of Evidence A)*. Early transfer of patients at risk for malignant brain edema to an institution with neurosurgical expertise should be considered. (Revised from the previous guideline)
2. Decompressive surgical evacuation of a space-occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression *(Class I; Level of Evidence B)*. (Revised from the previous guideline)
3. Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially lifesaving (*Class I; Level of Evidence B*). Advanced patient age and patient/family valuations of achievable outcome states may affect decisions regarding surgery. (Revised from the previous guideline)

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4. 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 (*Class I; Level of Evidence B*). (Unchanged from the previous guideline)
5. Placement of a ventricular drain is useful in patients with acute hydrocephalus secondary to ischemic stroke (*Class I; Level of Evidence C*). (Revised from the previous guideline)
6. Although aggressive medical measures have been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, the usefulness of these measures is not well established (*Class IIb; Level of Evidence C*). (Revised from the previous guideline)
7. Because of lack of evidence of efficacy and the potential to increase the risk of infectious complications, corticosteroids (in conventional or large doses) are not recommended for treatment of cerebral edema and increased intracranial pressure complicating ischemic stroke (*Class III; Level of Evidence A*). (Unchanged from the previous guideline)
8. Prophylactic use of anticonvulsants is not recommended (*Class III; Level of Evidence C*). (Unchanged from the previous guideline)

References

References are available in the full text of this guideline: http://stroke.ahajournals.org/lookup/doi/10.1161/STR.0b013e318284056a.

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