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No.: 691431- I

**COURT OF APPEALS OF THE STATE OF WASHINGTON
DIVISION I**

**BRUCE PLEASANT AND KIMBERLY PLEASANT,
a marital community,**

Appellants,

vs.

REGENCE BLUESHIELD, a Washington Corporation,

Respondent.

**REPLY BRIEF OF APPELLANTS
BRUCE AND KIMBERLY PLEASANT**

Rick J Wathen, WSBA #25539
Kimberly Larsen Rider, #42736
Attorneys for Appellants

Cole I Wathen I Leid I Hall
1000 Second Avenue, Ste 1300
Seattle, WA 98104
206.622.0494
206.587.2476

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I. RESPONDENT'S STATEMENT OF FACTS

A. Regence Mischaracterizes Bruce Pleasant's Medical History.

1. Inpatient Hospital Admission to Swedish Medical Center.

- Regence spends a great deal of time outlining the Pleasants' discussion of care and treatment options in light of the \$4,000.00, inpatient rehabilitation coverage limit. *Respondent's Brief*, p.6-7 (citing CP 232-35, 240, 245 and 247). Any discussion revolving around care and treatment options is irrelevant as to whether or not Regence wrongfully denied benefits to the Pleasants by limiting coverage under the inpatient rehabilitative services.

2. Admission to Skilled Nursing Facility.

- Mr. Pleasant was discharged and admitted into a nursing facility following the initial emergency room treatment. CP 12:5-6. While at the nursing facility, Mr. Pleasant's treatment plan included specified care designed to increase his strength so that he could continue receiving treatment for his stroke injuries. CP 12:6-7.

- Mr. Pleasant received treatment and prescribed medications at a “hospital” as defined by the policy of insurance. CP: 96-11 and 141:7-16. For example, Mr. Pleasant received medications called Enoxaparin and Latanoprost. CP 102 and 97, respectively. Additionally, Mr. Pleasant received numerous blood draws, laboratory tests, etc., for the purposes of monitoring his blood and recovery from the stroke. CP 106. He also received Visipaque injections associated with x-ray imaging conducted. CP 103 and 115-116. Mr. Pleasant also received a CT scan which was independent of his rehabilitative care. CP 106-108. Additionally, Mr. Pleasant received a mechanical embolectomy in treatment for his stroke in order to restore the flow of blood to Mr. Pleasant’s brain. CP 125-126, ¶2-5; see also, CP 605:18.
- The treatment was medically necessary following Mr. Pleasant’s March 2010 stroke as determined by his treating medical providers:

Mr. Pleasant received treatment while at the rehabilitation center. He received certain treatment which was medically necessary regardless of the setting in which he received the treatment. Examples include medication,

laboratory work, and a CT scan. Additionally, Mr. Pleasant underwent a procedure to remove and replace a blood filter. Again, these are treatments Mr. Pleasant received related to his stroke. ***The procedures, lab work and medicines were needed regardless of Mr. Pleasant's setting. In other words, Mr. Pleasant would have needed these treatments whether or not he had been admitted for in-patient rehabilitative services.***

CP 125-126: ¶5 (emphasis added).

- Regence has taken the position that Mr. Pleasant's geographic location within the hospital dictates whether or not he is entitled to insurance coverage. CP 12:13-15 and CP 130:1-6. As such, Regence denied the expenses associated with medically necessary "procedures, lab work and medicines," despite the fact that Regence paid for these same types of medications and procedures during Mr. Pleasant's initial hospitalization. CP 95-111.

3. **Inpatient Rehabilitation Admission to Swedish Medical Center.**

- Regence contends that Swedish Rehabilitation Unit is a separate facility. *Respondent's Brief*, p.7-8 (citing CP 12,248-53 and 257). Regence falsely asserts that the Pleasants' contention that Bruce Pleasant was "readmitted

to a different floor of the same hospital that discharged him 30 days earlier is not accurate." *Respondent's Brief*, p. 8, footnote 6. These are red herrings. The Swedish Medical Center Cherry Hill Campus (Home of Swedish Heart & Vascular Institute and Swedish Neuroscience Institute") operates under a singular hospital license issued by the State of Washington. CP 502. It is the same facility operating under one license.

- Mr. Pleasant was admitted to the second floor of the Swedish Cherry Hill ICU directly following his stroke. CP 232; see also, Appendix G.¹ Following his stay at the nursing facility, Mr. Pleasant was then re-admitted to the fifth floor of the Swedish Medical Center Cherry Hill Campus. CP 12:7-9; see also, Appx. G.
- Regence citation to the pre-authorization of Swedish Cherry Hill is irrelevant and again illustrates Regence's attempt to misdirect the Court. *Respondent's Brief*, 8-9. The Pleasants are not claiming that the rehabilitative care received by Mr. Pleasant is not subject to the \$4,000.00, coverage limits.

¹ Appellants attach a floor plan of the Swedish Medical Center Cherry Hill Campus as Appendix G hereto.

Rather, the Pleasants are claiming that coverage is available for all ***medically necessary non-rehabilitative care*** (*i.e.*, medication expenses, x-ray expenses, lab work expenses, changing of his heart filter, etc.) that Mr. Pleasant received at the Swedish Medical Center, regardless of where he was located within the hospital.

- Mr. Pleasant received treatment and prescribed medications at a “hospital” as defined by the policy of insurance. CP: 96-11 and 141:7-16. Nevertheless, Regence has denied the expenses associated with these medically necessary procedures, lab work and medicines. CP 95-111.

B. Regence’s Coverage Determinations

1. Mechanical Embolectomy Procedure.

- Regence classifies a mechanical embolectomy procedure as an investigational procedure. *Respondent’s Brief*, p.10 (citing CP 789-96). Regence’s denial of the mechanical embolectomy procedure was based, in part, upon a medical “policy.”² The “policy” is not the insurance policy, but rather an internal procedural policy that is not part of the insurance contract. The subject medical “policy” was drafted by a

² The Medical Policy was identified following the close of discovery.

medical policy clinician whom Regence identifies as “the person who performs the literature review and gathers materials and does initial critical appraisal of the evidence.” CP 1549:2-5.³

Regence notes that its “policy” relies in part on a recommendation by the American Heart Association. *Respondent’s Brief*, p.20 (citing CP 789-96); see also, Appendix H.⁴ This is inadmissible hearsay. Dr. Richard Rainey admitted that he was not a qualified expert regarding mechanical embolectomies. CP 1548 at 10:8-10 and 12:8-17. Therefore he cannot rely on the medical “policy.”

Again, this medical “policy” is not part of the policy of insurance. **Moreover, the medical “policy” was not produced until after the discovery cut-off.** CP 1198:13-14; CP 1207.

³ A medical policy clinician is not a doctor but “either a nurse or has some other advanced training, like an MPH.” CP 1549:5-13. It is the medical policy clinician who conducts the research to draft an initial draft of the medical policy that is then reviewed by doctors. *Id.*

⁴ Regence has never produced a copy of the article to which the medical “policy” cites. The Pleasants attach a copy of the article, “Guidelines for the Early Management of Adults with Ischemic Stroke,” *Circulation* 2007; 115 ((20): e478-534, hereto as Appendix H. Moreover, Regence misrepresents the American Heart Association’s recommendations regarding the “estimate of certainty of treatment effect.” *Respondent’s Brief* at 20. The article in fact notes that the benefit of a mechanical embolectomy is greater than or equal to the risk and that the procedure may be considered. See, Appx., H at e481.

- Regence's assertion that the mechanical embolectomy procedure did not improve Mr. Pleasant's condition is incorrect. *Respondent's Brief*, p. 10, footnote 12.

Result Impression

Intra-arterial thrombectomy and thrombolysis as described with no significant change in the right middle cerebral occlusion. There has been some improvement in the collaterals from the right anterior cerebral to the distal middle cerebral territory. There were no complications.

CP 1194.

Regence asserts that its reference to a URL constitutes sufficient notice of denial. *Respondent's Brief*, p. 11.⁵ A citation to a URL is not sufficient. Moreover, Despite Plaintiffs' specific requests for discovery regarding the mechanical embolectomy, Regence failed to provide any evidence justifying its conclusion that the procedure is "investigational." CP 1204: ¶¶9. Regence relied on its medical "policy" regarding mechanical embolectomies to justify its denial of Mr. Pleasant's claim. CP 699:15-20 and 7011:1-2. However, the medical "policy" relied upon by

⁵ Regence's citation to the Explanation of Benefits ("EOB") supposedly sent to Mr. Pleasant is actually a citation to a payment voucher and not the purported document. CP 1192. Regence later references the same incorrect citation in support of its argument. *Respondent's Brief*, 29.

Regence is not part of the contract of insurance and was produced after the discovery cut-off. CP 1198:13-14; CP 1207. The trial court erred in accepting the medical “policy” as evidence. Appx. B.

- Regence failed to identify any witness who will testify concerning the alleged investigational nature of the mechanical embolectomy procedure. The witness who was offered, Dr. Rainey, is not qualified to opine as to Regence's determination of mechanical embolectomy's investigational status to a reasonable degree of medical certainty because he has no background or training in mechanical embolectomies.⁶ CP 1548 at 10:8-10. In fact, Dr. Rainey specifically testified that he could not render an opinion as to whether mechanical embolectomies are an effective treatment for the treatment of strokes as it was outside the scope of his expertise. CP 1548 at 12:8-17. In short, there was a complete absence of evidence on the part of Regence concerning its denial of Mr. Pleasant's mechanical embolectomy procedure.

2. Inpatient Rehabilitation Admission.

- Regence contends that Bruce Pleasant's May 2010 admission to Swedish qualified as an Inpatient Rehabilitation

⁶ Moreover, Dr. Rainey is not qualified as an expert witness. CP 1523.

Admission under the Policy thus limiting any and all treatment received there to the \$4,000.00, cap.

Respondent's Brief, p.12. However, as established by the evidence, during his May 2010 stay at Swedish Medical Center, a singularly licensed hospital, Mr. Pleasant received medically necessary care which falls outside the scope of the referenced definition of "Inpatient Rehabilitation Admission."

- Mr. Pleasant received treatment and prescribed medications at a "hospital" as defined by the policy of insurance. CP: 96-11 and 141:7-16.

C. Trial Court's Procedural History

- Regence's contention the trial court permitted the Pleasants to assert a new claim for the denial of the mechanical embolectomy procedure is meritless. *Respondent's Brief*, p.15. Washington is a notice pleading state. The Pleasants asserted in their complaint that Regence wrongfully denied benefits by limiting coverage under the inpatient rehabilitative services provision, despite the fact that Bruce Pleasant received treatment for other non-rehabilitative services. CP 2-3,1735 and 1881-1882.

II. ARGUMENT

There are three issues before the appellate court: (1) whether Regence failed to present evidence necessary to support its denial of the mechanical embolectomy procedure under *Celotex*; (2) whether Regence wrongfully denied benefits to the Pleasants by limiting coverage under the inpatient rehabilitative services provision despite the fact that Mr. Pleasant received treatment for other non-rehabilitative services; and (3) whether Regence violated the Washington Consumer Protection Act.

A. Standard of Review.

Regence fails to address the applicable legal standard regarding the burden of proof with respect to the insurance contract. *Respondent's Brief*, 16.⁷ It is well established that the burden is on an insurer to prove that a claim is not covered because of an exclusionary provision in the policy. *Brown v. Snohomish County Physicians, Corp.*, 120 Wn.2d 747, 758-59, 845 P.2d 334 (1993), citing *Burrier v. Mutual Life Ins. Co. of New York*, 63 Wn.2d 266, 270, 387 P.2d 58 (1963); *Pemco v. Rash*, 48 Wn.App. 701, 703, 740 P.2d 370 (1987).

⁷ Regence's analysis sets forth that "a plaintiff seeking coverage has the burden to show that the claimed loss falls within the terms of the insurance contract." *Waite v. Aetna Cas. & Syr. Co.*, 77 Wn.2d 850, 853, 467 P.2d 847 (1970). However, Regence fails to acknowledge that the burden shifted once Mr. Pleasant established that the treatment was reasonable and medically necessary. The burden then shifted to Regence to establish the exclusions.

Language in an insurance policy is ambiguous if it is fairly/reasonably susceptible to more than one common sense interpretation; such an ambiguity must be liberally construed in favor of benefiting the insured. *Mutual of Enumclaw v. Cross*, 103 Wn.App. 52, 10 P.3d 440 (2000); *Robinson v. PEMCO Insurance*, 71 Wn.App. 746, 862 P.2d 614 (1993). In Washington State, any ambiguity in the health insurance policy must be read in favor of coverage. *McCarty v. King County Medical Services Corp.* 175 P.2d 653, 26 Wn.2d 660 (1946). Exclusionary clauses are to be construed narrowly. *Cook v. Evanson*, 920 P.2d 1223 83 Wn.App.149 (1996); *McMahan and Baker Inc. v. Continental Casualty Company*, 843 P.2d 1133 68 Wn.App. 573.

Exclusionary clauses are narrowly construed for the purpose of providing maximum coverage for an insured person. *George v. Farmers Insurance Company of Washington*, 23 P.3d 552, 106 Wn.App. 430 (2001); see also, *County Mutual Insurance Company v. McCauley*, 974 P.2d 1288 95 Wn.App. 305. As a result, they are strictly construed against the insurer and will not be extended beyond the clear and unequivocal meaning. *Firemans's Fund Ins. Co. v. Puget Sound Escrow Closers, Inc.*, 96 Wn.App. 227, 979 P.2d 872 (1999); *Brown v. Snohomish County Physicians Corp.*, 822 P.2d 336, 63 Wn.App. 788 (1992), reversed on other grounds; 120 Wn.2d 747.

B. Regence Failed to Prove the Exclusion Upon Which Regence Based Its Denial as Required Under *Celotex*.

Summary judgment should be granted if a party “fails to make a showing sufficient to establish the existence of an element essential to that party’s case, and on which that party will bear the burden of proof at trial.” See, *Celotex Corp. v. Catrett*, 477 U.S. 317, 322, 91 L.Ed. 2d 265, 106 S.Ct. 2548 (1986). “In such a situation, there can be ‘no genuine issue as to any material fact,’ since a complete failure of proof concerning an essential element of the nonmoving party’s case necessarily renders all other facts immaterial.” *Celotex, supra*, at 322-23.

Under *Celotex*, Regence bears the burden of proof in establishing the investigational status of the mechanical embolectomy procedure. To meet the *Celotex* standard, Regence was required to present specific evidence establishing the investigational status of the mechanical embolectomy procedure. Regence failed to do so. Specifically, Regence failed to provide any documentation in response to discovery concerning the mechanical embolectomy. Moreover, the medical “policy” on which Regence relied was not produced in discovery. In fact, the medical “policy” was not produced until after the discovery cut-off. As a

result, the trial court erred by not finding coverage as a matter of law.

Additionally, Regence failed to identify any qualified witnesses to testify regarding the alleged investigational nature of the mechanical embolectomy procedure. Regence's reliance on the declaration of Dr. Richard Rainey is misplaced because the declaration failed to: (1) articulate what Regence **actually** investigated, evaluated and/or assessed under each prong of the criteria within the context of a mechanical embolectomy; (2) failed to address whether Regence properly conveyed the basis of its denial to the Pleasants in accordance with the policy and WAC; and (3) failed to establish that Regence's determination that the investigational classification of the subject procedure is based upon **a reasonable degree of medical certainty**.

Dr. Rainey admits he was not qualified to opine as to Regence's classification of the subject procedure as investigational, to a reasonable degree of medical certainty, because he has no background or training in mechanical embolectomies. CP 1548 at 10:8-10. In fact, Dr. Rainey specifically testified that he could not render an opinion as to whether mechanical embolectomies are an effective treatment for the treatment of strokes as it was outside the

scope of his expertise. CP 1548 at 12:8-17. Regence's own reviewing neurosurgeon (who, unlike Dr. Rainey, is qualified to opine as to such) vehemently opposes Regence's classification noting that such a determination is "**unwise, inappropriate, indefensible.**" CP 1564. At the very least, the claims file evidences an internal dispute regarding the investigational status of the mechanical embolectomy procedure sufficient to overcome summary judgment.

Regence's attempt to distance itself from the opinions of Dr. Collada by stating that "Dr. Collada is not and never has been an employee or agent of Regence" is without merit. *Respondent's Brief*, p. 11, footnote 13 (citing CP 1552 (28:18-24)). Regence sent out requests **asking** doctors, including Dr. Collada, for their opinions for its own purposes of evaluation. After ascertaining medical opinions which clearly evoke at least a question as to the procedure's investigational status, Regence cannot make a carte blanche determination to classify a treatment as investigational, a determination which Regence knew to be "unwise, inappropriate and indefensible." To allow Regence to make such a unilateral determination, which becomes binding upon its insureds, is not supported.

In short, there was a complete failure of evidence on the part of Regence concerning its denial of Mr. Pleasant's mechanical embolectomy procedure. As a result, the trial court erred by not finding coverage as a matter of law.

1. **Regence's reliance on *Parsons* is misplaced.**

Regence cites to the unpublished decision of *Parsons v. Sisters of Charity of Leavenworth Health Systems, Inc.*, 2012 WL 3026395; 2012 U.S. App. LEXIS 15375 (9th Cir. July 25, 2012) (appeal from *Parsons v. Sisters of Charity of Leavenworth Health Sys.*, 832 F. Supp. 2d 1222, 2011 U.S. Dist. LEXIS 57958 (D. Mont., 2011)). *Respondent's Brief*, p. 17; see also, Appendix I.⁸ In *Parsons*, the health care insurance policy and benefit plan declined to cover the plaintiff for participating in a ***clinical trial*** for autologous bone marrow transplant (ABMT) because the trial was deemed "experimental and investigational," and therefore not covered by the plan. *Parsons* at *2. The procedure had not received FDA final approval. *Id.*, *3.

In stark contrast, the mechanical embolectomy procedure at issue in this case has received final FDA approval. CP 1532-1536. As a result, the mechanical embolectomy procedure has already

⁸ A courtesy copy of *Parsons v. Sisters of Charity of Leavenworth Health Systems, Inc.*, has been attached hereto as Appendix I.

been through the rigors of FDA approval. Regence's reliance on *Parsons* is entirely misplaced.

C. The Pleasants are Entitled to Coverage for All Reasonable and Necessary Medical Treatment.

Pursuant to the plain language of the Policy, there is no question that the Swedish Medical Center is a hospital. Moreover, Mr. Pleasant is entitled to coverage for all services provided at the hospital unless specifically excluded elsewhere. Because there is no dispute that the treatment Mr. Pleasant received was medically necessary and reasonable, all treatment is therefore presumed to be covered under the Policy – unless specifically excluded. As articulated above, Regence bears the burden of proving any exclusionary clauses relied upon.

1. The “In-Patient” limit is not applicable for other treatment.

The basic exclusionary clause relied upon by Regence only limits coverage for rehabilitative care which is *specifically* for the purpose of receiving speech, physical, or occupational therapy. Thus, the exclusionary clause only applies if a patient is admitted specifically for rehabilitative services and only limits coverage to specific rehabilitative care, not other non-rehabilitative care services. However, section 8.7.1, of the Policy provides coverage when the insured is confined in a hospital. In this particular case, Mr. Pleasant received care at the Swedish Medical Center which by

any definition is a hospital. Coverage is available for all non-rehabilitative care.

2. Regence denied coverage for medications for which no exclusionary clause or language exists.

Regence has denied coverage for certain items which are covered under the policy of insurance for which there is no exclusionary or limiting language. For example, Regence has denied all coverage for all medications received by Mr. Pleasant during his second hospitalization. However, paragraph 6.1.11 of the Policy specifically provides coverage for drugs for the in-patient unless otherwise excluded under the contract.

The policy contains no pertinent exclusionary language. Regence has never articulated the exclusionary language which precludes Mr. Pleasant from receiving coverage for medications while hospitalized.

Pursuant to the plain language of the policy, Mr. Pleasant is entitled to coverage for all in patient benefits. At section 8.7.1, the Policy specifically provides benefits for the services and supplies provided by the hospital. Unquestionably, there were services and supplies provided by the hospital for which Mr. Pleasant is entitled to coverage. The same holds true for virtually every other expense incurred by Mr. Pleasant. As such, the trial court erred in denying the Pleasants summary judgment on the issue of coverage.

3. **Mr. Pleasant's geographic location within Swedish Hospital does not dictate coverage.**

Regence has taken the untenable position that the mere fact that Mr. Pleasant was on a different floor of the exact same hospital that the policy somehow excludes coverage for procedures which are clearly not rehabilitative services.

However, Dr. Clawson testified that Mr. Pleasant "received certain treatment which was **medically necessary** regardless of the setting in which he received the treatment." CP 125, ¶5 (emphasis added). Such treatments are covered under the Regence Policy.

In advancing its argument, Regence requests this Court to **infer** policy language by concluding that **ANY** medications, x-rays, surgical procedures, tests, etc., an insured person receives while also receiving rehabilitation is not covered. CP 561.

Washington Courts have held that: "we will not add language to the policy that the insurer did not include." *Fluke Corp. v. Hartford Accident*, 102 Wn.App. 237, 7 P.2d 825 (2000) citing *American National Fire Insurance Company v. V&L Trucking and Construction Co.*, 134 Wn.2d 413, 430, 951 P.2d 250 (1998).

Again, Swedish Medical Center operates under a "single hospital license." CP 502-520. There is no doubt but that the Swedish Hospital Medical Center is a hospital. In fact, nowhere in the Regence policy is treatment or services an insured may receive

limited just because the insured is on a different floor of the same hospital. CP 561. As a result, the only fair and sensible reading of the Regence policy is that the policy limits only rehabilitative care to \$4,000.00. *Id.*

D. Regence Violated WAC 284-30-380(1), WAC 284-30-330(13) and WAC 284-44-043.

In this case, Regence has failed to provide the Pleasants of any explanation, reasonable or otherwise, supporting the basis of its denial of the mechanical embolectomy procedure. Other than simply advising Mr. Pleasant that the procedure is investigational, Regence has wholly failed to provide any authority, law, or other justification, throughout the course of the original claims handling, or the course of this litigation justifying its denial of the mechanical embolectomy procedure. Moreover, not only did Regence fail to explain its basis for denial in violation of WAC, Regence did not offer another treatment option in its place. In these circumstances, Regence has violated the Washington Administrative Code and therefore violated the Consumer Protection Act at RCW 19.86, *et seq.*

DATED THIS 5TH day of March, 2013.

COLE | WATHEN | LEID | HALL, P.C.



Rick J Wathen, WSBA #25539

Kimberly Larsen Rider, WSBA # 42736

Attorneys for Appellants/Plaintiffs

1000 Second Avenue, Suite 1300

Seattle, WA 98104

T: 206.622.0494

F: 206.587.2476

rwathen@cwlhlaw.com

krider@cwlhlaw.com

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Rick J Wathen, WSBA #25539
Kimberly Larsen Rider, #42736
Attorneys for Appellants

Cole I Wathen I Leid I Hall
1000 Second Avenue, Ste 1300
Seattle, WA 98104
206.622.0494
206.587.2476

I hereby certify that on March 5, 2013, copies of the following document(s):

REPLY BRIEF OF APPELLANTS BRUCE AND KIMBERLY PLEASANT

was served on counsel at the following address via hand-delivery and email:

Stephania Camp Denton
Law Offices of Mills Meyers Swartling
1000 Second Avenue, 30th Floor
Seattle, WA 98104-1064
Phone: 206 382-1000
Fax: 206-386-7343
sdenton@mms-seattle.com

I declare under penalty of perjury under the laws of the State of Washington that the foregoing is true and correct.

DATED this 5th day of March, 2013, at Seattle, Washington.

A handwritten signature in black ink, appearing to read 'Kimberly Larsen Rider', is written over a horizontal line.

Kimberly Larsen Rider, WSBA # 42736

APPENDIX G

Swedish Medical Center

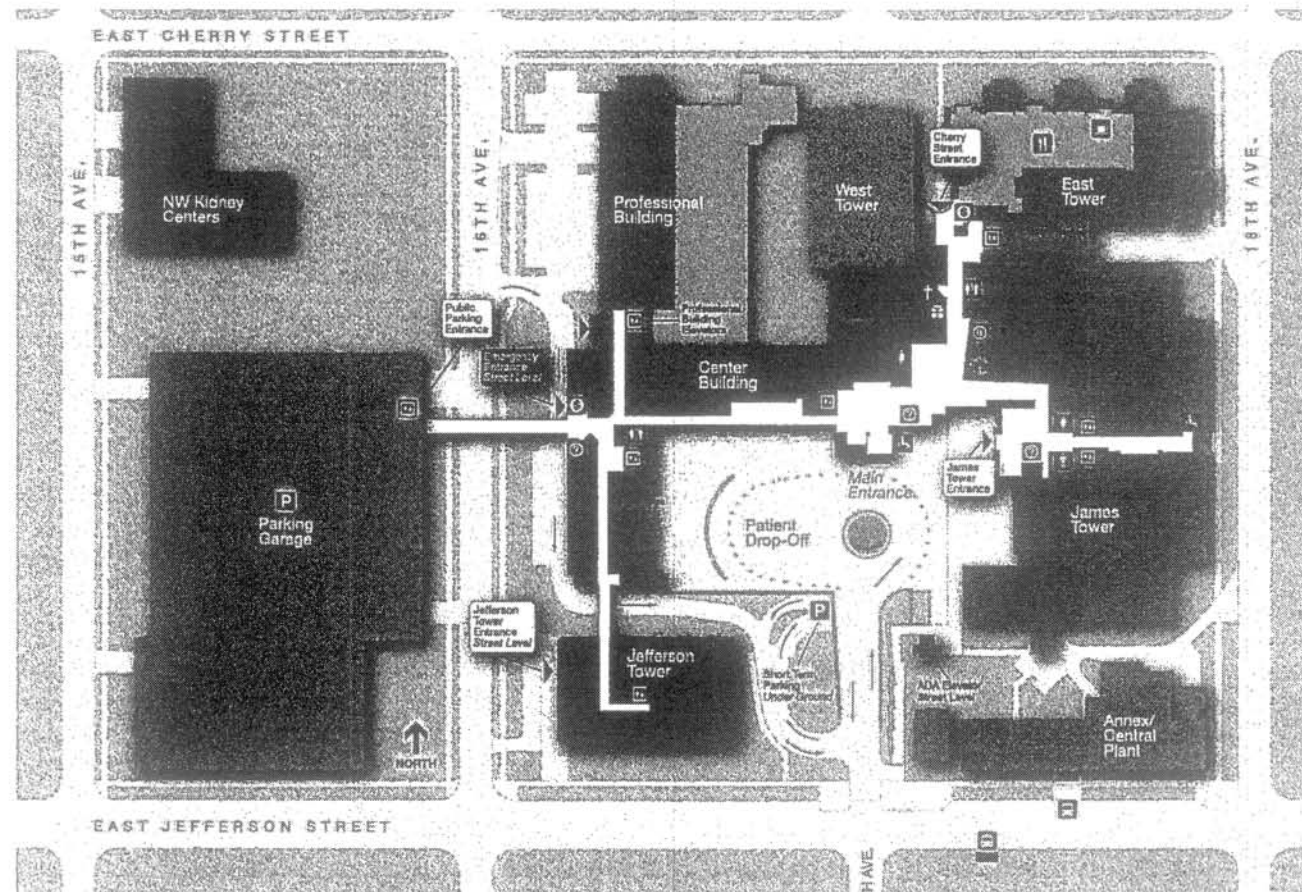
Cherry Hill Campus

Home of
Swedish Heart & Vascular Institute
and Swedish Neuroscience Institute

First Floor Plan

Key	
ATM	
Chapel	
Dining Room	
Espresso Cart	
Elevator	
Gift Shop	
Information	
Pharmacy	
Restrooms	
Waiting Room	
Wheelchair Accessible	

See reverse for driving directions



Center Building	Floor
Admitting/Patient Registration	1
Chapel	1
Emergency Department	A
Gift Shop Main Lobby	1
Heart Center	1
Information	1
Interventional and Intensive Care Units	2
Radiology (CT/MRI/NucMed/Ultrasound/x-ray)	B
Radiology Registration	1
Wound Healing Center	A

East Tower	Floor
Auditorium	A
Dining Room (Cafeteria)	1
Patient Rooms	2-6
Psychiatric Services	2
James Tower	Floor
Cardiology Offices	4-6
Center for Health and Fitness	1
Education & Conference Center	1
Outpatient Lab (LabCorp)	2
Pharmacy	1
Neuroscience Offices	5

Sleep Disorders Center	A
Seattle Cyberknife Center	A
Jefferson Tower	Floor
Cardiac Surgery Office	1
Breast Center	3
Swedish Physicians Clinic	5
Vascular Surgery Office	1
Professional Building	Floor
Family Medicine	1

West Tower	Floor
Ambulatory Infusion & Bronchoscopy Center	1
Inn at Cherry Hill	5

For special assistance or to check lost and found, visit Security on A level next to Emergency Department.

1. The first step in the process of identifying and assessing the risks of a project is to identify the risks. This is done by listing all the potential risks that could affect the project. The risks are then categorized into three groups: high, medium, and low. High risks are those that have a high probability of occurring and a high impact on the project. Medium risks are those that have a moderate probability of occurring and a moderate impact on the project. Low risks are those that have a low probability of occurring and a low impact on the project.

2. The second step in the process is to assess the risks. This is done by evaluating the likelihood of each risk occurring and the potential impact of each risk on the project. The risks are then ranked in order of priority, with the highest priority risks being those that have the highest probability of occurring and the highest impact on the project.

3. The third step in the process is to develop a risk management plan. This plan outlines the strategies and actions that will be taken to manage the risks. The plan should include a list of the risks, a description of the strategies and actions that will be taken to manage each risk, and a timeline for the implementation of the plan.

4. The fourth step in the process is to implement the risk management plan. This involves putting the strategies and actions outlined in the plan into practice. The project manager should monitor the risks regularly and update the risk management plan as needed.

5. The fifth step in the process is to review the results of the risk management process. This involves evaluating the effectiveness of the risk management strategies and actions and making any necessary adjustments to the plan.

APPENDIX H

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

Harold P. Adams, Jr, Gregory del Zoppo, Mark J. Alberts, Deepak L. Bhatt, Lawrence Brass, Anthony Furlan, Robert L. Grubb, Randall T. Higashida, Edward C. Jauch, Chelsea Kidwell, Patrick D. Lyden, Lewis B. Morgenstern, Adnan I. Qureshi, Robert H. Rosenwasser, Phillip A. Scott and Eelco F.M. Wijdicks

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AHA/ASA Guideline

REPRINT

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

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

Harold P. Adams, Jr, MD, FAHA, Chair; Gregory del Zoppo, MD, FAHA, Vice Chair;
Mark J. Alberts, MD, FAHA; Deepak L. Bhatt, MD;
Lawrence Brass, MD, FAHA†; Anthony Furlan, MD, FAHA; Robert L. Grubb, MD, FAHA;
Randall T. Higashida, MD, FAHA; Edward C. Jauch, MD, FAHA; Chelsea Kidwell, MD, FAHA;
Patrick D. Lyden, MD; Lewis B. Morgenstern, MD, FAHA; Adnan I. Qureshi, MD, FAHA;
Robert H. Rosenwasser, MD, FAHA; Phillip A. Scott, MD, FAHA; Eelco F.M. Wijdicks, MD, FAHA

Purpose—Our goal is to provide an overview of the current evidence about components of the evaluation and treatment of adults with acute ischemic stroke. The intended audience is physicians and other emergency healthcare providers who treat patients within the first 48 hours after stroke. In addition, information for healthcare policy makers is included.

Methods—Members of the panel were appointed by the American Heart Association Stroke Council's Scientific Statement Oversight Committee and represented different areas of expertise. The panel reviewed the relevant literature with an emphasis on reports published since 2003 and used the American Heart Association Stroke Council's Levels of Evidence grading algorithm to rate the evidence and to make recommendations. After approval of the statement by the panel, it underwent peer review and approval by the American Heart Association Science Advisory and Coordinating Committee. It is intended that this guideline be fully updated in 3 years.

Results—Management of patients with acute ischemic stroke remains multifaceted and includes several aspects of care that have not been tested in clinical trials. This statement includes recommendations for management from the first contact by emergency medical services personnel through initial admission to the hospital. Intravenous administration of recombinant tissue plasminogen activator remains the most beneficial proven intervention for emergency treatment of stroke. Several interventions, including intra-arterial administration of thrombolytic agents and mechanical interventions, show promise. Because many of the recommendations are based on limited data, additional research on treatment of acute ischemic stroke is needed. (*Circulation*. 2007;115:e478-e534.)

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

†Deceased.

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This guideline was approved by the American Heart Association Science Advisory and Coordinating Committee on January 6, 2007. A single reprint is available by calling 800-242-8721 (US only) or writing the American Heart Association, Public Information, 7272 Greenville Ave, Dallas, TX 75231-4596. Ask for reprint No. 71-0398. To purchase additional reprints, call 843-216-2533 or e-mail kelle.ramsay@wolterskluwer.com.

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The present document is a comprehensive guideline statement on the management of patients with acute ischemic stroke that supercedes the prior statement and interim updates.¹⁻³ These guidelines have been developed by a panel of physicians with a broad range of expertise, including vascular neurology, neurocritical care, emergency medicine, neurosurgery, and interventional neuroradiology/endovascular neurosurgery. The intended audience for these guidelines includes physicians, emergency medical services (EMS) personnel, and other medical personnel who deal with the emergency diagnosis and treatment of patients with suspected ischemic stroke. In addition, components of these guidelines are very relevant to health policy decision makers and administrators. The goal of these guidelines is to provide updated recommendations that may be used by physicians who provide acute stroke care within the first hours to time of initial diagnosis, treatment, and initial hospitalization. In addition, the guideline also includes information that should be useful for nonphysician EMS personnel and for hospitals. The emphasis of these guidelines is the diagnosis and emergency treatment of patients with acute ischemic stroke. Information about the management of acute and subacute neurological and medical complications is also included. The panel recognizes that measures to prevent early recurrent stroke are also a component of acute management. In general, the medical or surgical interventions administered to prevent recurrent stroke are similar to those prescribed to patients with recent transient ischemic attacks or to other high-risk persons. The reader is referred to another recent statement that addresses the management of risk factors, the prescription of antithrombotic medications, and the use of surgical or endovascular interventions to prevent recurrent stroke.⁴

In writing these guidelines, the panel applied the rules of evidence and the formulation of strength of recommendations used by other panels of the American Heart Association (AHA)⁴ (see the Figure and Table 1). The data were collected through a systematic review of the literature. Because of the wide scope of the guidelines, the members of the panel were assigned primary reviews 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 cases in which definitive data were not available, no specific recommendation was made. *Italics* indicate recommendations that have been changed or added since the publication of the previous guideline. In other 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. For many of these interventions, it is unlikely that randomized trials will ever be performed. An example is the recommendation to perform endotracheal intubation to protect the airway in a comatose patient.

I. Prehospital Management and Field Treatment

Recent data indicate that 29% to 65% of patients with signs or symptoms of acute stroke access their initial medical care via local EMS (Table 2), which confirms the role of EMS in the chain of survival.⁵⁻¹³ Notably, an estimated 19% to 60% of stroke patients present within 3 hours of stroke and 14% to 32% of those arrive within 2 hours of symptom onset. Although just over half of all stroke patients use EMS access to health care, those who do utilize EMS comprise the majority of patients presenting within the 3-hour window.¹³⁻¹⁶

EMS activation appears to be a function primarily of individuals other than the patient, with one report indicating that a family member, paid caregiver, coworker, or other bystander accounted for 62% to 95% of 9-1-1 activation calls.^{6,9} In addition to bystander recognition of a problem, other reported predictors of EMS use by stroke patients include stroke severity,¹⁷ presence of intracranial hemorrhage,^{9,18} age,^{9,18} sense of urgency,⁹ unemployment,⁶ and race (black).¹⁸

The benefits of EMS activation by patients with stroke symptoms appear to occur in both the prehospital and in-hospital settings. Hospital arrival is faster for patients who use EMS/9-1-1 as their initial medical contact than for those who contact their primary physician or hospital directly¹⁸ or a primary care site.¹⁹ Not surprisingly, EMS use is strongly associated with shorter time periods from symptom onset to hospital arrival, although this may reflect a greater sense of urgency on the patient's or bystander's part rather than reduced transport time.^{8,9,12} Similarly, EMS use is strongly associated with decreased time to initial physician examination,^{9,10,13,20} initial computed tomography (CT) imaging,^{9,10,12} and neurological evaluation.⁹

"Estimate of Certainty (Precision) of Treatment Effect"

		"Size of Treatment Effect"		
		Class IIa	Class IIb	Class III
		<i>Benefit >> Risk</i> <i>Additional studies with focused objectives needed</i>	<i>Benefit ≥ Risk</i> <i>Additional studies with broad objectives needed; Additional registry data would be helpful</i>	<i>Risk > Benefit</i> <i>No additional studies needed</i>
		IT IS REASONABLE to perform procedure/administer treatment	Procedure/Treatment MAY BE CONSIDERED	Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
Level A	Multiple (≥ 3) population risk strata evaluated* General consistency of direction and magnitude of effect	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
Level B	Limited (2-3) population risk strata evaluated*	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or non-randomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment not useful/effective and may be harmful Limited evidence from single randomized trial or non-randomized studies
Level C	Very limited (1-2) population risk strata evaluated*	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard-of-care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment 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
				is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different sub-populations, such as gender, age, history of diabetes, history of prior MI, history of heart failure, and prior aspirin use. 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. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACC/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All recommendations in this guideline have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

Figure. Applying classification of recommendations and level of evidence.

TABLE 1. Definition of Classes and Levels of Evidence Used in AHA Recommendations

Classification	
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
Level of evidence	
A	Data derived from multiple randomized clinical trials
B	Data derived from a single randomized trial or nonrandomized studies
C	Consensus opinion of experts
Level of evidence for diagnostic recommendation	
A	Data derived from multiple prospective cohort studies that used a reference standard applied by a masked evaluator
B	Data derived from a single grade A study or one or more case-control studies or studies that used a reference standard applied by an unmasked evaluator
C	Consensus opinion of experts

On the basis of the aforementioned information, communities should encourage 9-1-1 activation and use for patients with symptoms of acute stroke.

Data from the TLL Temple Foundation Stroke Project controlled trial indicate that educational interventions on stroke identification and management targeting patients, EMS, hospitals, and community physicians increased thrombolytic use in patients with ischemic stroke from 2.21% to 8.65% as compared with communities that did not have such programs, which saw only a 0.06% increase. For patients with ischemic stroke who were eligible for thrombolytic therapy, rates of tissue-type plasminogen activator (tPA) use increased from 14% to 52% in intervention communities. The benefit from this aggressive intervention program was sustained at 6 months after intervention.^{21,22}

A. EMS Assessment

EMS assessment begins with the initial 9-1-1 contact (Table 2). The role of the dispatch system is to ensure immediate triage and dispatch of appropriate EMS providers when acute stroke is suspected by either the caller or the dispatcher.²³ Data from 2 systems indicate that dispatchers correctly suspected or identified 52% of patients ultimately proven to have had a stroke on initial telephone evaluation.^{7,24} These data imply that educational programs should be aimed at dispatchers to increase their awareness of stroke symptoms.

TABLE 2. Stroke Chain of Survival

Detection	Recognition of stroke signs and symptoms
Dispatch	Call 9-1-1 and priority EMS dispatch
Delivery	Prompt transport and prehospital notification to hospital
Door	Immediate ED triage
Data	ED evaluation, prompt laboratory studies, and CT imaging
Decision	Diagnosis and decision about appropriate therapy
Drug	Administration of appropriate drugs or other interventions

Stroke should be given a priority dispatch similar to that for acute myocardial infarction or trauma.²⁵

After ambulance arrival on the scene, EMS providers should obtain a focused history and patient assessment, provide necessary stabilization and treatment, and transport immediately to the closest, most appropriate facility (Table 3). The word *appropriate* is key because it means that an ambulance may bypass a hospital that does not have the resources or institutional commitment to treat patients with stroke if a more appropriate hospital is available within a reasonable transport interval. Advance notice to the receiving emergency department (ED) of the impending arrival of a potential stroke patient, along with information on comorbid conditions and estimated time of symptom onset, will speed the subsequent ED assessment.

Critical elements of the patient's history must include information on time of symptom onset (Table 4). This may require obtaining information from bystanders or, preferably, transporting witnesses with the patient. Similarly, next of kin, if available, may be needed for information or consent and should travel to the receiving hospital concurrently. Telephone numbers, including cellular telephone numbers, of witnesses or relatives may help the ED to clarify the history or seek consent for treatment. A list of the patient's medications, or the medication containers themselves, should be sought, with particular attention paid to identifying anticoagulant (both oral and injectable), antiplatelet, and antihypertensive drug use.

After the patient's airway, breathing, and circulation (ABCs) are assessed and stabilized, common presenting signs of stroke should be sought and a focused examination completed. Prehospital stroke assessment tools have proved effective in identifying stroke patients in the field. The Los Angeles Prehospital Stroke Screen uses patient history, physical findings, and finger stick glucose determination to identify stroke patients.²⁶ The Cincinnati Prehospital Stroke

TABLE 3. Guidelines for EMS Management of Patients With Suspected Stroke

Recommended	Not Recommended
Manage ABCs	Dextrose-containing fluids in nonhypoglycemic patients
Cardiac monitoring	Hypotension/excessive blood pressure reduction
Intravenous access	Excessive intravenous fluids
Oxygen (as required O ₂ saturation <92%)	
Assess for hypoglycemia	
<i>Nil per os</i> (NPO)	
Alert receiving ED	
Rapid transport to closest appropriate facility capable of treating acute stroke	

Scale is an alternative instrument with fewer data elements (Table 5), requiring only 30 to 60 seconds to complete.²⁷ Other prehospital stroke evaluation tools exist, although data on their validity are limited.

B. EMS Management

Guidelines for EMS management are presented in Table 3.^{25,28} After initial stabilization, it is recommended that patient transport commence as soon as possible, with cardiac monitoring and intravenous access established during transport, if possible. Isotonic crystalloids (most commonly normal saline solution) are recommended for resuscitation, if needed. Dextrose-containing fluids should be avoided unless hypoglycemia is present or strongly suspected because excessive glucose may be injurious to stroke patients. No recommendations can be offered on the prehospital management of hypertension in patients with suspected stroke, and intervention is best accomplished after hospital arrival.

It is well recognized that hypoglycemic patients may have symptoms that mimic an acute stroke, manifesting focal symptoms, altered speech, and/or cognitive changes, and therefore EMS assessment of blood glucose has been a routine practice for many years. A single report suggests that a more selective approach may be possible, with blood glucose measurement advocated only in the presence of a history suspicious for hypoglycemia or inability to obtain

adequate patient information.²⁹ That study is limited, however, by its retrospective methodology and an upper confidence interval of 2.4% for the likelihood of failing to identify a hypoglycemic patient. At present, checking blood glucose concentrations in most patients with stroke is a prudent step, even among patients without a history of diabetes mellitus or use of insulin.

The availability of resources to care for patients with acute stroke varies widely both among and within communities. The National Institutes of Health (NIH) Task Force report, "Improving the Chain of Recovery for Acute Stroke in Your Community," recommends identifying hospitals capable of providing acute stroke care and creating a transport system to these centers based on patient location. Such systems require advanced planning and frequent updating and should incorporate EMS representatives, community leaders, hospitals, and physicians to ensure clear guidance for EMS providers with regard to patient destination.

Identification of an effective neuroprotective therapy may further expand the role of EMS in the treatment of acute stroke. The feasibility of initiation of hypothermia has also been demonstrated in the prehospital setting.³⁰ Of importance for future research is the fact that it appears possible to incorporate EMS into the research process, with EMS personnel having demonstrated success in facilitating physician cell phone elicitation of consent from patients and in delivering experimental stroke therapy.^{31,32}

TABLE 4. Key Components of History

Onset of symptoms
Recent events
Stroke
Myocardial infarction
Trauma
Surgery
Bleeding
Comorbid diseases
Hypertension
Diabetes mellitus
Use of medications
Anticoagulants
Insulin
Antihypertensives

C. Air Medical Transport

Air medical (helicopter) transport for patients with acute stroke appears beneficial, although the data are limited. Helicopters may extend the range of thrombolytic therapy to rural areas.³³ They could deliver teams to administer tPA and subsequently transfer treated patients,³⁴ expand enrollment for acute stroke studies,³⁵ and facilitate early definitive diagnosis and operative intervention in nontraumatic intracranial hemorrhage.³⁶ It is important to note that helicopter transfer of stroke patients for potential thrombolysis is cost-effective for a wide range of system variables.³⁷

Protocols for the use of air medical transfer from facilities unable to provide acute stroke care should be developed in advance. Air medical transfer should be considered for patients who cannot receive treatment locally and who could reach a treating facility within the available time window.^{33,38}

TABLE 5. Prehospital Stroke Identification Instruments**Los Angeles Prehospital Stroke Screen**

Last time patient known to be symptom free, Date _____ Time _____

Screening criteria

Age >45 y	Yes	Unknown	No
No history of seizures or epilepsy	Yes	Unknown	No
Symptoms present <24 h	Yes	Unknown	No
Not previously bedridden or wheelchair bound	Yes	Unknown	No
If unknown or yes			
Blood glucose 60 to 400 mg/dL	Yes	No	

Examination

Facial smile grimace	Normal	Right droop	Left droop
Grip	Normal	Right weak	Left weak
		No grip	No grip
Arm strength	Normal	Right drift	Left drift
		Right falls	Left falls
Based on examination, patient has unilateral weakness	Yes	No	

If items are yes or unknown, meets criteria for stroke

Cincinnati Prehospital Stroke Scale

Facial droop

Normal—both sides of face move equally

Abnormal—one side of face does not move as well as the other

Arm drift

Normal—both arms move the same or both arms do not move at all

Abnormal—one arm either does not move or drifts down compared to the other

Speech

Normal—says correct words with no slurring

Abnormal—slurs words, says the wrong words, or is unable to speak

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In addition, telemedicine may be used as a way to bring stroke expertise to patients in rural or small hospitals. Preliminary data suggest that such electronic methods may be increasingly useful.^{39–43}

D. Conclusions and Recommendations

Public educational programs likely will increase the proportion of patients with stroke who will utilize EMS as their first contact with the healthcare system. This trend should be encouraged. In response, EMS should have protocols in place to rapidly assess, treat, and transport patients. The objectives of the EMS phase of stroke care are as follows: (1) rapid identification of stroke as the cause of the patient's findings, (2) elimination of comorbid conditions that could mimic stroke, (3) stabilization, (4) rapid transportation of the patient to the closest appropriate ED, and (5) notification of the receiving institution about impending arrival of a patient with suspected stroke. Such steps are especially critical for the use of time-dependent therapies. Community and physician educational programs on acute stroke treatment appear to enhance the use of recombinant tPA (rtPA), and these programs should be encouraged. Strategies such as telemedicine or air medical transport (helicopter) may provide access to specialized stroke care when it is not available locally. Such approaches may increase the number of patients who can be

treated, especially in rural or otherwise underserved areas. To maximize therapeutic options, treatment guidelines and transfer protocols should be established in advance to ensure orderly patient transition from a prehospital to a hospital environment.

The recommendations that follow were not included in the previous guidelines.

Class I Recommendations

1. Activation of the 9-1-1 system by patients or other members of the public is strongly supported because it speeds treatment of stroke (Class I, Level of Evidence B). 9-1-1 Dispatchers should make stroke a priority dispatch.
2. To increase the number of patients who can be seen and treated within the first few hours after stroke, educational programs to increase public awareness of stroke are recommended (Class I, Level of Evidence B).
3. To increase the number of patients who are treated, educational programs for physicians, hospital personnel, and EMS personnel also are recommended (Class I, Level of Evidence B).
4. Brief assessments by EMS personnel as outlined in Tables 3 and 5 are recommended (Class I, Level of Evidence B).

5. The use of a stroke identification algorithm such as the Los Angeles or Cincinnati screens is encouraged (Class I, Level of Evidence B).
6. The panel recommends that EMS personnel begin the initial management of stroke in the field, as outlined in Table 3 (Class I, Level of Evidence B). The development of stroke protocols to be used by EMS personnel is strongly encouraged.
7. Patients should be transported rapidly for evaluation and treatment to the closest institution that provides emergency stroke care as described in the statement (Class I, Level of Evidence B). In some instances, this may involve air evacuation. EMS personnel should notify the receiving ED so that the appropriate resources may be mobilized.

Class II Recommendation

1. Telemedicine can be an effective method to provide expert stroke care to patients located in rural areas (Class IIa, Level of Evidence B). Additional research and experience on the usefulness of telemedicine are encouraged.

II. Designation of Stroke Centers

In an attempt to improve the organization and delivery of care to stroke patients, the Brain Attack Coalition published 2 sets of recommendations, one for primary stroke centers (PSCs) and, more recently, one for comprehensive stroke centers (CSCs).^{44,45} A PSC has the personnel, programs, expertise, and infrastructure to care for many patients with uncomplicated strokes, uses many acute therapies (such as intravenous rtPA), and admits such patients into a stroke unit. The CSC is designed to care for patients with complicated types of strokes, patients with intracerebral hemorrhage or subarachnoid hemorrhage, and those requiring specific interventions (eg, surgery or endovascular procedures) or an intensive care unit type of setting.

The specific elements of a PSC and a CSC will not be reviewed in the present document because they are well covered in the articles cited above. Many of the elements in a PSC or a CSC, including stroke units, written care protocols, availability of physicians with neurological expertise, and neurosurgical volumes, are associated with improved outcomes among patients treated for stroke.^{44,45} Since the publication of the PSC article in 2000,⁴⁴ numerous published studies have demonstrated the utility and effectiveness of such centers.^{22,46–51} One study found that a PSC increased the use of intravenous rtPA from 1.5% to 10.2% in 2 years.⁴⁶ Another study found that 7 of the 11 elements of a PSC were associated with increased use of intravenous tPA.⁴⁷ Additional areas of disease performance that may be added include performance of a lipid profile, dysphagia screening, and the presence of a rehabilitation plan.

The utility of a CSC is beginning to emerge. Studies show that a CSC increases the use of lytic agents and that a CSC may improve overall care and outcomes.^{52,53} In-hospital death rates were reduced by almost 50% in hospitals with a vascular neurologist and were reduced by 24% in those with a stroke team.⁵⁴ Such centers have acted as a regional resource for stroke care with good results and will be pivotal for further

TABLE 6. Standardized Measures for Stroke: JCAHO Primary Stroke Centers

tPA considered
Screen for dysphagia
Deep vein thrombosis prophylaxis
Lipid profile during hospitalization
Smoking cessation
Education about stroke
Plan for rehabilitation considered
Antithrombotic medications started within 48 hours
Antithrombotic medications prescribed at discharge
Anticoagulants prescribed to patients with atrial fibrillation

advancements in acute stroke care, stroke prevention, and rehabilitation.^{38,55,56}

A. Stroke Center Certification

The certification or designation of some hospitals as PSCs or CSCs is progressing rapidly. The American Stroke Association convened an expert panel to study this issue for PSCs, with the conclusion that a variety of certification processes might be developed and lead to improved care and outcomes.⁵⁷ Another panel is currently meeting to evaluate various options for CSC certification. One study showed that self-certification was likely to lead to a significant overestimation of a hospital's compliance with published recommendations for a PSC.⁵⁸ Thus, these data and anecdotal experience suggest that outside independent evaluations of hospitals as stroke centers should lead to more accurate assessment of a facility's true capabilities.

The Joint Commission on the Accreditation of Healthcare Organizations (JCAHO) began a formal process for the certification of PSCs in February 2004 (Table 6). As of February 2006, ~200 hospitals in the United States had been certified as PSCs by the JCAHO. The JCAHO certification process includes a detailed evaluation of a hospital's staffing, education, disease management programs, outcomes, and infrastructure (see www.JCAHO.org for details). Several states have developed or are exploring a state-based certification process for PSCs, primarily using the state health department or a related government agency as the certifier. At this time the American Stroke Association and JCAHO have taken preliminary steps that may lead to a formal certification process for CSCs.

The preferential routing of acute stroke patients to a PSC has been demonstrated to increase the proportion of patients cared for at stroke-capable centers and to increase the proportion of patients treated with thrombolytic therapy to >10%.⁴⁸ Direct routing of stroke patients whose symptoms started <3 hours ago to a PSC or a CSC has been implemented or is in the process of implementation in 7 states, covering >25% of the US population. The states of Florida, New Jersey, Maryland, Massachusetts, Michigan, New Mexico, and Texas have laws or policies mandating that acute stroke patients be taken to the nearest stroke center. In other states, the limited number of such centers makes preferential routing logistically infeasible. Stroke centers in rural areas

TABLE 7. Stroke Mimics and Clinical Features

Conversion disorder	Lack of cranial nerve findings, neurological findings in a nonvascular distribution, inconsistent examination
Hypertensive encephalopathy	Headache, delirium, significant hypertension, cerebral edema
Hypoglycemia	History of diabetes, serum glucose low, decreased level of consciousness
Complicated migraine	History of similar events, preceding aura, headache
Seizures	History of seizures, witnessed seizure activity, postictal period

often use helicopter transportation or telemedicine technologies to provide rapid transportation and expertise to expedite treatment at outlying hospitals.^{33,53} However, this is clearly an area that will evolve as the number of stroke centers increases, their geographic distribution expands, and the concept is embraced by the medical community.

Stroke centers should not be viewed in isolation. Rather, they should be part of a larger support network sometimes referred to as a *stroke system of care*. Such a system would encompass issues such as prevention, education, acute care, rehabilitation, and quality improvement.⁵⁹ In addition, as the number of stroke centers increases, such facilities may form a network of hospitals that would be useful for testing new therapies for acute stroke.

B. Conclusions and Recommendations

Robust data demonstrate the efficacy of specialized stroke services in improving outcomes of patients with stroke. Thus, there is a strong impetus to develop such specialized stroke services across the United States. Both primary (PSC) and comprehensive (CSC) centers are needed. At present, the process of identification of PSCs is ahead of that used to develop CSCs. The details of the organization of such services may vary among institutions or in different parts of the country to reflect demographic or geographic variables. Statewide or regional programs are being developed. A method to designate stroke centers, such as the JCAHO program, is being used to ensure that centers have the expertise and resources to provide modern stroke care. Plans for EMS to bypass institutions that do not have the capability to provide modern stroke care need to be developed.

The following recommendations were not included in the prior stroke guidelines.

Class I Recommendations

1. The creation of PSCs is strongly recommended (Class I, Level of Evidence B). The organization of such resources will depend on local variables. The design of several community-based PSCs that provide emergency care and that are closely associated with a CSC, which provides more extensive care, has considerable appeal.
2. The development of CSC is recommended (Class I, Level of Evidence C).
3. Certification of stroke centers by an external body, such as JCAHO, is encouraged (Class I, Level of Evidence B). The panel encourages additional medical centers to seek such certification.
4. For patients with suspected stroke, EMS should bypass hospitals that do not have resources to treat stroke and go to the closest facility capable of treating acute stroke (Class I, Level of Evidence B).

III. Emergency Evaluation and Diagnosis of Acute Ischemic Stroke

Given the narrow therapeutic windows for treatment of acute ischemic stroke, timely evaluation and diagnosis of ischemic stroke are paramount.⁶⁰ Hospitals that maintain an ED must create efficient pathways and processes to rapidly identify and evaluate potential stroke patients. The physician's evaluation, diagnostic testing, including neuroimaging, and contact with a physician with stroke expertise should be performed concurrently. A consensus panel convened by the National Institute of Neurological Disorders and Stroke (NINDS) established goals for time frames in these steps in the evaluation of stroke patients in the ED.^{25,61} 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 2).⁶¹ By using this template and the time goals, hospitals and EDs can create effective systems for optimizing stroke patient care.⁶²

All 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 the deficits. Roughly half of all acute stroke patients access the ED through 9-1-1 and EMS. Prehospital notification of the arrival of a patient with a potential stroke expedites evaluation and diagnosis, and therefore hospitals should request notification from local EMS providers.^{63,64} For the remaining 50% of stroke patients, the ED staff should maintain a high level of suspicion for stroke in patients presenting through the ED lobby to minimize delays in triage. Early implementation of stroke pathways and stroke team notification should occur in parallel with the ED evaluation and management.

A. Immediate Evaluation

The initial evaluation of a potential stroke patient is similar to that of other critically ill patients: stabilization of the ABCs. This is quickly followed by a secondary 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 stroke-like symptoms), identify other conditions requiring immediate intervention, and determine potential causes of the stroke for early secondary prevention (Table 7).

1. History

The single most important piece of historical information is the time of symptom onset. The current definition of the time of stroke onset is when patients were at their 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." Often a patient's current symptoms were preceded by similar symptoms that subsequently resolved. Currently, for patients who had neurological symptoms that completely resolved, the therapeutic clock is reset, and the time of symptom onset begins anew. It is important to note, however, that the longer the transient neurological deficits last, the greater is the chance of detecting neuroanatomically relevant focal abnormalities on diffusion-weighted and apparent diffusion coefficient imaging.⁶⁵ Whether this represents an increased risk of hemorrhage with thrombolysis remains to be determined.

Additional historical items include circumstances around 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 a diagnosis of another cause for the patient's symptoms (Table 7). It is important to ask about risk factors for arteriosclerosis and cardiac disease in all patients, 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.⁶⁶ Bystanders or family witnesses should be asked for information about onset time and historical issues, and therefore EMS personnel should be encouraged to identify witnesses and bring them in the ambulance when patients are unable to speak or provide history. Validated tools for identification of stroke patients within an ED are available.⁶⁷

2. Physical Examination

The general physical examination continues from the original assessment of the ABCs and should include pulse oximetry and body temperature. Examination of the head and neck may reveal signs of trauma or seizure activity (eg, contusions, tongue lacerations), carotid disease (bruits), or congestive heart failure (jugular venous distention). The cardiac examination focuses on identifying concurrent myocardial ischemia, valvular conditions, irregular rhythm, and, in rare cases, aortic dissection, which could precipitate a cardioembolic event. Similarly, the respiratory and abdominal examinations seek to identify other comorbidities. Examination of the skin and extremities may also provide insight into important systemic conditions such as hepatic dysfunction, coagulopathies, or platelet disorders (eg, jaundice, purpura, petechia).

3. Neurological Examination and Stroke Scale Scores

The emergency physician's neurological examination should be brief but thorough. It is enhanced by use of a formal stroke score or scale, such as the NIH Stroke Scale (NIHSS). The scale may be used by a broad spectrum of non-neurological healthcare providers (Table 8).^{24,68,69} Use of a standardized examination helps to ensure that the major components of a neurological examination are performed in a timely fashion. These scores not only help to quantify the degree of neurological deficit but also facilitate communication between healthcare professionals, identify the possible location of vessel occlusion, provide early prognosis, and help to identify patient eligibility for various interventions and the potential for complications.^{42,70-72} Several studies have demonstrated that emergency physicians committed to stroke care may

TABLE 8. National Institutes of Health Stroke Scale

Tested Item	Title	Responses and Scores
1A	Level of consciousness	0—alert 1—drowsy 2—obtunded 3—coma/unresponsive
1B	Orientation questions (2)	0—answers both correctly 1—answers one correctly 2—answers neither correctly
1C	Response to commands (2)	0—performs both tasks correctly 1—performs one 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) 2—severe (loss 2 modalities)

correctly identify and safely treat stroke patients, especially with the use of such standardized scales.^{73,74} All hospital systems should ensure access to neurological expertise when required.⁷⁵

TABLE 9. Immediate Diagnostic Studies: Evaluation of a Patient With Suspected Acute Ischemic Stroke

All patients
Noncontrast brain CT or brain MRI
Blood glucose
Serum electrolytes/renal function tests
ECG
Markers of cardiac ischemia
Complete blood count, including platelet count*
Prothrombin time/international normalized ratio (INR)*
Activated partial thromboplastin time*
Oxygen saturation
Selected patients
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)

MRI indicates magnetic resonance imaging.

*Although it is desirable to know the results of these tests before giving rtPA, thrombolytic 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) use of anticoagulants is not known.

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4. Diagnostic Tests

Several tests should be performed routinely in patients with suspected ischemic stroke to identify systemic conditions that may mimic or cause stroke or that may influence therapeutic options (Table 9). These tests include blood glucose, electrolytes, complete blood count with platelet count, prothrombin time, activated partial thromboplastin time, international normalized ratio, and renal function studies. Hypoglycemia may cause focal symptoms and signs 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 prothrombin time/international normalized ratio is important. Because time is critical, thrombolytic therapy should not be delayed while waiting for the results of the prothrombin time, activated partial thromboplastin time, or platelet count unless a bleeding abnormality or thrombocytopenia is suspected, the patient has been taking warfarin and heparin, or anticoagulation use is uncertain.

5. Cardiac Tests

A clinical cardiovascular examination, cardiac enzyme tests, and a 12-lead ECG should be performed in all stroke patients (Table 9).⁷⁶ Cardiac abnormalities are prevalent among patients with stroke, and the patient can have an acute cardiac condition that mandates urgent treatment. For example, acute

myocardial infarction can lead to stroke, and acute stroke can lead to myocardial ischemia.^{77–79} In addition, cardiac arrhythmias can occur among patients with acute ischemic stroke.^{77,78,80,81} Atrial fibrillation, an important potential cause of stroke, can be detected in the acute setting.⁸² Cardiac monitoring should be conducted routinely after an acute cerebrovascular event to screen for serious cardiac arrhythmias.⁸³

Chest radiography was previously recommended for the evaluation of all patients with acute ischemic stroke.¹ A subsequent study found that clinical management was altered in only 3.8% of patients who had routine chest radiographs at the time of admission for stroke, which suggests that the test is of modest, but not nil, value.⁸³

Examination of the cerebrospinal fluid is indicated if the patient has symptoms suggestive of subarachnoid hemorrhage and a CT scan does not demonstrate blood. Fortunately, the clinical features of subarachnoid hemorrhage differ considerably from those of ischemic stroke. Electroencephalography may be helpful for evaluating patients in whom seizures are suspected as the cause of the neurological deficits or in whom seizures could have been a complication of the stroke.⁸⁴ Seizure in the absence of imaging confirmation of acute ischemia is a relative contraindication for the use of rtPA in acute ischemic stroke.

Additional tests may be performed as indicated by the patient's history, symptoms, physical findings, or comorbidities (Table 9). A toxicology screen, blood alcohol level, arterial blood gas, and pregnancy test should be obtained if the physician is uncertain about the patient's history or as suggested by findings on examination.

B. Conclusions and Recommendations

The evaluation and initial treatment of patients with stroke should be performed as a priority in the hospital ED. The development of an organized protocol and stroke team should 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. This evaluation should be performed by the physicians in the ED. The goals are to determine whether the patient has had a stroke and to establish potential contraindications for emergency treatment with agents such as rtPA. A stroke rating scale, such as the NIHSS, provides important information about the severity of stroke. It provides prognostic information, and the score may influence decisions about acute treatment. Some of the recommendations included in the present statement are influenced by the NIHSS. This scale can be performed with a reasonable degree of accuracy by practitioners in a broad range of specialties. Education in the nuances of NIHSS can improve the accuracy of this scale.

Because time is critical, a limited number of diagnostic tests are recommended. These tests should be available on a 24-hours-per-day, 7-days-per-week basis. These tests are used to screen for ischemic stroke, to exclude important alternative diagnoses (especially intracerebral hemorrhage), to assess for serious comorbid diseases, and to search for acute medical or neurological complications of the stroke

(Table 9). Examination of the cerebrospinal fluid has a limited role in the evaluation of patients with suspected stroke. Additional diagnostic studies, including cardiac and vascular imaging, often are time consuming and may delay emergency treatment. Thus, most of these tests are not done until after the acute treatment or after the patient is admitted to the hospital.

The recommendations that follow are similar to those included in previous statements except recommendation I under Class III.

Class I 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 decide 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.
2. The use of a stroke rating scale, preferably the NIHSS, is recommended (Class I, Level of Evidence B). Hospitals (ie, administration) must provide the necessary resources to use such a scale.
3. A limited number of hematologic, coagulation, and biochemistry tests are recommended during the initial emergency evaluation (Table 9) (Class I, Level of Evidence B).
4. Patients with clinical or other evidence of acute cardiac or pulmonary disease may warrant chest x-ray (Class I, Level of Evidence B).
5. An ECG is recommended because of the high incidence of heart disease in patients with stroke (Class I, Level of Evidence B).

Class III Recommendations

1. Most patients with stroke do not need a chest x-ray as part of their initial evaluation (Class III, Level of Evidence B). *This is a change from the previous guideline.*
2. Most patients with stroke do not need an examination of the cerebrospinal fluid (Class III, Level of Evidence B). The yield of brain imaging is very high for detection of intracranial hemorrhage. The clinical course of subarachnoid hemorrhage or acute central nervous system infections usually is distinct from that of ischemic stroke. Examination of the cerebrospinal fluid may be indicated for evaluation of a patient with a stroke that may be secondary to an infectious illness.

IV. Early Diagnosis: Brain and Vascular Imaging

A. Brain Imaging

As therapeutic options evolve, brain imaging strategies are playing an increasingly important role in the initial evaluation of patients with acute stroke (Table 9). Brain imaging findings, including the size, location, and vascular distribution of the infarction, as well as the presence of bleeding, affect both short-term and long-term treatment decisions. In addition, information about the possible degree of reversibility of ischemic injury, intracranial vessel status, and cerebral

hemodynamic status may be obtained by modern imaging studies.⁸⁵ Neuroimaging tests might improve selection of patients who could be treated with reperfusion therapies by identifying those with regions of salvageable brain tissue, a low risk for hemorrhagic transformation, or occlusions of large arteries that might or might not be amenable to therapy. CT and magnetic resonance imaging (MRI) are being used as initial imaging options. The most commonly obtained brain imaging test is noncontrast CT, but individual centers able to obtain MRI with efficiency equal to that of CT are using an MRI strategy in patients without MR contraindications.^{86–90} Additional research is required.^{91,92} As a result, it is generally agreed that the performance of these tests should not delay treatment with intravenous tPA.^{86,91–93}

1. Non-Contrast-Enhanced CT Scan of the Brain

It is agreed that emergency, non-contrast-enhanced CT scanning of the brain accurately identifies most cases of intracranial hemorrhage and helps discriminate nonvascular causes of neurological symptoms (eg, brain tumor). The prior guidelines recommended that CT be the primary diagnostic brain imaging study for evaluation of patients with suspected stroke.⁹⁴ Although CT is the "criterion standard" with which other brain imaging studies are compared, it is relatively insensitive in detecting acute and small cortical or subcortical infarctions, especially in the posterior fossa.⁹⁵ In most cases, the use of a contrast infusion does not provide additional information and is not necessary unless it is required for CT angiography (and, more recently, CT perfusion) or concern exists about a brain tumor or infectious process.

With the advent of tPA treatment, interest has grown in using CT to identify subtle, early signs of ischemic brain injury (early infarct signs) or arterial occlusion (hyperdense vessel sign) that might affect decisions about treatment. In addition, the loss of the gray-white differentiation in the cortical ribbon (particularly at the lateral margins of the insula) or the lentiform nucleus and sulcal effacement can often be detected within 6 hours in up to 82% of patients with large-vessel anterior circulation occlusions.^{96,97} These signs are associated with poorer outcomes.^{98,99}

In addition, widespread signs of early infarction are correlated with a higher risk of hemorrhagic transformation after treatment with thrombolytic agents. In combined data from 2 trials of intravenous tPA administered within 3 hours of symptom onset, CT evidence of early edema or mass effect was accompanied by an 8-fold increase in the risk of symptomatic hemorrhage.⁶⁶ In a second analysis, early infarct signs involving more than one third of the territory of the middle cerebral artery (MCA) were not independently associated with increased risk of adverse outcome after tPA treatment, and as a group these patients still benefited from therapy.¹⁰⁰ In a European trial in which thrombolytic 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 intracerebral hemorrhage, whereas those with less involvement benefited the most from thrombolytic treatment.^{99,101} However, physicians' ability to reliably and reproducibly recognize the early CT changes is variable.^{102–106} Use of scoring systems for

early CT changes may improve identification of cerebral ischemia and may provide valuable prognostic information but is not validated for outcome or patient selection for acute treatments.^{107,108} Further studies are needed to determine the significance of early infarct signs and their role in treatment decision making.¹⁰⁹

For patients who are candidates for treatment with rtPA, the goal is to complete the CT examination within 25 minutes of arrival at the ED, with the study interpreted within an additional 20 minutes (door-to-interpretation time of 45 minutes).⁶¹ A subsequent CT scan often is obtained if the patient worsens neurologically and may be especially helpful in identifying hemorrhagic transformation after administration of rtPA.⁶⁶

2. Multimodal CT

Recent technological advances have led to increased interest in more sophisticated multimodal approaches to acute stroke imaging. The multimodal CT approach may include noncontrast CT, perfusion CT, and CT angiography studies. Two types of perfusion techniques are currently available. Whole-brain perfusion CT provides a map of cerebral blood volume, and it is postulated that regions of hypoattenuation on these cerebral blood volume maps represent the ischemic core.¹¹⁰ Although this technique has the advantage of providing whole-brain coverage, it is limited by its inability to provide measures of cerebral blood flow or mean transit time. Alternatively, the second technique, dynamic perfusion CT, has the potential to provide absolute measures of cerebral blood flow, mean transit time, and cerebral blood volume. Dynamic perfusion CT is currently limited to 2 to 4 brain slices and provides incomplete visualization of all pertinent vascular territories.

Recent reports demonstrate a high degree of sensitivity and specificity for detecting cerebral ischemia with both of these perfusion CT techniques.^{111–113} In addition, several studies have suggested that perfusion CT may be able to differentiate thresholds of reversible and irreversible ischemia and thus identify the ischemic penumbra.^{114,115}

Helical CT angiography provides a means to rapidly and noninvasively evaluate the vasculature, both intracranially and extracranially, in acute, subacute, and chronic stroke settings and thus to provide potentially important information about the presence of vessel occlusions or stenoses.^{116,117} The feasibility of this technique has been demonstrated in the acute stroke setting, with preliminary data suggesting high diagnostic accuracy for evaluation of large-vessel intracranial occlusions as compared with ultrasound and digital subtraction angiography.^{118–120}

These techniques have the advantage of relatively rapid data acquisition and can be performed with conventional CT equipment. Disadvantages include iodine contrast and additional radiation exposure. The role of perfusion CT and CT angiography in making acute treatment decisions has not yet been established.

3. Multimodal MRI

The multimodal MRI approach for acute stroke evaluation includes diffusion-weighted imaging (DWI), perfusion-weighted imaging (PWI), MR angiography, gradient echo,

and often fluid-attenuated inversion recovery or T2-weighted sequences. Standard MRI sequences (T1 weighted, T2 weighted, and proton density) are relatively insensitive to the changes of acute ischemia.¹²¹ DWI allows visualization of ischemic regions within minutes of symptom onset^{122–131} and early identification of the lesion size, site, and age. It can detect relatively small cortical or subcortical lesions, including those in the brain stem or cerebellum, areas often poorly visualized with standard CT scan techniques. DWI also provides information about the involved vascular territory and has a high sensitivity (88% to 100%) and specificity (95% to 100%) for detecting ischemic lesions, even at very early time points.

PWI, usually performed with the rapid administration of an intravenous paramagnetic contrast agent, provides relative measures of cerebral hemodynamic status. Investigations of the best PWI analytical method focus on identifying the highest correlation of ischemic volume with acute clinical deficits (symptomatic hypoperfusion) or with volume of chronic infarct (tissue at risk).

Studies have demonstrated that the initial volumes of the lesions seen on DWI and PWI correlate well with the final size of the stroke found on follow-up brain imaging.^{129,132,133} In addition, these lesion volumes correlate well with severity of stroke as rated by both clinical scales and outcomes. These findings suggest that DWI might provide helpful early prognostic information.^{125,132}

The ischemic penumbra is roughly approximated on MRI as regions of perfusion change without a corresponding diffusion abnormality (diffusion-perfusion mismatch). However, several studies indicate that, at least in some circumstances, the initial diffusion abnormality is reversible and the visually thresholded perfusion volumes overestimate the penumbra.^{134,135} Sequential MRI studies performed in patients being treated with thrombolytic therapy have shown that the technique may visualize salvage of mismatch-defined penumbral tissue with smaller volumes of infarction among patients who have successful recanalization.^{134,136}

Efforts are under way to develop multiparametric MRI criteria that could identify regions of irreversible infarction from potentially reversible ischemia or portend a high risk of hemorrhagic complications after thrombolytic therapy.^{137–139} A recent phase II trial of intravenous administration of the thrombolytic agent desmoteplase showed a signal of potential therapeutic benefit when MRI was used to select patients with diffusion-perfusion mismatch for treatment 3 to 9 hours from onset.¹⁴⁰ However, insufficient evidence currently exists to recommend this approach for selecting patients for acute therapies in routine practice.

Two prospective studies recently demonstrated that MRI is as accurate as CT in detecting hyperacute intraparenchymal hemorrhage in patients presenting with stroke symptoms within 6 hours of onset when gradient echo MRI sequences were used.^{88,141} These findings suggest that MRI may be used as the sole imaging modality to evaluate acute stroke patients, including candidates for thrombolytic treatment. However, in patients presenting with symptoms suggestive of subarachnoid hemorrhage, a CT scan should be performed.

Gradient echo sequences also have the ability to detect clinically silent prior microbleeds not visualized on CT. Some data suggest that microbleeds represent markers of bleeding-prone angiopathy and increased risk of hemorrhagic transformation after antithrombotic and thrombolytic therapy.^{142–144} However, other studies have not found an increased risk in patients with small numbers of microbleeds.¹⁴⁵ The importance of the presence of large numbers of microbleeds on MRI in thrombolytic decision making remains uncertain.

MR angiography is increasingly used for noninvasive screening of the extracranial and intracranial circulation. When compared with digital subtraction angiography for detection of cervical and intracranial stenoses, sensitivity and specificity have ranged from 70% to 100%.^{146,147} In the intracranial vasculature, MR angiography is useful in identifying acute proximal large-vessel occlusions but cannot reliably identify distal or branch occlusions.

A potential diagnostic advantage of MRI over CT in non-tPA situations in suspected stroke has been demonstrated. MRI is better at distinguishing acute, small cortical, small deep, and posterior fossa infarcts; at distinguishing acute from chronic ischemia; and at identifying subclinical satellite ischemic lesions that provide information on stroke mechanism.^{95,124,129,148–167} Limitations of MRI in the acute setting include cost, relatively limited availability of the test, and patient contraindications such as claustrophobia, cardiac pacemakers, or metal implants. Advantages include the avoidance of exposure to ionizing radiation and iodinated contrast and greater spatial resolution.

4. Other Brain Imaging Techniques

Oxygen-15 positron-emission tomography may quantify regional brain perfusion and oxygen consumption.^{168–172} However, logistical and pragmatic considerations limit the application of positron-emission tomography in the setting of acute stroke. Xenon-enhanced CT provides a quantitative measurement of cerebral blood flow by using inhaled xenon but is not currently widely available.¹⁷³ Single-photon emission CT, which is minimally invasive and measures relative cerebral blood flow, might be able to identify thresholds for reversible ischemia and could be helpful in predicting outcomes or monitoring responses to treatment.^{174–176} Limitations include lack of availability, expense, and difficulty associated with tracer preparation.

B. Other Vascular Imaging

In addition to the aforementioned CT and MR angiography, transcranial Doppler ultrasonography, carotid duplex sonography, and catheter angiography have been used to detect intracranial or extracranial vessel abnormalities. Transcranial Doppler ultrasonography and angiography have been used to monitor the effects of thrombolytic therapy over time and can help to determine prognosis.^{177–179}

In patients whose symptoms started <8 hours ago, these tests may be helpful in selecting candidates for intervention. A variety of ancillary tests are available to help clinicians reach accurate pathophysiological and etiologic stroke diagnoses and provide information that can be critical for effective prevention of recurrent stroke.^{180,181} Vascular imaging is

a key component of the evaluation. The selection of tests needs to be tailored to the individual patient and clinical setting.

C. Conclusions and Recommendations

Brain imaging remains a required component of the emergency assessment of patients with suspected stroke. Both CT and MRI are options for imaging the brain, but for most cases and 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 examine the initial scan. In particular, the scan should be evaluated for evidence of early signs of infarction. Baseline CT findings, including the presence of ischemic changes involving more than one third of a hemisphere, have not been predictors of responses to treatment with rtPA when the agent is administered within the 3-hour treatment window. Information about multimodal CT and MRI of the brain suggests that these diagnostic studies may help in the diagnosis and treatment of patients with acute stroke. Imaging of the intracranial or extracranial vasculature in the emergency assessment of patients with suspected stroke is useful at institutions providing endovascular recanalization therapies. The usefulness of vascular imaging for predicting responses to treatment before intravenous administration of thrombolytic agents has not been demonstrated.

Class I Recommendations

1. Imaging of the brain is recommended before initiating any specific therapy to treat acute ischemic stroke (Class I, Level of Evidence A). *This recommendation has not changed from the previous guideline.*
2. In most instances, CT will provide the information to make decisions about emergency management (Class I, Level of Evidence A). *This recommendation has not changed from the previous guideline.*
3. The brain imaging study should be interpreted by a physician with expertise in reading CT or MRI studies of the brain (Class I, Level of Evidence C). *This recommendation has been added since the previous guideline.*
4. Some findings on CT, including the presence of a dense artery sign, are associated with poor outcomes after stroke (Class I, Level of Evidence A). *This recommendation has not changed from the previous guideline.*
5. Multimodal CT and MRI may provide additional information that will improve diagnosis of ischemic stroke (Class I, Level of Evidence A). *This recommendation has been added since the previous guideline.*

Class II Recommendations

1. Nevertheless, data are insufficient to state that, with the exception of hemorrhage, any specific CT finding (including evidence of ischemia affecting more than one third of a cerebral hemisphere) should preclude treatment with rtPA within 3 hours of onset of stroke (Class IIb, Level of Evidence A). *This recommendation has not changed from the previous guideline.*
2. Vascular imaging is necessary as a preliminary step for intra-arterial administration of pharmacological agents, surgical procedures, or endovascular interven-

tions (Class IIa, Level of Evidence B). *This recommendation has not changed from the previous guideline.*

Class III Recommendations

1. Emergency treatment of stroke should not be delayed in order to obtain multimodal imaging studies (Class III, Level of Evidence C). *This recommendation has been added since the previous guideline.*
2. Vascular imaging should not delay treatment of patients whose symptoms started <3 hours ago and who have acute ischemic stroke (Class III, Level of Evidence B). *This recommendation has been added since the previous guideline.*

V. General Supportive Care and Treatment of Acute Complications

A. Airway, Ventilatory Support, and Supplemental Oxygen

Maintaining adequate tissue oxygenation is important in the setting of acute cerebral ischemia. The goals are to prevent hypoxia and potential worsening of the brain injury. The most common causes of hypoxia are partial airway obstruction, hypoventilation, aspiration pneumonia, and atelectasis. Patients with decreased consciousness or signs of brain stem dysfunction have the greatest risk of airway compromise because of impaired oropharyngeal mobility and loss of protective reflexes.^{182–184} The prognosis of patients who require endotracheal intubation generally is poor; ~50% of these patients are dead within 30 days after stroke.^{185,186} Pneumonia is among the leading complications of stroke and is an important cause of death after the cerebrovascular event.¹⁸⁷ It is most likely to develop among patients who are seriously ill, and prevention of early aspiration and protection of the airway may be a way to lessen this complication.

Elective intubation also may help in the management of patients who have severely increased levels of intracranial pressure or have malignant brain edema after stroke.^{185,188} No clinical trial has tested the utility of endotracheal intubation in the management of critically ill patients with stroke, and we anticipate that none will be done. It is generally agreed that an endotracheal tube should be placed if the airway is threatened.^{182,188}

After ischemic stroke, some patients develop Cheyne-Stokes pattern of respiration, with decreases in oxygen saturation that can be readily reversed with oxygen supplementation.¹⁸⁹ A small pilot study found that high-flow oxygen may be associated with a transient improvement in neurological impairments.¹⁹⁰ The results of a controlled study do not support the use of supplemental oxygen at 3 L/min for most patients with acute ischemic stroke.¹⁹¹ However, patients with acute stroke should be monitored with pulse oximetry with a target oxygen saturation level $\geq 92\%$.^{25,192} Most patients with acute stroke do not need supplemental oxygen; however, if pulse oximetry or blood gas determination indicates hypoxia, oxygen should be administered.

Hyperbaric oxygen may be used to treat patients with ischemic neurological symptoms secondary to air embolism or caisson disease.¹⁹³ Studies that have tested the use of hyperbaric oxygen in stroke have been inconclusive or have

shown that the intervention does not improve outcomes.^{194–196} Data from a small trial suggest that hyperbaric oxygen therapy may be harmful.¹⁹⁶ A systematic review found no evidence that hyperbaric oxygen improved outcomes after stroke or brain injury.¹⁹⁷ At present, data do not support the routine use of hyperbaric oxygen in the treatment of patients with acute ischemic stroke.

B. Temperature

Increased body temperature (fever) in the setting of acute ischemic stroke is associated with poor neurological outcome (increased risk of morbidity and mortality), possibly secondary to increased metabolic demands, enhanced release of neurotransmitters, and increased free radical production.^{198–205} The source of any fever should be ascertained. The fever may be secondary to a cause of stroke, such as infective endocarditis, or may represent a complication, such as pneumonia.

Because of the negative effects of fever, lowering an acutely elevated body temperature might improve the prognosis of patients with stroke.²⁰⁶ Measures include antipyretic medications and cooling devices. Small clinical trials have tested the utility of aspirin, ibuprofen, or acetaminophen in lowering body temperatures and in improving outcomes after stroke. Sulter et al²⁰⁷ found that either aspirin or acetaminophen was modestly successful in achieving normothermia but that patients with a temperature $>38^{\circ}\text{C}$ were relatively unresponsive to treatment. In a small, randomized trial, Kasner et al²⁰⁸ 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 al²⁰⁹ tested 2 different doses of acetaminophen in a small clinical trial. They concluded that a daily dosage of 6000 mg might have a potential beneficial effect in lowering body temperature. A small placebo-controlled trial found that acetaminophen might lower body temperature by a mean of 0.26°C within 4 hours of starting treatment.²¹⁰ In another clinical trial, Dippel et al²¹⁰ compared the effects of placebo, ibuprofen, or acetaminophen on body temperature in 75 patients with recent stroke. Although treating fever after stroke makes intuitive sense, no data demonstrate that the use of medications to lower body temperature among either febrile or afebrile patients improves neurological outcomes after stroke. Seeking and treating the source of fever are reasonable.

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, and lessen the impact of excitatory amino acids.²¹¹ Deep hypothermia often is administered to protect the brain in major operative procedures. Mild to moderate hypothermia is associated with improved neurological outcomes among patients with cardiac arrest.^{212–214} 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.²¹⁵ Several small clinical studies have evaluated the feasibility of inducing modest

hypothermia for treatment of patients with acute ischemic stroke.^{216–223} Two small studies evaluated the utility of hypothermia in treating patients with malignant cerebral infarctions; results were mixed.^{224,225} Potential side effects of therapeutic hypothermia include hypotension, cardiac arrhythmias, and pneumonia.²²⁶ In a systematic review of available data, Correia et al²²⁷ could find no evidence that physical cooling would improve outcomes after stroke. Although strong experimental and clinical evidence indicates that induced hypothermia can protect the brain in the presence of 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 neuroprotection section of this statement.

C. Cardiac Monitoring and Treatment

Although patients with heart disease are at high risk for ischemic stroke, both myocardial ischemia and cardiac arrhythmias are potential complications of acute cerebrovascular diseases.^{228,229} Patients with infarctions of the right hemisphere, particularly those involving the insula, may have an increased risk of cardiac complications, presumably secondary to disturbances in autonomic nervous system function.^{78,230–234} ECG changes secondary to stroke include ST-segment depression, QT dispersion, inverted T waves, and prominent U waves.^{235–237} Elevations in blood levels of enzymes attributable to injury to myocardial muscle also may be found.⁷⁹ The most common arrhythmia detected in the setting of stroke is atrial fibrillation, which either may be related to the cause of stroke or may be a complication. Other potentially life-threatening cardiac arrhythmias are relatively uncommon, but sudden death may occur.^{77,238} No clinical trials have tested the utility of cardiac monitoring for most patients with ischemic stroke or the use of cardiac protective agents or medications to prevent serious cardiac arrhythmias. Still, general consensus exists that patients with acute ischemic stroke should have cardiac monitoring for at least the first 24 hours and that any serious cardiac arrhythmia should be treated. The utility of prophylactic administration of medications to prevent cardiac arrhythmias among patients with stroke is not known.

D. Arterial Hypertension

An elevated blood pressure is often detected in the first hours after stroke. Elevations in blood pressure >160 mm Hg are detected in >60% of patients with acute stroke.²³⁹ Both elevated and low blood pressures are associated with poor outcome after stroke.²⁴⁰ For every 10-mm Hg increase >180 mm Hg, the risk of neurological deterioration increased by 40% and the risk of poor outcome increased by 23%. The elevation in blood pressure may be secondary to the stress of the cerebrovascular event, a full bladder, nausea, pain, pre-existing hypertension, a physiological response to hypoxia, or a response to increased intracranial pressure.^{241,242} In a study that correlated acute blood pressure values with other findings in the setting of acute stroke, Vemmos et al²⁴³ found that among patients with most subtypes of ischemic stroke, elevated blood pressure was correlated with a past history of

hypertension or severity of neurological impairments. The same investigators found a U-shaped relationship between death and admission blood pressure; both elevated and low admission levels were associated with high rates of early and late death.²⁴³ They also correlated death due to brain injury and brain edema with high initial blood pressure levels. Castillo et al²⁴⁰ have reported similar findings. Using the data from the Glycine Antagonist in Neuroprotection (GAIN) study, Aslanyan et al²⁴⁴ found that an elevated baseline mean arterial blood pressure was not independently associated with an unfavorable outcome after stroke. However, elevations in mean blood pressure during the first days after stroke had an unfavorable effect on outcomes. The same investigators showed that an elevated pulse pressure (the difference between systolic and diastolic blood pressure values) was independently associated with poor outcomes 3 months after stroke.²⁴⁵

Theoretical reasons for lowering blood pressure include reducing the formation of brain edema, lessening the risk of hemorrhagic transformation of the infarction, preventing further vascular damage, and forestalling early recurrent stroke. In addition, urgent antihypertensive therapy may be needed to treat patients with stroke who also have hypertensive encephalopathy, aortic dissection, acute renal failure, acute pulmonary edema, or acute myocardial infarction.^{242,246} Conversely, aggressive treatment of blood pressure may lead to neurological worsening by reducing perfusion pressure to ischemic areas of the brain.^{242,247,248}

In a majority of patients, a decline in blood pressure occurs within the first hours after stroke even without any specific medical treatment.²⁴¹ The blood pressure often falls spontaneously when the patient is moved to a quiet room, the patient is allowed to rest, the bladder is emptied, or the pain is controlled. In addition, treatment of increased intracranial pressure may result in a decline in arterial blood pressure.

There are several questions about the management of arterial hypertension in the setting of acute stroke.^{249–251} Should patients previously taking antihypertensive medications continue taking them during the first hours after stroke? Are some of these medications contraindicated or indicated? Should new antihypertensive agents be started? What level of blood pressure would mandate initiation of new antihypertensive treatment? Which medication should be administered in this situation? Unfortunately, definite answers to these questions are not available. Since the publication of the last guidelines, several clinical studies have provided additional information.

A randomized trial testing nimodipine found that unfavorable outcomes among patients treated with the medication were associated with lowering of the blood pressure.^{252,253} Reanalyzing some of the data from the studies of nimodipine, Fogelholm et al²⁵⁴ noted that favorable outcomes were associated with higher levels of blood pressure among patients with mild to moderate strokes receiving nimodipine. The converse was true among patients with severe strokes. In a study that involved 115 patients admitted within 24 hours of stroke, Oliveira-Filho et al²⁵⁵ noted that systolic blood pressure dropped by $\approx 28\%$ during the first day whether or not medications were prescribed. They noted an adverse effect on outcomes with lowering of the blood pressure, with an association found with degree in decline. Each

10% decline was associated with an increased odds ratio of 1.89 in unfavorable outcomes. The impact was similar to the effects of age or NIHSS scores. Castillo et al²⁴⁰ noted that drops in either systolic or diastolic blood pressure of >20 mm Hg were associated with early neurological worsening, higher rates of poor outcomes or death, and larger volumes of infarctions. They noted that the early administration of antihypertensive agents to patients with systolic blood pressures >180 mm Hg was associated with a marked increase in likelihood of early deterioration, poor neurological outcome, or death.

Several small inconclusive studies have tested calcium channel-blocking agents, angiotensin-converting enzyme inhibitors, diuretics, β -blockers, and nitrates, with generally inconclusive or conflicting results.^{256,257} A multicenter, placebo-controlled trial tested the utility of candesartan when started 1 day after stroke.²⁵⁸ The dosage of medication was increased on day 2 if the patient's systolic blood pressure was >160 mm Hg systolic or >100 mm Hg diastolic. Rescue therapy with intravenous antihypertensive agents was permitted for patients with severely elevated blood pressures. At day 7, other antihypertensive agents could be administered to treat persisting elevated blood pressures. The trial was halted prematurely because of a higher rate of deaths and recurrent vascular events in the placebo-treated group. However, the differences in outcomes were not seen in the first few months after stroke, and the divergence between treatment groups was seen only after 1 year. In a small study, patients were given either captopril or amlodipine for treatment of hypertension beginning 1 day after stroke; moderate reductions in blood pressure were associated with improved short-term outcomes.²⁵⁹ In another small, randomized study, Eames et al²⁶⁰ found no major reduction in blood pressure among patients treated with bendroflumazide, and they concluded that this agent was not effective in treating hypertension after stroke. Large, well-designed trials are needed to clarify the management of arterial hypertension after acute stroke. A trial testing the utility of antihypertensive therapy in the setting of stroke (Controlling Hypertension and Hypotension Immediately Post-Stroke [CHHIPS]) is ongoing.²⁶¹

Because of the lack of unambiguous data, the appropriate treatment of arterial hypertension in the setting of acute ischemic stroke remains controversial. Although severe hypertension may be considered an indication for treatment, no data define the levels of arterial hypertension that mandate emergency management.²⁴⁷ However, the aforementioned data suggest that the systolic blood pressure level that would prompt treatment would be >180 mm Hg.²⁴⁰ A systolic blood pressure >185 mm Hg or a diastolic blood pressure >110 mm Hg is a contraindication to intravenous administration of rtPA.^{66,262} Still, it is not clear whether those values should be the threshold for starting emergency treatment outside the setting of administration of rtPA. Although no definitive data from controlled trials are available, in the absence of other organ dysfunction necessitating rapid reduction in blood pressure or in the setting of thrombolytic therapy, there is little scientific evidence and no clinically established benefit for rapid lowering of blood pressure among persons with acute ischemic stroke.²⁴⁷ Some data indicate that rapid and steep reductions in blood pressure

TABLE 10. Approach to Arterial Hypertension in Acute Ischemic Stroke

Indication that patient is eligible for treatment with intravenous rtPA or other acute reperfusion intervention

Blood pressure level

Systolic >185 mm Hg or diastolic >110 mm Hg

Labetalol 10 to 20 mg IV over 1 to 2 minutes, may repeat $\times 1$;

or

Nitropaste 1 to 2 inches;

or

Nicardipine infusion, 5 mg/h, titrate up by 2.5 mg/h at 5- to 15-minute intervals, maximum dose 15 mg/h; when desired blood pressure attained, reduce to 3 mg/h

If blood pressure does not decline and remains >185/110 mm Hg, do not administer rtPA

Management of blood pressure during and after treatment with rtPA or other acute reperfusion intervention

Monitor blood pressure every 15 minutes during treatment and then for another 2 hours, then every 30 minutes for 6 hours, and then every hour for 16 hours

Blood pressure level

Systolic 180 to 230 mm Hg or diastolic 105 to 120 mm Hg

Labetalol 10 mg IV over 1 to 2 minutes, may repeat every 10 to 20 minutes, maximum dose of 300 mg;

or

Labetalol 10 mg IV followed by an infusion at 2 to 8 mg/min

Systolic >230 mm Hg or diastolic 121 to 140 mm Hg

Labetalol 10 mg IV over 1 to 2 minutes, may repeat every 10 to 20 minutes, maximum dose of 300 mg;

or

Labetalol 10 mg IV followed by an infusion at 2 to 8 mg/min;

or

Nicardipine infusion, 5 mg/h, titrate up to desired effect by increasing 2.5 mg/h every 5 minutes to maximum of 15 mg/h

If blood pressure not controlled, consider sodium nitroprusside

might be harmful. Pending more data, the consensus of the panel is that emergency administration of antihypertensive agents should be withheld unless the diastolic blood pressure is >120 mm Hg or unless the systolic blood pressure is >220 mm Hg (Table 10). The panel recognizes that no data show that these values are especially dangerous and emergency treatment is needed. However, the panel remains concerned by the evidence that aggressive lowering of blood pressure among patients may cause neurological worsening, and the goal is to avoid overtreating patients with stroke until definitive data are available.

When treatment is indicated, lowering the blood pressure should be done cautiously. Some strokes may be secondary to hemodynamic factors, and a declining blood pressure may lead to neurological worsening. A reasonable goal would be to lower blood pressure by 15% to 25% within the first day.²⁶³ Because no data support the administration of any specific antihypertensive agent in the setting of acute ischemic stroke, the treating physician should select medications for lowering blood pressure on a case-by-case basis. The recommendations in Table 10 are based on consensus and reflect the goal of rapidly reducing blood pressure, but, at the same time, the potential for a rapid reversal if the drop in blood pressure

leads to neurological worsening. The selection of an agent may be influenced by other medical conditions; for example, the presence of asthma would contraindicate the administration of a β -blocker. Because of a prolonged effect and the potential for a precipitous decline in blood pressure associated with the sublingual administration of nifedipine, this agent with this route of administration is not recommended.²⁶⁴

Among patients who are candidates for treatment with intravenous rtPA, attention to management of blood pressure is critical before, during, and after the administration of the medication.²⁶³ Excessively high blood pressure is associated with an increased risk of symptomatic hemorrhagic transformation.^{66,262,265,266} Failure to meet the blood pressure parameters of previous guidelines may be one of the explanations for an increased risk of hemorrhagic complications after administration of rtPA.^{267–269} Presumably, similar risks of bleeding will be associated with elevations of blood pressure among patients receiving other acute pharmacological or mechanical interventions to improve the perfusion to the brain. The suggestion to withhold such therapies among patients with markedly elevated blood pressure is based on potential safety risks. Conversely, excessively high blood pressures could be lowered successfully with medications to permit treatment with intravenous rtPA.

Arterial hypertension is a recognized risk factor for stroke and recurrent stroke. Many patients were taking medications before their stroke or are found to have sustained hypertension after their stroke. These patients will need long-term antihypertensive treatment; the primary question is the timing of the institution of such therapy. Limited data are available to guide these decisions. On the basis of the trial of candesartan, it appears that medications can be administered with a reasonable degree of safety when started ≈ 1 day after stroke.²⁵⁸ The timing of the reinstitution of treatment and the selection of medications will depend on the patient's neurological status, the underlying stroke mechanism, the patient's ability to swallow medications, and the presence of concomitant diseases. Presumably, most patients with mild to moderate strokes who are not at high risk for increased intracranial pressure may have their prestroke antihypertensive medications restarted 24 hours after their vascular event. The panel strongly endorses clinical research that will provide information about the safety and efficacy of restarting antihypertensive therapy among patients with stroke.

E. Arterial Hypotension

Persistent arterial hypotension is rare among patients with acute ischemic stroke, but it is associated with an increased likelihood of an unfavorable outcome.²⁷⁰ Castillo et al²⁴⁰ noted that the rates of neurological worsening, poor neurological outcomes, or death increased when the baseline systolic blood pressure was <100 mm Hg or the diastolic blood pressure was <70 mm Hg. The cause of hypotension should be sought; among the potential causes are aortic dissection, volume depletion, blood loss, and decreased cardiac output secondary to myocardial ischemia or cardiac arrhythmias. Patients with stroke may have depleted blood volume. Correction of hypovolemia and optimization of

cardiac output are important priorities during the first hours after stroke. Treatment includes volume replacement with normal saline and correction of cardiac arrhythmias, such as slowing a ventricular response to rapid atrial fibrillation. If these measures are ineffective, vasopressor agents such as dopamine may be used. Trials have tested the utility of volume expansion and drug-induced hypertension for treatment of acute ischemic stroke. These measures are described later in the present guideline.

F. Hypoglycemia

Because hypoglycemia may produce neurological signs that mimic ischemic stroke and because hypoglycemia itself may lead to brain injury, prompt measurement of the serum glucose concentration and rapid correction of a low serum glucose level are important.

G. Hyperglycemia

Hyperglycemia will be detected on admission in approximately one third of patients with stroke.^{271–273} Most patients have moderate elevations of glucose levels.²⁷⁴ Clinical studies demonstrate that the presence of hyperglycemia is associated with poor outcomes after ischemic stroke, including among patients treated with thrombolytic agents.^{275–279} A history of diabetes mellitus also is associated with a poorer outcome after stroke.^{280,281}

The detrimental effects of hyperglycemia are not clearly understood but include increasing tissue acidosis secondary to anaerobic glycolysis, lactic acidosis, and free radical production.^{281,282} Hyperglycemia also may affect the blood-brain barrier and the development of brain edema²⁸¹ and may be associated with an increased risk of hemorrhagic transformation of the infarction.²⁸³ Unfortunately, the contribution of hyperglycemia to poor outcomes may be affected by other factors.²⁸⁴ Elevations of blood glucose concentration may be secondary to the stress of the acute cerebrovascular event.²⁸⁵ In particular, hyperglycemia after stroke in nondiabetic patients may be a stress response.²⁸⁵ Candelise et al²⁸⁶ found that hyperglycemia is a marker of a more severe stroke. Thus, the poor outcomes among patients with hyperglycemia may in part reflect the seriousness of the vascular event itself. Recent clinical and imaging studies have highlighted the importance of hyperglycemia as a negative prognostic factor.^{271,278–280,282} Baird et al²⁸⁰ found that persistent hyperglycemia (blood glucose level >200 mg/dL) during the first 24 hours after stroke independently predicted expansion of the volume of ischemic stroke and poor neurological outcomes. These reports provide reasonable evidence that persistent elevations of blood glucose levels are associated with neurological worsening.^{281,287} These data suggest that management of hyperglycemia is an important part of acute management of patients with ischemic stroke. The outstanding issues relate to the effectiveness of management of stroke-associated hyperglycemia in improving outcomes after stroke and the level of glucose concentration that should be sought during the first 24 hours. On the basis of the aforementioned data, the panel concluded that the level of hyperglycemia that previously mandated emergency treatment in the setting of stroke was too high. The exact level of blood glucose that should

prompt interventions is not known. A reasonable approach would be to initiate treatment among patients with a blood glucose level >200 mg/dL. The management of hyperglycemia among patients with stroke likely will be influenced by the approach to treating elevated blood glucose levels among patients with other critical illnesses, including patients who have had cardiac arrest. The changes are dramatic. Several studies have looked at the utility of intensive insulin protocols in treating critically ill patients with a broad range of illnesses.^{288–293} In general, the desired level of blood glucose has been in the range of 80 to 140 mg/dL. Frequent monitoring of blood glucose levels and adjustments of insulin are required. These studies have demonstrated a reduction in death and important complications, including infections and renal failure, with aggressive management of hyperglycemia. The frequency of hypoglycemic episodes appears to be low. Physicians treating patients with severe stroke should be aware of the new regimens for treating hyperglycemia. Gray et al²⁷⁴ found that plasma glucose levels spontaneously decline in many patients. A small clinical trial tested the safety of short-term administration of glucose, insulin, and potassium to patients with moderate hyperglycemia.²⁹⁴ The intervention could be given safely, but plasma glucose levels were not significantly lower than in the control group. A subsequent report about a larger cohort treated by the same investigators found that infusions of glucose, insulin, and potassium significantly reduced blood pressure, but no differences in outcomes were noted 7 days after stroke.²⁹⁵ Bruno et al²⁹⁶ treated 24 patients with markedly elevated serum glucose levels (mean 14.7 mmol/L) within 12 hours of onset of stroke. With insulin infusions that required frequent adjustments in response to serum levels, they were able to achieve desired glucose control within 5 hours. Symptomatic hypoglycemia occurred in 5 patients. It is unclear whether the intervention affected outcomes. A British trial (United Kingdom Glucose Insulin in Stroke Trial) is testing the utility of a strategy of achieving euglycemia after stroke.²⁷⁴ Despite the lack of data to guide decisions about management, consensus exists that hyperglycemia should be controlled after stroke.²⁹⁷ A reasonable goal would be to treat those patients' elevated glucose concentrations (140 to 180 mg/dL). The approach would be similar to that prescribed for other acutely ill patients with concomitant hyperglycemia.

H. Conclusions and Recommendations

Most of the recommendations about general acute management are based on limited data. Some of the aspects of acute management may never be tested in clinical trials, whereas other aspects of treatment, such as the best strategy for treatment of hyperglycemia or arterial hypertension, likely will be clarified by ongoing or future clinical research. Pending such trials, many of the suggestions that follow are based on consensus and thus are Grade C recommendations.

Class I Recommendations

1. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction causing compromise of the airway (Class

I, Level of Evidence C). *This recommendation has not changed from previous statements.*

2. Hypoxic patients with stroke should receive supplemental oxygen (Class I, Level of Evidence C). *This recommendation has not changed since the previous guideline.*
3. It is generally agreed that sources of fever should be treated and antipyretic medications should be administered to lower temperature in febrile patients with stroke (Class I, Level of Evidence C). *This recommendation has not changed from previous statements.* Medications such as acetaminophen can lower body temperature modestly, but the effectiveness of treating either febrile or nonfebrile patients to improve neurological outcomes is not established. Additional research on utility of emergency administration of antipyretic medications is under way.
4. General agreement supports the use of cardiac monitoring to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. It is generally agreed that cardiac monitoring should be performed during the first 24 hours after onset of ischemic stroke (Class I, Level of Evidence B). *This recommendation has not changed from previous statements.*
5. The management of arterial hypertension remains controversial. 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, it is generally agreed that a cautious approach to the treatment of arterial hypertension should be recommended (Class I, Level of Evidence C). Patients who have other medical indications for aggressive treatment of blood pressure should be treated. *This recommendation has not changed from previous statements.*
6. Patients who have elevated blood pressure and are otherwise eligible for treatment of rtPA may have their blood pressure lowered 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 lytic therapy is started. *This recommendation has not changed from previous statements.* If medications are given to lower blood pressure, the clinician should be sure that the blood pressure is stabilized at the lower level before treating with rtPA and maintained below 180/105 mm Hg for at least the first 24 hours after intravenous rtPA treatment. Because the maximum interval from stroke onset until treatment with rtPA is short, many patients with sustained hypertension above recommended levels cannot be treated with intravenous rtPA.
7. 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 thrombolysis (Class I, Level of Evidence C). *This recommendation has been added since the previous guideline.*
8. It is generally agreed that patients with markedly elevated blood pressure may have their blood pressure lowered. A reasonable goal would be to lower blood pressure by $\approx 15\%$ 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). *This recommendation has changed from previous statements in that a potential goal for lowering blood pressure is now included.* Research testing the effects of early treatment of arterial hypertension on outcomes after stroke is under way. The panel looks forward to any data that will clarify this management decision.

9. It is generally agreed that the cause of arterial hypotension in the setting of acute stroke should be sought. Hypovolemia should be corrected with normal saline, and cardiac arrhythmias that might be reducing cardiac output should be corrected (Class I, Level of Evidence C). *This recommendation was not included in previous statements.* The utility of volume expansion and the use of medications to increase blood pressure to treat ischemic stroke are discussed elsewhere in the present guideline.
10. It is generally agreed that hypoglycemia should be treated in patients with acute ischemic stroke (Class I, Level of Evidence C). The goal is to achieve normoglycemia. Marked elevation of blood glucose levels should be avoided. *This recommendation was included in previous statements.*

Class II Recommendations

1. No data are available to guide selection of medications for the lowering of blood pressure in the setting of acute ischemic stroke. The recommended medications and doses included in Table 10 are based on general consensus (Class IIa, Level of Evidence C). *The recommendations in Table 10 have changed from the previous statements.*
2. Evidence from one clinical trial indicates that initiation of antihypertensive therapy within 24 hours of stroke is relatively safe. Thus, it is generally agreed that antihypertensive medications should be restarted at ≈ 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). *This recommendation was not included in previous statements.*
3. Evidence indicates that persistent hyperglycemia (>140 mg/dL) during the first 24 hours after stroke is associated with poor outcomes, and thus it is generally agreed that hyperglycemia should be treated in patients with acute ischemic stroke. The minimum threshold described in previous statements likely was too high, and lower serum glucose concentrations (possibly >140 to 185 mg/dL) probably should trigger administration of insulin, similar to the procedure in other acute situations accompanied by hyperglycemia (Class IIa, Level of Evidence C). *This is a change from previous statements.* Close monitoring of glucose concentrations with adjustment of insulin doses to avoid hypoglycemia is recommended. Simultaneous administration of glucose and potassium also may be appropriate. The results of ongoing research should clarify the management of hyperglycemia after stroke.

Class III Recommendations

1. Nonhypoxic patients with acute ischemic stroke do not need supplemental oxygen therapy (Class III, Level of Evidence B). *This recommendation has not changed from previous statements.*
2. 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). *This recommendation has changed from previous statements.*
3. Although data demonstrate the efficacy of hypothermia for improving neurological outcomes after cardiac arrest, the utility of induced hypothermia for the treatment of patients with ischemic stroke is not established. At the present time, insufficient evidence exists to recommend hypothermia for treatment of patients with acute stroke (Class III, Level of Evidence B). *This recommendation has not changed from previous statements.* Additional research on the safety and efficacy of induced hypothermia for treatment of patients with stroke is under way.

VI. Intravenous Thrombolysis

A. Recombinant Tissue Plasminogen Activator

Intravenous thrombolytic therapy for acute stroke is now generally accepted.²⁹⁸ The US Food and Drug Administration (FDA) approved the use of intravenous rtPA in 1996, partly on the basis of the results of the NINDS rtPA Stroke Study, in which 624 patients with ischemic stroke were treated with placebo or rtPA (0.9 mg/kg IV, maximum 90 mg) within 3 hours of symptom onset, with approximately one half treated within 90 minutes.⁶⁶ The study was conducted in 2 parts. In 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 part II, the pivotal efficacy trial, the primary end point was a global odds ratio for a favorable outcome, defined as complete or nearly complete neurological recovery 3 months after stroke. Favorable outcomes were achieved in 31% to 50% of patients treated with rtPA, as compared with 20% to 38% of patients given placebo. The benefit was similar 1 year after stroke.²⁹⁹ The major risk of treatment was symptomatic brain hemorrhage, which occurred in 6.4% of patients treated with rtPA and 0.6% of patients given placebo. However, the death rate in the 2 treatment groups was similar at 3 months (17% versus 20%) and 1 year (24% versus 28%).^{66,299} Although the presence of edema or mass effect on baseline CT scan was associated with higher risk of symptomatic intracranial hemorrhage, follow-up study demonstrated that the presence of early ischemic changes on CT scan was not associated with adverse outcome.^{100,266} Indeed, in the Australian trial of streptokinase, early CT evidence of edema was not associated with an increased risk of hemorrhagic conversion.³⁰¹ The likelihood of favorable outcome also was affected by the severity of deficits and the patient's age. Patients with mild to moderate strokes (NIHSS score <20) and persons younger than 75 years of age had the greatest potential for a favorable response to treatment.³⁰² The chances of a complete or nearly

complete recovery among patients with severe stroke (NIHSS score of ≥ 20) improved with treatment, but overall success in this group of critically ill patients was low.³⁰² In 2 large trials, the European Cooperative Acute Stroke Study (ECASS) and ECASS-II, intravenous rtPA was not more effective than placebo in improving neurological outcomes 3 months after stroke.^{303,304} The dosage of rtPA used in ECASS was marginally higher than that used in the NINDS trials, and patients were treated up to 6 hours after stroke. Patients with CT evidence of low attenuation (edema and/or ischemia) involving more than one third of the territory of the MCA were less likely to have a good outcome after treatment with rtPA than were those who received placebo.^{98,305} However, the numbers were small, and the difference did not reach statistical significance. A post hoc analysis concluded that the patients treated within 3 hours appeared to benefit from rtPA.³⁰⁶ In the ECASS-II trial, 800 patients were assigned randomly to treatment with either rtPA (0.9 mg/kg IV) or placebo. More than one third of the patients in each group made an excellent recovery, and no significant benefit was noted from treatment. A post hoc analysis of ECASS-II showed that the likelihood of either death or dependency was lower among the patients treated with rtPA.³⁰³ The trial included vigorous methodology to avoid recruitment of patients with CT changes consistent with multilobar infarctions.⁹⁸ As a result, the strokes among the patients admitted in ECASS-II were less severe than in the other studies, and the generally more favorable prognosis among patients may have reduced the likelihood of detecting a therapeutic effect. Still, the rate of symptomatic intracranial hemorrhage was increased with rtPA treatment (8.8% versus 3.4%). An American trial tested rtPA up to 5 hours after stroke.³⁰⁷ Results were similar in that approximately one third of the patients in both treatment groups made an excellent recovery. The rate of symptomatic hemorrhage was higher in the treatment group (7% versus 1.1%). Subsequent to the approval of rtPA for treatment of patients with acute ischemic stroke, several groups reported on the utility of the treatment in a community setting.^{269,308–313} Some groups reported rates of intracranial hemorrhage and favorable outcomes that are similar to those found in the NINDS trials, but others have not. It is now clear that the risk of hemorrhage is proportional to the degree to which the NINDS protocol is not followed.^{269,314,315} Besides a risk of intracranial hemorrhage, other potential adverse experiences include systemic bleeding, myocardial rupture if the agent is given within a few days of acute myocardial infarction, and reactions such as anaphylaxis or angioedema, although these events are rare.²⁹⁸ Debate about time of initiation of rtPA treatment merits attention. The NINDS investigators reported a time-to-treatment interaction in a subgroup analysis of the NINDS rtPA Trial.⁶⁰ Treatment with rtPA initiated within 90 minutes of symptom onset was associated with an odds ratio of 2.11 (95% confidence interval, 1.33 to 3.55) for favorable outcome at 3 months as compared with placebo. In comparison, the odds ratio for good outcome at 3 months for treatment with rtPA initiated within 90 to 180 minutes was 1.69 (95% confidence interval, 1.09 to 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 rtPA for acute stroke confirmed a time effect, but the upper limit of the treatment window may be as late as 5 to 6 hours.³¹⁶ Investigation of the early time epoch in the NINDS trial revealed a potential confounder in the original data: 19% of the patients treated with 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 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.³¹⁷ The adjusted odds ratio for 3-month favorable outcome (odds ratios for treatment compared with placebo) for the subgroup of patients from the NINDS rtPA Stroke Trial 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 rtPA therapy positively influenced outcome. In a separate analysis by an independent group, an identical finding was reached: Baseline imbalances in the numbers of patients with mild stroke do not explain the overall study result.³¹⁸

B. Other Thrombolytic Agents

Clinical trials of streptokinase were halted prematurely because of unacceptably high rates of hemorrhage, and this agent should not be used.^{319–322} Other intravenously administered thrombolytic agents, including reteplase, urokinase, anistreplase, and staphylokinase, might have been considered for treatment of patients with acute ischemic stroke. None of these agents has been tested extensively. Tenecteplase appears promising as an effective thrombolytic with fewer bleeding complications than wild-type rtPA, but pivotal studies are under way.³²³ Desmoteplase has been tested in a pilot study; results appear promising.^{189,324}

C. Defibrinogenating Enzymes

Ancrod, an enzyme derived from snake venom that degrades fibrinogen, was tested in a series of clinical studies. A preliminary trial found that ancrod treatment improved outcomes after stroke, with patients with blood fibrinogen levels < 100 mg/dL having the best responses.^{325,326} A subsequent study found a favorable benefit-risk profile for patients. Further studies of ancrod continue, given the potentially favorable combination of antithrombotic activity and mild thrombolytic effect.^{327,328}

D. Conclusions and Recommendations

Intravenous administration of rtPA is the only FDA-approved medical therapy for treatment of patients with acute ischemic stroke.³ Its use is associated with improved outcomes for a broad spectrum of patients who can be treated within 3 hours of stroke onset. Earlier treatment (ie, within 90 minutes) may be more likely to result in a favorable outcome. Later treatment, at 90 to 180 minutes, also is beneficial. Patients

TABLE 11. Characteristics of Patients With Ischemic Stroke Who Could Be Treated With rtPA

Diagnosis of ischemic stroke causing measurable neurological deficit
The neurological signs should not be clearing spontaneously.
The neurological signs should not be minor and isolated.
Caution should be exercised in treating a patient with major deficits.
The symptoms of stroke should not be suggestive of subarachnoid hemorrhage.
Onset of symptoms <3 hours before beginning treatment
No head trauma or prior stroke in previous 3 months
No myocardial infarction in the previous 3 months
No gastrointestinal or urinary tract hemorrhage in previous 21 days
No major surgery in the previous 14 days
No arterial puncture at a noncompressible site in the previous 7 days
No history of previous intracranial hemorrhage
Blood pressure not elevated (systolic <185 mm Hg and diastolic <110 mm Hg)
No evidence of active bleeding or acute trauma (fracture) on examination
Not taking an oral anticoagulant or, if anticoagulant being taken, INR ≤ 1.7
If receiving heparin in previous 48 hours, aPTT must be in normal range.
Platelet count $\geq 100\,000\text{ mm}^3$
Blood glucose concentration $\geq 50\text{ mg/dL}$ (2.7 mmol/L)
No seizure with postictal residual neurological impairments
CT does not show a multilobar infarction (hypodensity $>1/3$ cerebral hemisphere).
The patient or family members understand the potential risks and benefits from treatment.

INR indicates international normalized ratio; aPTT, activated partial thromboplastin time.

with major strokes (NIHSS score >22) have a very poor prognosis, but some positive treatment effect with rtPA has been documented.³²⁹ Because the risk of hemorrhage is considerable among patients with severe deficits, the decision to treat with rtPA should be made with caution. Treatment with rtPA is associated with symptomatic intracranial hemorrhage, which may be fatal. In the original NINDS trials, the risk of symptomatic bleeding was $\approx 6\%$.¹⁰⁰ Recent community-based studies and registries report lower rates of hemorrhage.^{269,330–333} Recommendations for the management of intracranial hemorrhage after treatment with rtPA are provided in the AHA Stroke Council's updated guideline statement on management of intracerebral hemorrhage, which is being issued contemporaneously with this statement. The best methods for preventing bleeding complications are careful selection of patients and scrupulous ancillary care, especially close observation, and monitoring of the patient with early treatment of arterial hypertension. Factors that affect decisions about administration of rtPA are outlined in Table 11, and the treatment regimen for administration of rtPA is included in Table 12. Case series have suggested that thrombolysis may be used in patients with seizures at the time of presentation when evidence suggests that residual deficits are due to ischemia rather than the postictal state.^{334,335} The use of anticoagulants and antiplatelet agents should be delayed for 24 hours after treatment.

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.
Perform neurological assessments every 15 minutes during the infusion and every 30 minutes thereafter for the next 6 hours, then hourly until 24 hours after treatment.
If the patient develops severe headache, acute hypertension, nausea, or vomiting, discontinue the infusion (if rtPA is being administered) and obtain emergency CT scan.
Measure blood pressure every 15 minutes for the first 2 hours and subsequently every 30 minutes for the next 6 hours, then hourly until 24 hours after treatment.
Increase the frequency of blood pressure measurements if a systolic blood pressure is ≥ 180 mm Hg or if a diastolic blood pressure is ≥ 105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels (see Table 10).
Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters.
Obtain a follow-up CT scan at 24 h before starting anticoagulants or antiplatelet agents.

Although written consent is not necessary before administration of rtPA for treatment of stroke, a full discussion of the potential risks and benefits of treatment with rtPA with the family and the patient if possible is recommended.

Although other thrombolytic agents, including defibrinogenating drugs, are being tested, none has been established as effective or as a replacement for rtPA.

Class I 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 Table 11 (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 the patient is described in Table 12. *This recommendation has not changed from previous statements.*
- 2. Besides bleeding complications, physicians should be aware of the potential side effect of angioedema that may cause partial airway obstruction (Class I, Level of Evidence C).** *This recommendation has been added since the previous guidelines.*

Class II Recommendations

- 1. A patient whose blood pressure can be lowered safely with antihypertensive agents may be eligible for treatment, and the physician should assess the stability of the blood pressure before starting rtPA (Class IIa, Level of Evidence B).** An elevated blood pressure that requires a continuous infusion of sodium nitroprusside may not be sufficiently stable for the patient to receive rtPA. However, because time is limited, most patients with markedly elevated blood pressure cannot be managed adequately and still meet the 3-hour requirement.

This recommendation has not changed from previous guidelines.

2. A patient with a seizure at the time of onset of stroke may be eligible for treatment as long as the physician is convinced that residual impairments are secondary to stroke and not a postictal phenomenon (Class IIa, Level of Evidence C). *This recommendation differs from the previous statements and represents a broadening of eligibility for treatment with rtPA.*

Class III Recommendations

1. The intravenous administration of streptokinase for treatment of stroke is not recommended (Class III, Level of Evidence A). *This recommendation has not changed from previous guidelines.*
2. The intravenous administration of anisoylated plasminogen activator, tenecteplase, reteplase, desmoteplase, urokinase, or other thrombolytic agents outside the setting of a clinical trial is not recommended (Class III, Level of Evidence C). *This recommendation is new.*

VII. Intra-Arterial Thrombolysis

The 2003 guidelines concluded that intra-arterial administration of at least one specific thrombolytic agent, recombinant prourokinase, appears to be of some benefit in treatment of carefully selected patients with acute ischemic stroke secondary to occlusion of the MCA.² This conclusion was based on the results of a prospective, randomized, placebo-controlled phase III study testing the effectiveness of intra-arterial thrombolysis with prourokinase among patients with stroke of <6 hours' duration secondary to occlusion of the MCA.³³⁶ In the primary intent-to-treat analysis, 40% of the 121 patients treated with recombinant prourokinase and 25% of the 59 control patients had a modified Rankin Scale score of 0 to 2 at 90 days ($P=0.04$). Recanalization of the MCA was achieved in 66% of the patients treated with recombinant prourokinase and 18% of the patients in the control group ($P<0.001$). Intracranial hemorrhage with neurological deterioration within 24 hours of treatment occurred in 10% of patients treated with recombinant prourokinase and in 2% of the control group ($P=0.06$). No difference in overall death rate was seen between the 2 groups. The FDA has not approved the drug, and recombinant prourokinase is not currently available for clinical use. Extrapolation to rtPA, the widely used intravenous cerebral thrombolytic drug, and to urokinase, which is chemically similar to the prourokinase prodrug, is based on consensus and case series data. Extrapolation to other lytic agents is more speculative.

The intra-arterial approach has been promoted because a high concentration of thrombolytic agents may be delivered into the thrombus.³³⁷ Despite the uncontrolled observation that recanalization rates may be higher with intra-arterial thrombolysis than with intravenous thrombolysis,³³⁷ clinical benefit may be counterbalanced by delays to initiating treatment with the intra-arterial approach. On the basis of 1999–2001 National Hospital Discharge Survey data,³³⁸ there were 1 796 513 admissions for ischemic stroke between 1999 and 2001. Of these admissions, 1314 (0.07%) underwent intra-arterial thrombolysis, and 11 283 (0.6%) underwent intravenous thrombolysis. A second estimate is derived from the

Greater Buffalo and Erie County stroke study that suggested that intravenous or intra-arterial thrombolysis was used in 1.4% and 0.3% of 1590 patients admitted in 11 hospitals.³²⁹ Intra-arterial administration of rtPA to patients with ischemic stroke who are expected to have limited response to intravenous therapy has gained popularity. Potential reasons include severe neurological deficits (NIHSS score ≥ 10), presentation between 3 and 6 hours after symptom onset, recent history of major surgical procedures, and occlusion of major cervical and/or intracranial vessels. However, only limited data support the usefulness of intra-arterial therapy in these situations.

New evidence since the publication of the last guidelines is summarized in subsequent sections. More emphasis has been placed on deriving information from the initial angiogram, with emphasis on the site of occlusion and identification of collateral supply to the affected region. New data suggest that this information may be incorporated into a scheme to stratify patients into the expected rate of recanalization and short-term outcome after intra-arterial thrombolysis.^{337,339,340}

A small randomized, multicenter trial compared intravenous urokinase with intra-arterial urokinase within the first 6 hours of acute ischemic stroke.³⁴¹ Patients fulfilling the selection criteria were randomly assigned to receive urokinase 900 000 U via intravenous ($n=14$) or intra-arterial ($n=13$) approach. The study was terminated prematurely because 7 patients (26%) died: 4 in the intravenous group and 3 in the intra-arterial group. Although patients treated with intra-arterial therapy showed greater and earlier improvement, no significant difference was seen in primary and secondary outcomes. Recently, a cohort study was reported from Japan's Multicenter Stroke Investigator's Collaboration (J-MUSIC).³⁴² The modified Rankin Scale score at discharge was lower in the urokinase group than in the control group (mean, 2.8 in the urokinase group versus 3.3 in the control group; $P=0.03$). A favorable outcome (modified Rankin Scale score of 0 to 2) was more frequently observed in the urokinase group (51%) than in the control group (34%; $P=0.01$). A third study³⁴³ randomized 16 patients with angiographic evidence of posterior circulation vascular occlusion who presented within 24 hours of symptom onset to either intra-arterial prourokinase or conservative management. Some imbalance between groups existed, with greater severity of deficit at baseline observed in the treatment arm. Good outcomes were observed in 4 of 8 patients who received intra-arterial urokinase and in 1 of 8 patients in the control group.

It has been proposed that patients be selected for intra-arterial thrombolysis on the basis of radiological criteria. A nonrandomized study³⁴⁴ compared outcomes of 83 patients with or without a hyperdense artery sign on initial CT scan treated with intravenous or intra-arterial rtPA. An increased likelihood of favorable outcomes, indicated by a significant improvement in the discharge NIHSS score, was noted with intra-arterial rtPA treatment, irrespective of the presence or absence of hyperdense artery sign. A less favorable outcome in discharge NIHSS score was noted with intravenous rtPA in patients with a hyperdense artery sign than in those without the hyperdense artery sign. This suggests that differential response to intravenous rtPA in patients with hyperdense

artery sign³⁴⁴ on initial CT scan is not observed with intra-arterial thrombolysis.

A. Conclusions and Recommendations

Since the publication of the last guidelines, no new Class I evidence has been published. Intra-arterial administration of at least one specific thrombolytic agent appears to be of benefit in the treatment of carefully selected patients with acute ischemic stroke secondary to occlusion of the MCA. New evidence about the use of intra-arterial urokinase in patients with vertebral or basilar artery occlusion treated within 24 hours of symptom onset and patients with embolic stroke involving the anterior circulation within 4.5 hours of symptom onset suggests that intra-arterial therapy may be used. Patients who are evaluated within 6 hours of symptoms but who are ineligible to receive intravenous thrombolysis because of recent surgery or other procedures may be candidates for intra-arterial thrombolysis.^{345,346}

New criteria have been established to determine the qualifications of physicians who can perform intra-arterial thrombolysis on the basis of recent statements from professional organizations and clinical trials.

Class I Recommendations

1. Intra-arterial thrombolysis is an option for treatment of selected patients who have major stroke of <6 hours' duration due to occlusions of the MCA and who are not otherwise candidates for intravenous rtPA (Class I, Level of Evidence B). *This recommendation has not changed since previous guidelines.*
2. Treatment requires the patient to be at an experienced stroke center with immediate access to cerebral angiography and qualified interventionalists. Facilities are encouraged to define criteria to credential individuals who can perform intra-arterial thrombolysis (Class I, Level of Evidence C). *This recommendation has been added since previous guidelines.*

Class II Recommendation

1. Intra-arterial thrombolysis is reasonable in patients who have contraindications to use of intravenous thrombolysis, such as recent surgery (Class IIa, Level of Evidence C). *This recommendation was not included in the previous guideline.*

Class III Recommendation

1. The availability of intra-arterial thrombolysis should generally not preclude the intravenous administration of rtPA in otherwise eligible patients (Class III, Level of Evidence C). *This recommendation has not changed from previous guidelines.*

VIII. Anticoagulants

Physicians have used anticoagulants to treat patients with acute ischemic stroke for >50 years. These medications continue to be prescribed commonly.³⁴⁷ Despite their widespread use, the usefulness of emergency anticoagulation is the subject of debate.^{348–352} Disagreements exist about the best agent to administer, the route of administration, the use of a bolus dose to start treatment, the level of anticoagulation

required, and the duration of treatment. In a small randomized trial, Toth³⁵³ found no increase in serious bleeding complications with the use of a bolus dose to start heparin anticoagulation. A weight-based nomogram for administration of heparin after stroke has been developed.³⁵⁴ This approach seems to lessen the necessity for frequent adjustments in dose. In the past, panels of the AHA have concluded that the data about the utility of heparin in the management of stroke are either uncertain or largely negative.^{1–3,355,356} Besides the uncertainty about efficacy, the safety concern exists that urgent anticoagulation may lead to symptomatic intracranial hemorrhage. Physicians have been uncertain about the severity of neurological impairments or the initial CT findings that would contraindicate the early use of heparin.

Anticoagulants often are prescribed to patients with recent stroke in an effort to prevent early recurrent stroke and to improve neurological outcomes. The Cerebral Embolism Study Group estimated that the risk of early recurrent embolism was ≈12% among untreated patients with embolic stroke.^{357,358} A Norwegian trial testing urgent anticoagulation among patients with recent stroke and atrial fibrillation found the risk of recurrent stroke to be ≈8% in 1 week.³⁵⁹ Other trials testing anticoagulants in stroke have found the rates of early recurrent stroke to be much lower (in the range of 0.3%/d to 0.5%/d).^{360–362} These relatively low rates mean that detection of a therapeutic effect in prevention of early recurrent stroke by anticoagulation will be difficult.

A. Heparin

The International Stroke Trial tested 2 doses (5000 U/d or 25 000 U/d) of subcutaneously administered heparin when the medication was started within 48 hours of stroke.³⁶¹ Although the trial included randomization in its design, investigators and patients knew the nature of the treatment. Dual randomization meant that approximately one half of the patients receiving heparin also were receiving aspirin. Neither monitoring of the level of anticoagulation nor adjustment of dosages to biological responses was done. Thus, some patients may have received excessive doses of heparin, with an increased risk of bleeding complications, and others may have had inadequate dosages, with a resultant loss of effectiveness. In addition, patients enrolled in this very large trial did not need to have a brain imaging study before treatment. Although heparin was effective in lowering the risk of early recurrent stroke, an increased rate of bleeding complications negated this benefit. A subgroup analysis looking at the effects of heparin among patients with atrial fibrillation did not demonstrate a benefit from the agent.³⁶³

A Swedish study testing the utility of heparin for treatment of patients with progressing stroke did not demonstrate a benefit from the anticoagulant.³⁶⁴ Recently, 2 small European trials have tested the utility of heparin in treatment of patients with recent stroke.^{365,366} Investigators tested continuously intravenously administered heparin starting with a bolus dose with adjustments in dosage in response to activated partial thromboplastin time in a small clinical trial that enrolled patients within 12 hours of onset of stroke. The multicenter trial treated 32 patients with heparin and 35 with aspirin (control). No significant differences in outcomes, recurrent

ischemic stroke, hemorrhagic worsening, or death were noted between the 2 treatment groups. A single-center study involved the randomization of patients with acute nonlacunar hemispheric infarctions to treatment with either adjusted intravenous infusions of heparin without an initial bolus dose or saline.³⁶⁵ The trial enrolled 418 patients (208 on heparin) within 3 hours of onset of stroke. Thirteen heparin-treated patients had symptomatic hemorrhagic complications (6.2%) (7 were fatal), and symptomatic hemorrhagic events were diagnosed in 3 control patients (1.4%). Favorable outcomes at 90 days were noted in 81 of 208 patients treated with heparin (38.9%) and 60 of 210 patients (28.6%) in the control group. A meta-analysis of the studies of heparin found no benefit from administration of the medication.³⁶⁷ However, this analysis was performed before the 2 recent reports about heparin were published. Nevertheless, the results of the relatively small study by Camerlingo et al³⁶⁵ likely would be dwarfed by the data from the International Stroke Trial.

B. Low-Molecular-Weight Heparins and Danaparoid

Several trials have tested low-molecular-weight (LMW) heparins or danaparoid for treatment of patients with acute ischemic strokes. Results generally have been negative. A trial in Hong Kong tested 2 doses of subcutaneously administered nadroparin given over 10 days after stroke.³⁶⁸ Although no benefit from treatment was found at the end of the treatment period or at 3 months, those who received the larger dose of nadroparin had a significantly lower death rate at 6 months than did the control group. Another trial of nadroparin failed to find any improvement in the rate of favorable outcomes with treatment, but the rate of serious bleeding was increased with the larger of 2 doses of LMW heparin.³⁶⁹ Berge et al³⁵⁹ compared the utility of dalteparin or aspirin for prevention of early recurrent stroke or improvement in neurological outcome among patients with presumed cardioembolic stroke. Although no significant differences were noted in outcomes or the rates of recurrent strokes, the patients taking aspirin had fewer second events. The rate of bleeding complications also was higher among patients who were treated with dalteparin than among those given aspirin. A German trial compared 4 different doses of certoparin; no differences in rates of favorable outcomes were noted among the groups, but the rate of serious bleeding complications was highest among the group that received the largest dose of the LMW heparin.³⁷⁰ An aspirin-controlled trial tested 2 different doses of subcutaneously administered tinazaparin in patients with recent stroke, with no differences in favorable outcomes, rates of recurrent stroke, death, or bleeding complications.³⁷¹

A randomized, double-blind, placebo-controlled trial tested the utility of a continuous intravenous infusion of the LMW heparinoid (danaparoid) in improving outcomes after acute ischemic stroke.³⁶² The trial halted recruitment of patients with moderate to severe stroke (NIHSS scores of ≥ 15) because of an increased risk of symptomatic intracranial hemorrhages. The medication did not lessen the risk of neurological worsening or early recurrent stroke, including among patients with cardioembolic events. No improvement in the chance of having a favorable or very favorable outcome

was found at 3 months. The trial included prespecified subgroup analyses among patients with different subtypes of ischemic stroke. The only subgroup that showed benefit from treatment included patients with stroke secondary to large-artery atherosclerosis.³⁷² This finding may be supported by the results of the study by Lovett et al,³⁷³ which found that the risk of early recurrent stroke was highest among patients with severe large-artery atherosclerotic disease. A study examining the usefulness of a LMW heparin in treating patients with stroke secondary to intracranial stenotic disease has been performed in Hong Kong and Singapore, but the results have not yet been published.

Some studies have compared the utility of heparin or LMW heparins in treatment of patients with recent stroke. Woessner et al³⁷⁴ compared the usefulness of subcutaneously administered enoxaparin or adjusted-dose heparin in a multicenter trial that randomized patients with either high-grade arterial stenoses or a cardioembolic source for stroke. No significant differences were noted between the 2 regimens. Another trial investigated the efficacy of subcutaneously administered enoxaparin in comparison to heparin for prevention of thromboembolic events among patients with lower-limb paralysis after stroke.³⁷⁵ The 2 medications had equal efficacy.

C. Anticoagulants as an Adjunctive Therapy

The administration of anticoagulants or antiplatelet agents is currently contraindicated during the first 24 hours after treatment with intravenous rtPA. This restriction is based on the regimen used in the NINDS trials.⁶⁶ Arterial reocclusion may follow successful recanalization with thrombolysis.³⁷⁶ Thus, there is interest in the use of an anticoagulant that may maintain arterial patency after thrombolytic therapy. The trials of intra-arterial administration of prourokinase used heparin as part of the treatment regimen, and the control group received only heparin.^{336,377,378} In the first study, both the success of recanalization and the risk of hemorrhage were increased among the patients who received the larger of the 2 doses of adjunctive heparin. Two small studies have tested the use of intravenously administered heparin after treatment with rtPA.^{379,380} No increase in bleeding complications has been reported. Heparin also has been given in combination with abciximab with a reasonable degree of safety.³⁸¹ The experience with adjunctive anticoagulation is limited. Neither safety nor effectiveness has been established, and additional research is needed.

D. Conclusions and Recommendations

The results of the recent trials show that early administration of either heparin or a LMW heparin/danaparoid is associated with an increased risk of bleeding complications. These medications increase the risk of symptomatic hemorrhagic transformation of ischemic strokes, especially among persons with severe events. These medications are also associated with a risk of serious bleeding in other parts of the body. Although the likelihood of bleeding appears to be lower than that associated with the administration of thrombolytic agents, it is sufficiently high to require convincing evidence of efficacy to justify urgent anticoagulation. The risk of bleeding appears not to be greatly affected by the use of a

bolus dose to start treatment or by the route of administration (subcutaneous or intravenous). Monitoring of the level of anticoagulation and adjustment of the dosages in response to levels probably increase the safety of treatment.

Present data indicate that early administration of heparin or the LMW heparins/danaparoid does not lower the risk of early recurrent stroke, including among patients with cardioembolic stroke. Early administration of anticoagulants does not lessen the risk of early neurological worsening. Data are not sufficient to indicate whether anticoagulants might have efficacy among some potentially high-risk groups, such as persons with intracardiac or intra-arterial thrombi. The efficacy of urgent anticoagulation is not established for treatment of patients with vertebrobasilar disease or an arterial dissection.

Most trials have not demonstrated the efficacy of anticoagulation in improving outcomes after acute ischemic stroke. One relatively small trial found that intravenous heparin, when administered within 3 hours of onset of stroke to patients with nonlacunar stroke, may improve outcomes. In light of the generally negative data, the results of this trial may need to be replicated. Because the time window for potentially effective treatment with heparin is the same as for intravenously administered rtPA, a study may be needed to test the relative efficacy of heparin or thrombolysis.

The role of anticoagulants as an adjunctive therapy in addition to mechanical or pharmacological thrombolysis has not been defined.

The following recommendations have not changed from previous guidelines.

Class III Recommendations

1. 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). This recommendation may change if additional data demonstrate the usefulness of very early intravenous administration of anticoagulants for treatment of patients with infarctions secondary to large-artery thrombosis or cardioembolism. Urgent anticoagulation should not be used in lieu of intravenous thrombolysis for treatment of otherwise eligible patients (Class III, Level of Evidence A).
2. Urgent anticoagulation 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).
3. Initiation of anticoagulant therapy within 24 hours of treatment with intravenously administered rtPA is not recommended (Class III, Level of Evidence B).

IX. Antiplatelet Agents

The 2003 guideline² recommendation that aspirin could be used after stroke was consistent with the recent Joint Guideline Statement from the AHA and the American Academy of Neurology.³⁵⁶ The administration of aspirin as an adjunctive therapy, within 24 hours of the use of thrombolytic agents, was not recommended. Aspirin was not indicated as a

substitute for other acute interventions, especially intravenous administration of rtPA, for the treatment of acute ischemic stroke.

A. Single Oral Antiplatelet Agent

Aspirin is the only oral antiplatelet agent that has been evaluated for the treatment of acute ischemic stroke. Two large trials^{360,361} each showed a nonsignificant trend in reduction in death or disability when treatment with aspirin was initiated within 48 hours of stroke. A small increase in bleeding complications was also noted. When the data from the 2 trials were combined, a modest but statistically significant benefit from aspirin was noted. The primary effect seemed to be in prevention of recurrent events. It is not clear whether aspirin limited the neurological consequences of the acute ischemic stroke itself.

The use of ticlopidine, clopidogrel, or dipyridamole in the setting of acute ischemic stroke has not been evaluated.³⁸² Initiation of treatment with clopidogrel in a daily dose of 75 mg does not cause maximal platelet inhibition for ≈ 5 days.³⁸³ This delay poses the issue of an early therapeutic effect for treatment of patients with acute stroke. A bolus dose of clopidogrel 300 mg inhibits platelet aggregation rapidly.³⁸⁴ A 300-mg loading dose of clopidogrel followed by daily doses of 75 mg/d has been recommended for treatment of patients with acute coronary syndrome (ACS) who have aspirin allergies.³⁸⁵ No data are available about the utility of this strategy in treating patients with acute ischemic stroke.^{386,387}

B. Combination of Oral Antiplatelet Agents

Although the combination of clopidogrel and aspirin is prescribed for patients with ACS, this combination has not been studied in the setting of acute ischemic stroke. No data are available about the use of other combinations of antiplatelet agents in the management of acute ischemic stroke.

C. Intravenous Antiplatelet Agents

The platelet glycoprotein IIb/IIIa inhibitors have been considered in the treatment of acute ischemic stroke because they may increase the rate of spontaneous recanalization and improve microvascular patency.^{388,389} A small case series³⁹⁰ demonstrated that intravenous abciximab administered between 3 and 24 hours after symptom onset in patients with supratentorial ischemic stroke may attenuate ischemic lesion growth as demonstrated by serial DWI. A double-blind, placebo-controlled, dose-escalation trial randomly allocated 74 patients to receive either an escalating dose of abciximab (54 patients) or placebo (20 patients) in a 3:1 ratio within 24 hours after ischemic stroke onset.^{390,391} No symptomatic intracerebral hemorrhages occurred in any group, which suggests that intravenous abciximab is relatively safe when administered within 24 hours of symptom onset in selected patients with ischemic stroke. A second randomized, double-blind, placebo-controlled phase II trial randomized 400 patients within 6 hours of ischemic stroke onset to intravenous abciximab or placebo.³⁹² The rates of symptomatic hemorrhage during the first 5 days after stroke were not significantly different between the abciximab and placebo groups (3.6% versus 1%). Treatment with abciximab showed a

nonsignificant shift in favorable outcomes defined by modified Rankin Scale scores at 3 months, after adjustment for baseline severity of stroke, age, and interval from stroke.^{391,392} A phase III, multinational, multicenter, randomized, double-blind, placebo-controlled study evaluating the safety and efficacy of abciximab in patients with acute ischemic stroke has been halted because of an increased rate of bleeding. Details are not yet available.

D. Conclusions and Recommendations

No new data are available about the utility of oral antiplatelet agents (used singly or in combination) for treatment of patients with acute ischemic stroke. Currently available data demonstrate a small but statistically significant decline in risk of mortality and morbidity when aspirin is started within 48 hours after onset of stroke. It appears that the primary effects of the aspirin are due to reduction of early recurrent stroke rather than limitation of the neurological consequences of the stroke. No data are available on the utility of other antiplatelet agents, including clopidogrel, given as monotherapy or in combination with aspirin for treatment of patients with acute ischemic stroke. The relative indications for the long-term administration of antiplatelet agents to prevent recurrent stroke are beyond the scope of this statement. However, the panel recommends the administration of such agents as part of management after acute stroke.

Ongoing research is testing the usefulness of intravenously administered antiplatelet agents (glycoprotein IIb/IIIa receptor blockers) when given alone or in combination with other interventions. Preliminary evidence suggests that these agents, when used alone, have an acceptable safety profile, but considerably more research is needed to determine whether these agents have a role in the management of acute stroke in conjunction with other therapies.

Class I Recommendation

1. The 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). *This recommendation has changed in that a dose of aspirin is now included.*

Class III Recommendations

1. Aspirin should not be considered a substitute for other acute interventions for treatment of stroke, including the intravenous administration of rtPA (Class III, Level of Evidence B). *These recommendations have not changed from previous statements.*
2. The administration of aspirin as an adjunctive therapy within 24 hours of thrombolytic therapy is not recommended (Class III, Level of Evidence A). *This recommendation has not changed.*
3. The administration of clopidogrel alone or in combination with aspirin is not recommended for the treatment of acute ischemic stroke (Class III, Level of Evidence C). *This recommendation was not included in the previous statement.* The panel supports research testing the usefulness of emergency administration of clopidogrel in the treatment of patients with acute stroke.

4. Outside the setting of clinical trials, the intravenous administration of antiplatelet agents that inhibit the glycoprotein IIb/IIIa receptor is not recommended (Class III, Level of Evidence B). *This recommendation has been added since the last guideline was published.*

X. Volume Expansion, Vasodilators, and Induced Hypertension

A. Hemodilution in Acute Ischemic Stroke

It is known that patients experiencing acute ischemic stroke may have a variety of abnormalities that increase whole-blood viscosity, including leukocyte activation, red cell aggregation, and reduced red cell deformability.^{393–395} In addition, elevated fibrinogen levels, which add to plasma viscosity, have been documented. On the basis of these findings, hemodilution, with or without venesection, has been studied. The goal is to improve cerebral blood flow to hyperperfuse potentially viable brain tissue supplied by leptomeningeal collaterals in an attempt to perfuse the ischemic penumbra.^{396–400}

Volume expansion and hemodilution have been demonstrated to improve blood flow but may reduce oxygen-carrying capacity at hematocrits <30%.^{401–408} As the hematocrit is reduced, oxygen delivery increases as much as 28% to 30%; however, at levels lower than this, oxygen delivery begins to decline.⁴⁰⁹

In patients with cerebral infarction, cerebral autoregulatory mechanisms are impaired, and hemodilution has been noted to increase cerebral blood flow in the infarcted as well as the contralateral hemisphere. Oxygen-carrying molecules such as perfluorocarbons or diaspirin cross-linked hemoglobin have been shown to reduce brain infarct size in animal models but have not yet been assessed and cannot be recommended in patients.^{383,410–417}

Investigations of intravascular volume and hemodilution in patients began in the 1960s. Initial reports, from studies that were not controlled and not randomized, were encouraging and suggested clinical benefits of intravascular volume expansion. In a review of recent trials for hemodilution in stroke, a combination of plasma volume expansion with or without venesection was used.^{387,416–422} Several trials used plasma volume expansion alone, either dextran 40 or hydroxyethyl starch and albumin in one trial.^{405,423–425} In all trials, and in the Multicenter Austrian Hemodilution Stroke Trial³⁸⁷ study in particular, hemodilution did not significantly reduce deaths within the first 4 weeks but did influence deaths within 3 to 6 months. Hemodilution also had no significant influence on death, dependency, or institutionalization/long-term care. In several trials, hemodilution was associated with a tendency toward reduction in deep venous thrombosis and pulmonary embolism at 3 to 6 months. Despite volume expansion and hemodilution, the risk of significant cardiac events did not increase.

Conclusions and Recommendations

The present data indicate that intentional hemodilution, with or without venesection in clinical practice, does not reduce case fatality or improve functional outcome in survivors. The data do not support the use of hypervolemia and isovolumic

hemodilution protocols, including dextran, albumin, and hydroxyethyl starch. The only possible exception for the use of hemodilution is in stroke patients with severe polycythemia.⁴²⁶ Maintenance of a normal circulating blood volume with regulation of metabolic parameters within physiological ranges is desirable.

Class III Recommendation

1. Hemodilution with or without venesection and volume expansion is not recommended for treatment of patients with acute ischemic stroke (Class III, Level of Evidence A). This recommendation has not changed since the previous guidelines were published.

B. Vasodilators in Acute Ischemic Stroke

Methylxanthine derivatives are known vasodilators that also have other activities such as inhibition of platelet aggregation, reduction of free radical release, and inhibition of thromboxane A₂ synthesis.^{404,427-429} On the basis of these characteristics, methylxanthine derivatives, specifically pentoxifylline, propentofylline, and pentifylline, have been evaluated in the setting of acute ischemic stroke.^{430,431} In one trial, pentoxifylline and propentofylline were administered via continuous intravenous infusion over a 3-day period in patients experiencing an acute ischemic event.⁴³² Other studies continued infusions for 5 days, as in the trial by Chan and Kay in 1993, or 7 days, as in the trial of Huber et al in 1993.^{433,434}

Early case fatality, defined as within 4 weeks, was evaluated in several trials of pentoxifylline.⁴³²⁻⁴³⁵ The trial conducted by Chan and Kay found a large reduction in the odds of early death; however, this was not borne out in other studies. Two trials demonstrated a nonsignificant reduction in early death or deterioration.^{433,435} One trial compared the combination of pentoxifylline and aspirin with aspirin alone and found a significant decrease in short-term deaths.⁴³³ However, this trial studied early death and deterioration, and no significant reduction in these combined events was observed. The trial by Huber et al in 1993 included 30 patients after propentofylline treatment and found no difference in late case fatality.⁴³⁴ The trial by Chan and Kay administered aspirin to both patient groups with the theoretical advantage that aspirin may potentiate the antiplatelet effects of pentoxifylline, which may explain the apparent clinical effectiveness. The trial by Hsu et al demonstrated that patients with profound neurological deficit derived the greatest benefit from pentoxifylline.⁴³²

Conclusions and Recommendations

On the basis of current data, neither pentoxifylline nor pentofylline has been shown to improve outcomes after stroke.

Class III Recommendation

1. The administration of medications such as pentoxifylline is not recommended for treatment of patients with acute ischemic stroke (Class III, Level of Evidence A). This recommendation has not changed since the previous guideline was published.

C. Induced Hypertension for the Management of Acute Ischemic Stroke

In the setting of acute stroke, patients may have an ischemic penumbra of brain tissue, which may have impaired perfusion but may not be irreversibly damaged. In this situation, a local drop in cerebral blood flow occurs, and cerebral arterioles dilate in an attempt to compensate and maintain flow to the potentially salvageable ischemic tissue.⁴³⁶ The magnitude of the low perfusion and duration of the ischemia are important variables.^{437,438} It is intuitively attractive that reperfusion of this area by dilatation of leptomeningeal collaterals may be advantageous.

The optimal management of blood pressure in patients experiencing acute ischemic neurological events remains controversial.^{247,439,440} Markedly elevated blood pressure after an acute ischemic event may increase the risk of conversion from an ischemic to a hemorrhagic lesion, with life-threatening implications.⁴⁴¹ However, inducing hypertension to increase cerebral blood flow has been attractive on the basis of experimental data.⁴³⁷ Preliminary studies suggest that there may be a role for induced hypertension.^{247,442-446} Other studies by Olsen demonstrated that the ischemic penumbra has impaired autoregulation and that induction of elevated blood pressure partially restores perfusion to the penumbra, as demonstrated by single-photon emission CT imaging.^{447,448} In a study by Rordorf et al, 30 patients with acute ischemic events were treated with intravenous phenylephrine, which was titrated to improvement of neurological deficit, as demonstrated in 33% of the patients.^{445,446} In this trial, patients were entered within 12 hours of the onset of symptoms but were excluded in the presence of recent or known cardiac ischemic events, congestive heart failure, intracerebral hemorrhage, or edema related to a completed infarction. Patients were maintained hypertensive for a period of 1 to 6 days, and neurological status at discharge was improved in those who had responded to the therapy. In other reports by Hillis et al, patients were randomized to induced hypertension or conventional management.^{443,444} Serial DWI and PWI studies were performed before and during the period of induced hypertension. After 3 days of treatment, patients who were treated with induced hypertension showed an improvement in neurological examination, no change in DWI lesion volume, and reductions in PWI abnormality.

Wityk et al used induced hypertension for treatment of patients who were within 12 hours of onset of symptoms but who could not be treated with thrombolytic therapy.^{449,450} They also advocated the use of DWI and PWI as a means to demonstrate improved perfusion to monitor such patients in an intensive care setting and when intervention is undertaken to achieve a target systolic blood pressure or mean arterial pressure of 20% to 30% above baseline. Other treatment options include withdrawing previous antihypertensive therapy, augmenting intravenous fluids, or starting intravenous phenylephrine. As part of the treatment paradigm, serial neurological examinations are performed to determine whether neurological improvement occurs; patients who show no improvement in a 30- to 60-minute period are considered nonresponders, and the intervention is stopped. Patients who have responded to this mode of therapy are

maintained at that level and weaned according to neurological examination and functional imaging. Data demonstrating the safety and efficacy of this strategy are needed.

Conclusions and Recommendations

Preliminary and small clinical studies suggest that drug-induced hypertension could be used in the management of some patients with acute ischemic stroke. However, data from large clinical trials are not available. Thus, the efficacy of this treatment strategy has not been established. The administration of vasopressors may be complicated by side effects, including myocardial ischemia, in some patients with stroke. Some patients may not be able to be treated with this therapy. The safety of drug-induced hypertension for treatment of stroke in a broad spectrum of patients has not been established. Further research is needed.

Class I Recommendation

1. In exceptional cases, 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). *This recommendation has been added since the previous guideline was published.*

Class III Recommendation

1. Drug-induced hypertension, outside the setting of clinical trials, is not recommended for treatment of most patients with acute ischemic stroke (Class III, Level of Evidence B). *This recommendation has been added since the previous guideline was published.*

XI. Surgical Interventions

A. Carotid Endarterectomy

Little information exists about the effectiveness of surgical treatment of patients with acute ischemic stroke. Most cases of immediate operation are performed in the setting of an acute stroke after carotid endarterectomy. Emergency carotid endarterectomy generally is not performed in other settings of acute ischemic stroke because the risks of the procedure are perceived to be high. The sudden restoration of blood flow might increase the development of brain edema or lead to hemorrhagic transformation, especially among patients with major infarctions. In addition, the time required for detecting the arterial lesion and mobilizing the operating room limits the utility of surgery.

However, some surgeons report encouraging results from emergency operations for patients with severe stenosis or occlusion of the internal carotid artery existing for ≤ 24 hours.^{324,386,451–460} In general, improvement after surgery was found among patients with mild to moderate neurological impairments. Still, the data are limited, and the usefulness of urgent surgery among patients with severe neurological deficits is even less clear.

The indications for immediate carotid endarterectomy in a patient with an acute ipsilateral ischemic stroke and an intraluminal thrombus associated with an atherosclerotic plaque at the carotid bifurcation are controversial. The morbidity associated with surgery appears to be high among

patients with an intraluminal thrombus demonstrated by cerebral angiography.^{461–464} Although some groups report low rates of complications and good neurological outcomes with immediate surgery,^{461–463} others have reported better results when the patients are treated initially with anticoagulants followed by delayed operation.⁴⁶⁴

B. Other Surgical Procedures

Immediate extracranial-intracranial arterial bypass for treatment of ischemic stroke failed to improve outcomes and was associated with a high risk of intracranial hemorrhage.⁴⁶⁵ However, some surgeons have reported favorable results with emergency bypass procedures.^{466,467} In an occasional patient with an acute neurological deficit secondary to an embolus of the MCA, outcome might be improved by an emergency microsurgical embolectomy of the MCA.^{468,469} Experience with immediate surgical procedures for treatment of acute ischemic stroke in the vertebrobasilar circulation is extremely limited.

C. Conclusions and Recommendations

Data on the safety and effectiveness of carotid endarterectomy and other operations for treatment of patients with acute ischemic stroke are not sufficient to permit a recommendation. Surgical procedures may have serious risks and may not favorably alter the outcome of the patient.

XII. Endovascular Interventions

Several endovascular interventions are being evaluated for the treatment of intracranial or extracranial arterial occlusions leading to acute ischemic stroke.^{470–473} Options include emergency angioplasty and stenting, mechanical disruption of the clot, and extraction of the thrombus. In most cases, the mechanical intervention has been combined with either intravenous or intra-arterial thrombolytic therapy.

A. Angioplasty and Stenting

Limited data are available about the use of angioplasty and stenting in the emergency treatment of intracranial or extracranial lesions in patients with acute ischemic stroke.^{474–476} Angioplasty and stenting have been used to treat patients with acute stroke secondary to carotid artery dissection.⁴⁷⁷ In one series, emergency angioplasty and stenting of the internal carotid artery were performed in conjunction with intra-arterial thrombolysis in 25 patients who had acute carotid artery occlusion with secondary artery-to-artery embolism to the MCA.⁴⁷⁸ Results were compared with another group of 25 patients who were treated medically; favorable outcomes were more frequent (56% versus 26%) among patients with endovascular treatment. Jovin et al⁴⁷⁹ were successful in achieving recanalization in 23 of 25 patients who had emergency stenting of the extracranial internal carotid artery. Brekenfeld et al⁴⁸⁰ treated 350 patients with intra-arterial urokinase and noted that recanalization could be increased with angioplasty and implantation of stents. Angioplasty with or without stenting has been combined with emergency administration of thrombolytic agents in patients with occlusions in the vertebrobasilar circulation.^{481,482}

B. Mechanical Clot Disruption

Noser et al⁴⁸³ treated 16 patients with occlusion of the MCA and 16 others with occlusion of the internal carotid artery with aggressive mechanical clot disruption. In most cases, the endovascular treatment was an adjunct to thrombolysis. A Swiss study of 350 patients treated with intra-arterial pharmacological thrombolysis found that mechanical fragmentation improved the success for recanalization.⁴⁸⁰ Berlis et al⁴⁸⁴ used an endovascular photoacoustic device to speed recanalization.

C. Clot Extraction

Devices have been used to extract thrombi from occluded intracranial arteries.^{485,486} In the Mechanical Embolus Removal in Cerebral Embolism (MERCI) trial, vessels were opened with a device that removed the thrombus from an intracranial artery.^{487–489} The device was associated with rapid opening of the artery, but the efficacy in recanalization and safety results achieved with the MERCI retrieval system were similar to those achieved with intra-arterial prourokinase in the Prolyse in Acute Cerebral Thromboembolism II (PROACT II) trial.³³⁶ The rate of recanalization of the MCA in MERCI was 45%, and it was 66% in PROACT II. In MERCI, 17 patients also received thrombolytic medications when the device was unable to achieve recanalization, but the outcomes of these patients were not reported. Although the FDA has approved the use of the MERCI device for reopening intracranial arteries, its clinical utility has not been established.

D. Conclusions and Recommendations

The area of endovascular treatment of patients with acute ischemic stroke shows great promise. A number of techniques and devices are being studied. Already, the FDA has approved one device to extract a thrombus from an occluded intracranial artery. Other devices likely will be approved in the future. Emergency angioplasty also may achieve a role in management. As with the intra-arterial administration of thrombolytics, the use of these devices will be limited to those comprehensive stroke centers that have the resources and physician expertise to perform these procedures safely.

Class II Recommendations

1. Although the MERCI device is a reasonable intervention for extraction of intra-arterial thrombi in carefully selected patients, the panel also recognizes that the utility of the device in improving outcomes after stroke is unclear (Class IIb, Level of Evidence B). *This recommendation has been added since the previous guideline.* The panel also recommends that the device be studied in additional clinical trials that will define its role in the emergency management of stroke. *This is the first time that a panel has made a recommendation about endovascular treatment of patients with acute ischemic stroke.*
2. The usefulness of other mechanical endovascular treatments is not established (Class IIb, Level of Evidence C). These devices should be used in the setting of clinical trials. *This recommendation has not changed from previous guidelines.*

XIII. Combination Reperfusion Therapy in Acute Stroke

Initial studies of thrombolytic therapy in acute ischemic stroke involved a single pharmacological agent given either intravenously or intra-arterially. Unfortunately, neither intravenous nor intra-arterial thrombolysis with only a single pharmacological agent is an efficient way to rapidly recanalize occluded major brain arteries. Even when it works, intravenous or intra-arterial rtPA takes at least 15 to 30 minutes to reopen an occluded major vessel such as the MCA, and no evidence indicates that other available thrombolytic agents are faster. Large-vessel occlusions of the internal carotid artery or basilar artery often are resistant to intravenous or intra-arterial thrombolysis with 1 agent. Recent transcranial Doppler ultrasonography studies suggest only a 30% complete recanalization rate for MCA occlusion after administration of intravenous rtPA, a 48% partial recanalization rate, and a 27% reocclusion rate.³⁷⁶ The MCA complete recanalization rate with intra-arterial recombinant prourokinase was only 20% after 2 hours, with a 63% partial recanalization rate and a 10% reocclusion rate within the first hour of treatment.³³⁶ The low rate of complete recanalization and the high rate of reocclusion with stroke thrombolysis is not surprising when it is considered that not even aspirin is allowed for 24 hours after intravenous rtPA.

Faster and more complete recanalization should translate into better patient outcomes. To achieve this, the trend in ACS has been to use multiple pharmacological agents and, increasingly, percutaneous coronary intervention. The impetus is the more rapid and complete recanalization of occluded or stenosed coronary arteries. The standard treatment in many ACS patients includes antiplatelet therapy with aspirin, clopidogrel, glycoprotein IIb/IIIa blockers, antithrombotic therapy with heparin or LMW heparin, and direct percutaneous coronary intervention.⁴⁹⁰ In patients with ACS, Thrombolysis in Myocardial Infarction (TIMI) 14⁴⁸⁷ reported the highest TIMI 3 complete recanalization rates with reduced-dose intravenous rtPA combined with the glycoprotein IIb/IIIa antagonist abciximab. However, the rate of brain hemorrhage was increased in patients >75 years of age who received reduced-dose reteplase and abciximab in the Global Utilization of Streptokinase and tPA for Occluded Arteries (GUSTO) V trial.⁴⁸⁸

To improve the efficiency of acute stroke thrombolysis in a way that is similar to treatment of ACS, multimodal combination therapies will need to be developed. Such combination therapy should not only increase the likelihood of favorable outcomes but should also reduce the likelihood of intracranial hemorrhage. The PROACT I study demonstrated that the recanalization efficacy and safety of recombinant prourokinase was affected by the concomitant use of heparin³⁷⁷; although the large dose of anticoagulant was associated with a higher rate of recanalization, it also was complicated by more bleeding. A major stimulus to the development of stroke thrombectomy devices has been the desire to improve the speed and completeness of recanalization as compared with an intra-arterially administered drug alone (see the section on endovascular therapy). External ultrasound has also been shown to enhance intravenous rtPA

in the Combined Lysis of Thrombus in Brain ischemia Using 2 MHz Transcranial Ultrasound and Systemic tPA (CLOT-BUST) study.⁴⁹¹ In CLOTBUST, complete MCA recanalization with dramatic clinical recovery occurred in 49% of patients receiving intravenous rtPA combined with transcranial ultrasound versus 30% in patients receiving intravenous rtPA only.

Another approach being evaluated is the initiation of intravenous thrombolysis in the interim period between initial evaluation and intra-arterial treatment.^{72,492} The Interventional Management of Stroke (IMS) study reported on 80 patients with an initial NIHSS score ≥ 10 treated with intravenous thrombolysis followed by intra-arterial thrombolysis.⁴⁹² Patients received intravenous rtPA (0.6 mg/kg, 60 mg maximum over 30 minutes) started within 3 hours of onset. Additional rtPA was then administered via microcatheter in 62 patients with persistent occlusion at the site of the thrombus up to a total dose of 22 mg over 2 hours of infusion or until recanalization occurred. The 80 subjects had a median baseline NIHSS score of 18. The 3-month mortality rate in treated patients (16%) was numerically lower than but not statistically different from the mortality rate observed in the placebo- (24%) and rtPA-treated subjects (21%) in the NINDS rtPA Stroke Trial. The rate of symptomatic intracerebral hemorrhage (6.3%) in IMS subjects was similar to that of rtPA-treated subjects (6.6%) but higher than the rate in placebo-treated subjects (1.0%; $P=0.018$) in the NINDS rtPA Stroke Trial. IMS subjects had a significantly better outcome at 3 months than NINDS placebo-treated subjects for all outcome measures. The new data support the previous phase I study⁷² and single-center case series⁴⁹³ supporting the safety of this approach. On the basis of the results of the phase II study, a phase III study has been planned.

The ongoing IMS II study again uses reduced-dose intravenous rtPA combined with intra-arterial rtPA but now delivered through an ultrasonic EKOS catheter in an attempt to accelerate thrombolysis. Intra-arterial administration of alteplase after intravenous administration of alteplase (0.6 mg/kg) may provide benefit in patients with initial NIHSS score ≥ 10 who present within 3 hours of symptom onset.

A. Combination of Thrombolysis and Neuroprotective Therapies

There have also been very limited studies of combination cytoprotective and reperfusion therapy in acute stroke (lutealuzole,⁴⁹⁴ hypothermia,⁴⁹⁵ magnesium,³¹ clomethiazole⁴⁹⁶). Until randomized clinical efficacy trials can be completed, combination reperfusion therapies for acute stroke will remain experimental for the foreseeable future.

B. Thrombolysis and Antiplatelet Agents

Use of platelet glycoprotein IIb/IIIa inhibitors has been suggested to prevent platelet activation and reocclusion and is being evaluated in several phase I studies as adjunctive therapy to intra-arterial thrombolysis. Other clinical trials of combination plasminogen activator and glycoprotein IIb/IIIa inhibitors, some based on perfusion brain imaging, are under way. Three recently completed studies^{497–499} have suggested that intra-arterial administration of thrombolysis in combination with platelet

glycoprotein IIb/IIIa inhibitors may be safe and may potentially improve outcome. A multicenter study⁴⁹⁷ reported the results of treating patients with acute vertebralbasilar occlusion using a combination of an intravenous bolus of abciximab (0.25 mg/kg) followed by 12-hour infusion therapy (0.125 μ g/kg per minute) and intra-arterial rtPA in 47 patients. The results were compared with a retrospective cohort of 41 patients treated by intra-arterial rtPA monotherapy (median dosage, 40 mg). The rates of symptomatic intracranial hemorrhages were 13% and 12% for combination treatment and thrombolytic treatments, respectively. The combination treatment had higher rates of complete recanalization (45% versus 22%), favorable outcomes (34% versus 17%), and survival (62% versus 32%) compared with thrombolysis alone. A second study⁴⁹⁸ evaluated 26 patients with acute ischemic stroke (NIHSS score >10). Combined use of intravenous abciximab and intra-arterial urokinase thrombolysis in 10 patients was compared with intra-arterial urokinase alone in 16 patients. The recanalization rate was higher in the combined urokinase and abciximab group than in the urokinase group (90% versus 44%) with a trend of better functional outcome (50% versus 80%). No significant difference was noted in rates of symptomatic intracerebral hemorrhage (25% versus 30%). A prospective, nonrandomized, open-label trial⁵⁰⁰ was conducted to evaluate the safety of an escalating dose of reteplase in conjunction with intravenous abciximab in patients with acute ischemic stroke (3 to 6 hours after symptom onset) in 20 patients. The safety stopping rule was not activated in any of the tiers. One symptomatic intracerebral hemorrhage was observed in 1 of the 20 patients (1 U tier). Partial or complete recanalization was observed in 13 of the 20 patients. Thirteen patients demonstrated early neurological improvement, and favorable outcome at 1 month was observed in 6 patients.

C. Conclusions and Recommendations

The potential for combination interventions to restore perfusion to the brain given with or without neuroprotective therapies has great appeal. However, currently available data do not provide conclusive evidence for either the safety or efficacy of combinations of medications to improve cerebral perfusion. Data are limited with regard to the usefulness of mechanical devices to augment the effects of pharmacological thrombolysis to treat acute ischemic stroke. No data are available to demonstrate the efficacy of a neuroprotective intervention as a complement to thrombolysis or other therapies to restore perfusion.

Class III Recommendation

1. At present, combinations of interventions to restore perfusion cannot be recommended outside the setting of clinical trials (Class III, Level of Evidence B). This recommendation has been added since the previous guidelines were published.

XIV. Neuroprotective Agents

Medications 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. Although numerous interventions have shown promise in experimental studies, most clinical trials testing these therapies have produced disappointing results. In some circumstances, treated patients had poorer outcomes than did controls or the rates of adverse experiences were unacceptably high.⁵⁰¹ Although some of these clinical studies were small or may not have been well designed, others have been sufficiently large and methodologically strong to produce important information.⁵⁰² New medications and innovative clinical trial designs likely will result in future evidence that neuroprotective strategies could be helpful in treatment of stroke. These therapies could be administered alone or in combination with other interventions, including treatments to restore perfusion to the brain. One of the potential advantages of neuroprotective medications is that they could be started in the field and before completion of brain imaging studies.³¹

Nimodipine is approved for the prevention of ischemic stroke among persons with recent aneurysmal subarachnoid hemorrhage.⁵⁰³ The medication was tested in a large number of clinical trials with generally negative results.^{253,504–506} A meta-analysis of the trials performed before 1994 found no benefit from treatment.⁵⁰⁷ Subsequently, Horn et al⁵⁰⁸ treated patients within 6 hours of onset of stroke and found no benefit from nimodipine. In some cases, outcomes were poorer among patients treated with nimodipine than among controls.^{253,508} Presumably, the higher rates of poor outcomes were secondary to the antihypertensive effects of nimodipine.²⁵³ Trials of flunarizine, isradipine, and darodipine also were negative.^{509–511} Although nifedipine is used to treat elevated blood pressure in the setting of stroke, the agent has had limited testing for treatment of the stroke itself.⁵¹² A systematic review of the calcium channel-blocking agents found no evidence that these medications are effective in improving outcomes after stroke.⁵¹³

Several N-methyl-D-aspartate (NMDA) antagonists have been tested in clinical trials, with largely negative results. In several instances, the rates of serious adverse experiences were high. Although a pilot study found that selfotel might improve outcomes, subsequent clinical trials were halted prematurely because of an increased rate of unfavorable outcomes among treated patients.^{514–516} Other clinical trials tested aptiganel, but it was associated with a high rate of side effects, and no improvement in outcomes was found.^{517,518} Dextrorphan was associated with a high rate of adverse effects.⁵¹⁹ Although remacemide may lower the frequency of ischemic neurological complications associated with cardiac surgery, its effectiveness in the setting of stroke is not established.^{520,521} The NMDA antagonist AR-R15896AR was tested in a clinical trial, but side effects, including psychiatric disturbances, meant that the agent could not be tolerated by the patient.⁵²² A preliminary study of the α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid antagonist ZK 200775 showed that the medication led to declines in consciousness and possible neurological worsening. Studies of the glycine antagonist gavestinel found that the medication was relatively safe, but the likelihood of favorable outcomes

was not improved.^{523–525} The agent also was not effective in improving outcomes among patients with intracerebral hemorrhage.⁵²⁶ High doses of licostinel, an antagonist of glycine at the NMDA receptor, were associated with numerous side effects.⁵²⁷ Another glycine antagonist was associated with hepatotoxicity and likely will not be tested further.⁵²⁸ The polyamine glutamate antagonist eliprodil was tested in a clinical trial, but side effects were unacceptably high.⁵²⁹ A systematic review of the trials testing these medications found no improvements in rates of either death or favorable outcomes with treatment.⁵³⁰ Neither fosphenytoin nor sipatrigine has demonstrated effectiveness in treatment of acute stroke.^{531,532} Repinotan, a serotonin agonist, has shown some promise in preliminary studies.⁵³³

Lubeluzole was tested in several clinical trials, including one that evaluated the combination of the medication and rtPA.⁵³⁴ Although a pilot study suggested that the agent was safe and might reduce the death rate, subsequent larger clinical trials found no effects in reducing deaths or improving outcomes after stroke.^{535–537} A subsequent analysis of the trials concluded that there was no evidence for the effectiveness of lubeluzole.⁵³⁸ Trials tested the efficacy of clomethiazole, a γ -aminobutyric acid agonist, alone or in combination with rtPA.⁴⁹⁶ The medication also was used to treat patients with hemorrhagic stroke.^{539,540} Larger clinical trials failed to demonstrate efficacy of clomethiazole in improving outcomes after ischemic stroke.^{541–545} Diazepam is being tested, but the results of the trials are not available.⁵⁴⁶ Although a dose-escalation study of naloxone found the medication to be safe, no hint of efficacy was noted.⁵⁴⁷ No benefit has been reported from treatment with the opioid antagonist nalmefene, as noted in other clinical trials.^{548,549} The neuroprotective agent NXY-059 (Cerovive) has been tested in clinical trials in acute stroke.⁵⁵⁰ A recently published clinical trial showed a shift in the rate of favorable outcomes, as measured by the modified Rankin Scale, among patients treated with NXY-059.⁵⁵¹ The rate of symptomatic bleeding among patients given rtPA seemed to be reduced by the use of NXY-059. Other outcomes were not improved. The results of a second study, which have not been published but which have been announced, did not demonstrate efficacy with the use of NXY-059. A pilot study testing the combination of caffeine and alcohol when started within 6 hours of stroke found the intervention to be relatively safe.⁵⁵² Additional research on this combination is needed.

Magnesium 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.^{553–556} However, the agent was given up to 12 hours after onset of stroke. Another study is testing the utility of early administration of magnesium in the field.³¹ A trial of tirilazad was halted prematurely when an interim analysis showed that the medication was not likely to be effective.^{557,558} A review of all trials testing tirilazad, including in the treatment of subarachnoid hemorrhage, concluded that the medication did not improve outcomes.⁵⁵⁹ A dose-escalation study suggested that ebselen might be safe and effective in improving outcomes after stroke, and another clinical trial is under way.⁵⁶⁰ A small clinical trial found that

edaravone might improve outcomes.⁵⁶¹ Neither of these medications is available in the United States.

Citicoline, an agent that appears to stabilize membranes, has been tested in several clinical studies.^{562–564} The trials did not demonstrate efficacy from treatment. A subsequent meta-analysis reported that patients with moderate to severe stroke might be helped if the medication was started within 24 hours of onset of symptoms.⁵⁶⁵ This finding should not be considered definitive but rather a rationale for further testing of the medication in this subgroup of patients. Several trials of GM1-ganglioside, which also may stabilize membranes, have not demonstrated improved outcomes with treatment.^{566–569} A systematic review of this agent did not demonstrate any benefit from treatment.⁵⁷⁰ Piracetam also has been tested in several clinical trials, with mixed results.^{571–574} Reviews of the medication also have reached differing conclusions; although the agent may be effective in some patients with ischemic stroke, there may be a trend for increased risk of death among patients treated with piracetam.^{575,576} At present, the data are not sufficiently clear to draw a conclusion about the utility of this medication.

Medications that reduce the inflammatory response to ischemia also have been evaluated. A randomized trial of enlimomab (an intercellular adhesion molecule-1 antagonist) found that the rates of poorer outcomes, including death, were increased among patients receiving the agent.⁵⁷⁷ Another trial tested a neutrophil inhibitory factor; although the medication was safe, it did not improve outcomes.⁵⁷⁸ A small study testing cerebrolysin, an agent that has potential neurotrophic and neuroprotective actions, found that the agent was safe and might improve outcomes.⁵⁷⁹ Preliminary studies of trafermin (basic fibroblast growth factor) show conflicting results. One study found that the agent was well tolerated, but another showed a higher death rate among treated patients.^{580,580} Other potential neuroprotective therapies, which are being tested, include erythropoietin, interferon- β , adenosine A₁ receptor agonists, and nitric oxide synthase inhibitors.

Hypothermia is a potent intervention that slows cerebral metabolism and protects neurons in settings of acute ischemia. Neurological outcomes after cardiac arrest appear to be improved by early institution of hypothermia.^{212,213} Hypothermia also has been used to treat patients with severe brain edema.²²⁵ This physical intervention could be combined with neuroprotective medications or therapies to restore perfusion.⁵⁸¹ Cooling may be achieved by the use of external cooling devices or endovascular approaches.^{216,219,222,582} The desired level of body temperature has not been determined. In addition, cooling may be associated with serious adverse reactions, including hypotension, cardiac arrhythmias, or infections.^{226,583} These complications appear to be associated with the degree of induced hypothermia, with the risk of side effects being correlated with prolonged hypothermia and lower temperatures. In addition, the time required to achieve the desired body temperature may be considerable, and the “therapeutic effect” of the lower temperature might not be achieved until after most of the acute cellular effects of ischemia have occurred.²¹⁸ Pilot studies suggest that cooling may be feasible and safe; it might be a therapeutic alternative for treatment of acute stroke.^{218,220} However, a recent clinical

trial found that induced hypothermia with modest lowering of temperature did not lessen the ischemic consequences of surgery for treatment of ruptured aneurysms.²¹⁵ In addition, a systematic review found no definitive evidence that either physical or chemical cooling interventions improved outcomes after acute ischemic stroke.²²⁷ Early induced hypothermia holds promise, and additional research is under way.²¹¹

Conclusions and Recommendations

Considerable experimental and clinical research is required before an intervention with identified neuroprotective effects can be recommended for treatment of patients with acute ischemic stroke. Several steps to improve research have been recommended.⁵⁸⁴ It is hoped that ongoing studies of neuroprotective interventions, including hypothermia, potentially tested alone or in combination with measures to restore perfusion, will demonstrate safety and efficacy.

Class III Recommendation

1. **At present, no intervention with putative neuroprotective actions has been established as effective in improving outcomes after stroke, and therefore none currently can be recommended (Class III, Level of Evidence A). This recommendation has not changed from previous guidelines.**

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

A. Admission to the Hospital

Approximately 25% of patients may have neurological worsening during the first 24 to 48 hours after stroke. It is difficult to predict which patients will deteriorate.^{277,585–588} Besides progression of the initial stroke, the potential for preventable neurological or medical complications also means that patients with stroke should be admitted to the hospital in most circumstances.^{589–593} 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 rtPA, (3) facilitate medical or surgical measures aimed at improving outcome after stroke, (4) begin measures to prevent subacute complications, (5) plan for long-term therapies to prevent recurrent stroke, and (6) start efforts to restore neurological function through rehabilitation and good supportive care.

B. Specialized Stroke Care Units

Several studies, performed mainly in Europe, demonstrate the utility of comprehensive stroke units in lessening the rates of mortality and morbidity after stroke.^{594–606} The positive effects can persist for years. The benefits from treatment in a stroke unit are comparable to the effects achieved with intravenous administration of rtPA.⁶⁰⁷ In addition, stroke unit care can be given to a broad number of patients regardless of the interval from stroke or severity of the neurological impairments, including patients who cannot be treated with thrombolytic therapy. In general, a European stroke unit includes a geographically defined facility staffed by skilled

professionals, including physicians, nurses, and rehabilitation personnel. The unit may have monitoring capabilities to permit close observation of changes in patients' neurological status or medical complications.^{608,609} European stroke units usually do not include intensive care unit-level treatment, including ventilatory assistance. Regular communications and coordinated care also are key aspects of the unit. Standardized stroke orders or integrated stroke pathways improve adherence to best practices for treatment of patients with stroke.^{610–612}

Such specialized care is included in recommendations for a CSC. It should be noted that most stroke units in the United States have much shorter lengths of stay than do the units evaluated in the European studies, and most do not incorporate comprehensive rehabilitation care.

1. General Care

Most of the individual components of general medical management after admission to the hospital have not been tested in clinical studies.^{182,590–592,613} Thus, recommendations are based on customary care and the finding 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. The patient's neurological status and vital signs should be assessed frequently during the first 24 hours after admission. Most patients are first treated with bed rest, but mobilization usually begins as soon as the patient's condition is considered stable. 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, deep vein thrombosis, pulmonary embolism, and pressure sores.⁶¹³ In addition, prolonged immobility may lead to contractures, orthopedic complications, or pressure palsies.^{590,614,615} Frequent turning, the use of alternating pressure mattresses, and close surveillance of the skin help to prevent pressure sores. Measures to avoid falls are an important part of mobilization.⁶¹⁶

2. Nutrition and Hydration

Sustaining nutrition is important because dehydration or malnutrition may slow recovery.^{617,618} Dehydration is a potential cause of deep vein thrombosis after stroke. Impairments of swallowing are associated with a high risk of pneumonia.⁶¹⁹ Some patients cannot receive food or fluids 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 the greatest risk for aspiration. Swallowing impairments are associated with an increased risk of death.⁶²⁰ An abnormal gag reflex, impaired voluntary cough, dysphonia, incomplete oral-labial closure, a high NIHSS score, or cranial nerve palsies should alert the physician to the risk.^{621–623} A preserved gag reflex may not indicate safety with swallowing.⁶²⁴ An assessment of the ability to swallow is important before the patient is allowed to eat or drink. A water swallow test performed at the bedside is a useful screening tool, and documentation of this assessment is included as a quality-of-

care measure after stroke. A wet voice after swallowing is a predictor of a high risk for aspiration. A videofluoroscopic modified barium swallow examination may be performed if indicated.

Most patients are treated initially with intravenous fluids. Intravenous hyperalimentation is rarely necessary. When necessary, a nasogastric or nasoduodenal tube may be inserted to provide feedings and to expedite administration of medications.⁶²⁵ Some patients may not tolerate a nasogastric tube, which also is associated with risk for aspiration pneumonia. Placement of a percutaneous endoscopic gastrostomy (PEG) tube often is used to treat patients who will need prolonged tube feedings.⁶²⁶ Although this device usually requires less care, complications, including involuntary removal of the tube or peritonitis, may occur.⁶²⁷ The risk of aspiration pneumonia is not eliminated by the use of a PEG. Some evidence suggests that use of the PEG tube is superior to nasogastric tube feedings.⁶²⁸

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 nasogastric feeding started within 7 days of stroke in comparison to later intervals on outcomes, and (3) the effect of PEG feedings on outcomes in comparison to nasogastric feedings.^{629,630} The studies that addressed the latter 2 questions were relatively small and, although negative, do not provide definitive data. The trial showed that supplemental nutrition was not necessary.

Bowel management to avoid constipation and fecal impaction or diarrhea also is a component of ancillary care.⁶³¹ Some feedings administered via a PEG or nasogastric tube may cause osmotic gradients that lead to diarrhea.

3. 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.^{590,619,632–634} Aslanyan et al⁶³³ found that the development of pneumonia was associated with an increased risk of death (hazard ratio 2.2) or unfavorable outcome (odds ratio, 3.8).⁶³³ The appearance of fever after stroke should prompt a search for pneumonia, and appropriate antibiotic therapy should be administered. Protection of the airway and suctioning may help to lower the risk of aspiration. Measures to treat nausea and vomiting also may lower the risk of aspiration pneumonia. Exercise and encouragement to take deep breaths may help to lessen the development of atelectasis. Prophylactic administration of levofloxacin was not successful in lessening the risk of pneumonia or other infections in the first days after stroke.⁶³⁵

Urinary tract infections are relatively common among patients with stroke. This complication is most likely associated with more seriously affected patients.⁶³³ Bacteremia or sepsis is a potential complication. Screening of the urine 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.⁶³⁶ To ease care and to avoid skin complications, some patients will need an indwelling bladder catheter to treat

incontinence or urinary retention. Whenever possible, prolonged use of an indwelling catheter should be avoided because of the attendant increased risk of urinary infections. Condom catheters are not satisfactory. Intermittent catheterization may be needed. Acidification of the urine also may lessen the risk of infection. Anticholinergic agents may help in recovery of bladder function. Although prophylactic administration of antibiotics usually is not done, the medications should be prescribed for patients with evidence of urinary tract infections.

C. Deep Vein Thrombosis and Pulmonary Embolism

Pulmonary embolism accounts for $\approx 10\%$ of deaths after stroke, and the complication may be detected in $\approx 1\%$ of patients who have had a stroke.⁶³⁷ 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 deep vein thrombosis also slows recovery and rehabilitation after stroke. The risk of deep vein thrombosis is highest among immobilized and older patients with severe stroke.^{638–642}

The institution of measures to prevent deep vein thrombosis after stroke is a quality indicator for stroke centers in the United States.^{643,644} The options for lowering the risk of deep vein thrombosis include early mobilization, antithrombotic agents, and the use of external compression devices. The benefit of early mobilization is described above. Anticoagulants are given to prevent deep vein thrombosis and pulmonary embolism among seriously ill patients. Much of the support for the use of anticoagulants comes from clinical studies testing these agents in treating bedridden patients other than those with stroke.^{645,646} Meta-analysis demonstrated that these medications were effective among patients with stroke.⁶⁴⁷ Several clinical trials have demonstrated the utility of heparin and the LMW heparins in preventing deep vein thrombosis. There does not appear to be a significant difference in efficacy or safety between unfractionated heparin and the LMW heparins.^{648–660} The risk of serious bleeding complications seems to be relatively low.⁶⁵⁴ Long-term treatment usually involves the use of oral anticoagulants such as warfarin. Ridker et al⁶⁶¹ found that low-intensity warfarin therapy was effective in preventing recurrent venous thromboembolism. Ximelagatran also appears to be effective in lowering the risk of deep vein thrombosis, but this agent is not yet available in the United States. Aspirin also may be effective for patients who have contraindications to anticoagulants, although direct comparisons with anticoagulants are not available.^{662,663} Experience with the use of external compression of the veins in the lower extremities such as stockings or alternating pressure devices is limited.^{664–666} External compression may be useful for managing patients who cannot be treated with antithrombotic agents.^{654,655} Patients with pulmonary embolism from thrombi in the lower extremities and a contraindication for antithrombotic treatment may need the placement of a device to occlude the inferior vena cava.

1. Other Care

After stabilization of the patient's condition, rehabilitation, measures to prevent long-term complications, patient and family education, and family support may be started. Some patients may need treatment for depression. In addition, the patient should be evaluated to determine the most likely cause of stroke. Medical or surgical measures to prevent recurrent stroke should be initiated. Administration of antithrombotic agents (either antiplatelet agents or, in some cases, anticoagulants) before discharge is a quality-of-care indicator for stroke treatment in the United States. Measures to treat hyperlipidemia, diabetes mellitus, hypertension, and codeveloping heart disease also are important. Lifestyle changes include cessation of smoking and changes in diet. Changes in activity will reflect the patient's neurological impairments and overall health.

D. Conclusions and Recommendations

The management of patients after admission to the hospital remains a key component of overall treatment, and it is as 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 given to the large number of patients who are not eligible for treatment with the acutely administered interventions. These therapies can improve outcomes by lessening complications and speeding recovery from stroke.

Class I Recommendations

1. The use of comprehensive specialized stroke care (stroke units) incorporating rehabilitation is recommended (Class I, Level of Evidence A). *This recommendation is unchanged from the previous guideline.*
2. The use of standardized stroke care order sets is recommended to improve general management (Class I, Level of Evidence B). *This recommendation was not in previous guidelines.*
3. Early mobilization of less severely affected patients and measures to prevent subacute complications of stroke are recommended (Class I, Level of Evidence C). *This recommendation is unchanged from the previous guideline.*
4. Assessment of swallowing before starting eating or drinking is recommended (Class I, Level of Evidence B). *This recommendation is new.*
5. Patients with suspected pneumonia or urinary tract infections should be treated with antibiotics (Class I, Level of Evidence B). *This recommendation is similar to previous guidelines.*
6. Subcutaneous administration of anticoagulants is recommended for treatment of immobilized patients to prevent deep vein thrombosis (Class I, Level of Evidence A). The ideal timing for starting these medications is not known. *This recommendation is unchanged from the previous guideline.*
7. Treatment of concomitant medical diseases is recommended (Class I, Level of Evidence C). *This recommendation is unchanged from the previous guideline.*

8. Early institution of interventions to prevent recurrent stroke is recommended (Class I, Level of Evidence C). *This recommendation is similar to previous guidelines.*

Class II Recommendations

1. Patients who cannot take food and fluids orally should receive nasogastric, nasoduodenal, or PEG feedings to maintain hydration and nutrition while undergoing efforts to restore swallowing (Class IIa, Level of Evidence B). The timing of the placement of a PEG is uncertain. *This recommendation is new.*
2. Aspirin is a potential intervention to prevent deep vein thrombosis but is less effective than anticoagulants (Class IIa, Level of Evidence A). *This recommendation has been strengthened.*
3. The use of intermittent external compression devices is recommended for treatment of patients who cannot receive anticoagulants (Class IIa, Level of Evidence B). *This recommendation is unchanged from the previous guideline.*

Class III Recommendations

1. Nutritional supplements are not needed (Class III, Level of Evidence B). *This recommendation is new.*
2. Prophylactic administration of antibiotics is not recommended (Class III, Level of Evidence B). *This recommendation is new.*
3. If possible, the placement of indwelling bladder catheters should be avoided because of the associated risk of urinary tract infections (Class III, Level of Evidence C). Some patients may need prolonged catheter drainage of the bladder, and measures to lower risk of infection should be taken. *This recommendation is similar to previous guidelines.*

XVI. Treatment of Acute Neurological Complications

The most important acute neurological complications of stroke are (1) swelling of the ischemic tissue causing mass effect; (2) hemorrhagic transformation of the infarction with or without mass effect; and, less commonly, (3) seizures. A recent study (worsening defined as a decreasing NIHSS score of ≥ 1 point) found that more than one third of patients deteriorated because of progressive stroke, approximately one third because of brain swelling, 11% because of recurrent cerebral ischemia, and 10% because of parenchymal hemorrhage.⁶⁶⁷

A. Ischemic Brain Swelling

Brain swelling, when associated with astrocytic ischemia, is due to a cytotoxic reaction mediated by multiple factors, including free radicals.⁶⁶⁸ Progressive clinical deterioration due to swelling from MCA occlusion is seen more often in women and in patients with additional vascular territorial infarctions on initial CT.⁶⁶⁹ Brain swelling typically occurs in patients who have had an occlusion of the stem of the MCA and appears ≈ 4 days after the onset.⁶⁷⁰⁻⁶⁷⁴ Dramatic early swelling has been described and attributed to reperfusion edema and possibly effects of rtPA. The term *malignant* has been affixed to brain swelling to delineate a group of patients with a large territorial infarct that swells within 24 hours,

causing brain herniation signs.⁶⁷⁵ The proportion of patients with this so-called malignant form is unknown, and its clinical profile is not well defined. Rapid deterioration from cerebellar infarcts with swelling is also more common and may be associated with sudden apnea from brain stem compression and cardiac arrhythmias. The overall risk of brain swelling in patients with anterior circulation ischemic stroke is low and is estimated to be 10% to 20%.^{376,377} The incidence in posterior circulation stroke is unknown. An imaging study may predict deterioration from swelling. Early CT scan hypodensity, defined as <12 hours after onset, of $>50\%$ of the MCA territory and the presence of hyperdense MCA signs were independent predictors of neurological deterioration.⁶⁷¹ In addition, patients with MCA infarction who developed a mass effect on CT scan as identified by compression of the frontal horn, shift of the septum pellucidum, and, later, shift of the pineal gland are at risk of worsening clinically and developing clinical signs of brain herniation.⁶⁷¹ Perfusion CT scan performed within 6 hours of symptom onset could determine which patient would deteriorate from swelling. Large hypoattenuation (defined as greater than two thirds of the MCA territory) on enhanced CT and large hypoperfusion on CT perfusion maps predicted development of "malignant MCA infarct" with high sensitivity of 91% and specificity of 94%.⁶⁷⁶

Very few clinical signs predict clinical deterioration. Patients with bilateral ptosis and involvement of the nondominant hemisphere may be at a higher risk. Multivariable analysis found that a history of hypertension, history of heart failure, presence of elevated white blood cell count, presence of $>50\%$ MCA hypodensity, and involvement of additional vascular territory increased the development of fatal brain edema.⁶⁷⁷ The need for early mechanical ventilation increases the risk of death.⁶⁷⁸

In patients with MCA infarctions who develop brain edema, increased intracranial pressure probably occurs late in the course, if at all.⁶⁷⁹ Therefore, aggressive management of intracranial pressure in patients with early developing cerebral edema is not an established goal. One of the principles in the management of brain edema after MCA infarction is to prevent further deterioration from tissue displacement and brain stem shift.

Similarly, management of cerebellar swelling should include a decompressive suboccipital craniotomy to remove the necrotic tissue. Initial management of brain swelling should include restriction of free water to avoid hypo-osmolar fluid that may worsen edema. Factors that could exacerbate swelling such as hypoxemia, hypercarbia, and hyperthermia should be corrected. The head of the bed can be elevated at 20° to 30° in an attempt to help venous drainage. Antihypertensive agents, particularly those that include cerebral vasodilatation, should be avoided.

The treatment of patients with raised intracranial pressure, present at a late stage, is directed toward standard measures that include hyperventilation, osmotic diuretics, drainage of cerebral fluid, or decompressive surgery.⁶⁸⁰ No clinical trials address the efficacy of any of these aggressive management strategies after stroke. No evidence indicates that hyperventilation, corticosteroids in conventional or large doses, furo-

semide, mannitol, or glycerol or other measures that reduce intracranial pressure improve outcome in patients with ischemic brain swelling.^{681–690} Mannitol is typically used at 0.25 to 0.5 g/kg IV administered over 20 minutes, lowers intracranial pressure, and can be given every 6 hours.⁶⁹¹ The usual maximal dose is 2 g/kg. The effect of mannitol in patients with ischemic brain swelling is unknown, but it is often used as a temporizing measure before patients undergo decompressive craniectomy. Despite intensive medical management, the death rate is estimated to be as high as 50% to 70%.^{465,466}

Decompressive surgery, including hemicraniectomy and durotomy with temporal lobe resection, remains the most attractive option for ischemic brain swelling.^{692–701} Timing of surgery is poorly defined, with some opting for early (within 24 hours) intervention.⁷⁰² Recent studies have found that decompressive craniectomy may have a less favorable outcome than suggested.⁷⁰³ More disability may be expected in older patients (>55 years of age) and in patients with dominant infarctions.⁷⁰⁴ Additional surgery, “strokectomy,” of parts of the frontal or temporal lobe may be needed in younger patients who fail to improve.⁷⁰⁵ The timing of decompressive hemicraniectomy and indications remain unclear. Several randomized, controlled clinical trials are under way in Europe.⁷⁰⁶ An alternative option to control brain swelling is moderate hypothermia, defined as 33°C to 34°C, with the use of noninvasive or invasive cooling devices; this strategy is unproven, but feasibility trials are under way.

Patients with cerebellar infarct often develop acute hydrocephalus. If hydrocephalus is present, drainage of cerebral fluid through an intraventricular catheter can rapidly lower intracranial pressure; however, a concern about upward herniation of cerebellar tissue remains.^{707–710} Suboccipital craniotomy is the treatment to relieve both hydrocephalus and brain stem compression caused by large cerebellar infarctions.^{703,698,710–716}

B. Hemorrhagic Transformation

Considerable information exists about the natural rate of early hemorrhagic transformation of ischemic stroke.^{717–723} Some studies suggest that almost all infarctions have some element of petechial hemorrhage. With the use of CT, one prospective study estimated that ≈5% of the infarctions spontaneously developed symptomatic hemorrhagic transformations from frank hematomas.⁷²⁴ The location, size, and cause of stroke can influence the development of this complication. Further information about the influence of hemorrhagic transformation outcome in stroke is needed. Small asymptomatic petechiae are much less important than hematomas, which can be associated with neurological decline. The use of all anti-thrombotics, but especially anticoagulants and thrombolytic agents, increases the likelihood of serious hemorrhagic transformation.^{729,725–727} The early use of aspirin is also associated with a small increase in the risk of clinical detectable hemorrhage.

Management of patients with hemorrhagic infarction depends on the amount of bleeding and its symptoms and may include clot evacuation in deteriorating patients. A recent study found that hemorrhagic transformation in stroke patients was detected in one third of patients admitted to acute

rehabilitation, but functional outcome was not significantly different from that of patients who did not have hemorrhagic transformation on the first CT scan.⁷²⁸ Hemorrhagic conversion in patients with cerebellar infarct significantly increased the risk of deterioration.⁷²⁹ Recently, it has been suggested that gadolinium enhancement on T1-weighted MR images is predictive of hemorrhagic transformation, but this finding is unconfirmed.⁷³⁰

C. Seizures

The reported frequency of seizures during the first days of stroke ranges from 2% to 23% depending on study designs.^{704,731–734} The true risk of seizures appears to be toward the lower end of the estimate. Seizures are more likely to occur within 24 hours of stroke and are usually partial, with or without secondary generalization. Recurrent seizures develop in ≈20% to 80% of patients; however, recent estimates have found the rate of early postischemic stroke seizures to range from 2% to 33%. Late seizures vary from 3% to 67%.^{735,736} The risk of late seizures is higher in patients with preexisting dementia.⁷³⁷ Status epilepticus is uncommon.⁷³⁸ No data are available on the utility of prophylactic administration of anticonvulsants after stroke. Few data are available on the efficacy of anticonvulsants in the treatment of stroke patients who have experienced seizures. Thus, recommendations are based on the established management of seizures that may complicate any neurological illness.

D. Conclusions and Recommendations

Considerable research is needed on the prevention and treatment of neurological complications of acute ischemic stroke, including seizures, hemorrhagic transformation of the infarction, and brain edema. The latter, which is a leading cause of death after a major ischemic stroke, is a pressing issue. At present, neither medical nor surgical interventions have been established as effective in controlling brain edema, preventing the neurological consequences of increased intracranial pressure or herniation, or improving outcomes after stroke. Although several medical interventions are used traditionally to control edema and although surgical procedures may be a life-saving measure, it appears that earlier interventions may be associated with better clinical outcomes than waiting for the patient to have signs of profound neurological dysfunction, such as herniation. Until additional data are available, the recommendations that follow are based on general consensus or limited information.

Class I Recommendations

1. Patients with major infarctions affecting the cerebral hemisphere or cerebellum 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 B). *This recommendation has not changed since the previous guidelines. Because many hospitals may not have neurosurgical expertise, transfer of patients at risk for malignant*

brain edema to an institution that has such expertise should be considered. *This recommendation is new.*

2. Patients with acute hydrocephalus secondary to an ischemic stroke most commonly affecting the cerebellum can be treated with placement of a ventricular drain (Class I, Level of Evidence B). *This recommendation has not changed since the previous guidelines.*
3. Decompressive surgical evacuation of a space-occupying cerebellar infarction is a potentially life-saving measure, and clinical recovery may be very good (Class I, Level of Evidence B). Although data from clinical trials are not available, it is recommended for patients with major cerebellar infarction. *This recommendation has not changed since the previous guidelines.*
4. Recurrent seizures after stroke should be treated in a manner similar to other acute neurological conditions (Class I, Level of Evidence B). *This recommendation has not changed since the previous guidelines.*

Class II Recommendations

1. Although aggressive medical measures, including osmotherapy, have been recommended for treatment of deteriorating patients with malignant brain edema after large cerebral infarction, these measures are unproven (Class IIa, Level of Evidence C). Hyperventilation is a short-lived intervention. Medical measures may delay decompressive surgery. *This recommendation has not changed since the previous guidelines.*
2. Decompressive surgery for malignant edema of the cerebral hemisphere may be life-saving, but the impact of morbidity is unknown. Both the age of the patient and the side of the infarction (dominant versus non-dominant hemisphere) may affect decisions about surgery. 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 (Class IIa, Level of Evidence B). *This recommendation has been modified.*
3. No specific recommendation is made for treatment of patients with asymptomatic hemorrhagic transformation after ischemic stroke (Class IIb, Level of Evidence C). *This recommendation is new.* Treatment of symptomatic hemorrhagic transformation is addressed in the intracerebral hemorrhage management guideline being issued contemporaneously with this statement. Measures to lessen the likelihood of hemorrhagic complications of thrombolytic agents or other inter-

ventions to restore or improve perfusion such as careful control of arterial blood pressure are recommended.

Class III Recommendations

1. 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). *This recommendation has not changed since the previous guidelines.*
2. Prophylactic administration of anticonvulsants to patients with stroke but who have not had seizures is not recommended (Class III, Level of Evidence C). *This recommendation has not changed since the previous guidelines.*

E. Palliative Care

Unfortunately, some patients with stroke have a fatal brain injury. These critically ill persons have profound neurological impairments such as a persistent vegetative state or evidence of unstable vital signs. Other patients with stroke have serious preexisting medical or neurological illnesses, such as dementia, that have caused severe impairments, and the new cerebrovascular event may add more disability. Despite the interventions that are described in this outline, the prognosis of such patients often is very poor. Many people would not want to survive if a devastating stroke would lead to a persistent vegetative state or other condition of devastating incapacity.

An increasing number of patients have advanced directive statements that provide instructions about emergency treatment in a situation such as a massive stroke. Physicians should honor those directives. In other circumstances, such directives may not be available, and the patient's neurological status usually precludes decision making. Occasionally, a guardian with medical power of attorney can make the decision. Otherwise, the physician should involve family members. The physician should provide clear information about the nature of the stroke, the prognosis, and the treatment options. The family should be given the opportunity to select or withhold medical interventions. In such situation, the medical care may emphasize measures to keep the patient comfortable and to support the family during the terminal aspects of the stroke.

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Writing Group Disclosures

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Harold P. Adams, Jr	University of Iowa Carver College of Medicine	Boehringer Ingelheim†; Centocor (Johnson & Johnson)†; Eli Lilly†; Merck†; NMT Medical†; Sanofi†; Bristol-Myers Squibb†; GlaxoSmithKline*	AstraZeneca†; Merck*	Bayer*	None	American Board of Psychiatry and Neurology†	None
Gregory del Zoppo	Scripps Research Institute	None	None	None	None	Boehringer Ingelheim (overseas product for fibrinolysis)*	None
Mark J. Alberts	Northwestern University Medical School	Boehringer Ingelheim*; Bristol-Myers Squibb*; Sanofi-Synthelabo*	None	AstraZeneca*; Boehringer Ingelheim*; Bristol-Myers Squibb†; Sanofi-Synthelabo†	None	AstraZeneca*; Boehringer Ingelheim*; Bristol-Myers Squibb†; Sanofi-Synthelabo†	None
Deepak L. Bhatt	Cleveland Clinic Foundation	Bristol-Myers Squibb†; Eisai†; Ethicon†; Sanofi-Aventis†; The Medicines Company†	None	AstraZeneca*; Bristol-Myers Squibb*; Cardax*; Centocor*; Daiichi-Sankyo*; Eisai*; Eli Lilly*; GlaxoSmithKline*; Millenium*; Otsuka*; ParinGenix*; PDL*; Sanofi-Aventis*; Schering-Plough*; The Medicines Company*; tns Healthcare*	None	AstraZeneca*; Bristol-Myers Squibb†; Cardax*; Centocor*; Daiichi-Sankyo*; Eisai*; Eli Lilly*; GlaxoSmithKline*; Millenium*; Otsuka*; ParinGenix*; PDL*; Sanofi-Aventis*; Schering-Plough*; The Medicines Company*; tns Healthcare*	Provided expert testimony regarding antithrombotic therapy
Lawrence Brass	Yale University	Bristol-Myers Squibb*; Sanofi-Synthelabo*	None	Bristol-Myers Squibb*; Sanofi-Synthelabo*; Solvay Pharmaceuticals*; Wyeth*	None	AstraZeneca*; Bristol-Myers Squibb†; Merck*; ONO Pharmaceuticals*; Sanofi-Synthelabo*; Solvay Pharmaceuticals*; Wyeth*	None
Anthony Furlan	Cleveland Clinic Foundation	Bristol-Myers Squibb†; Sanofi†; Possis*	None	None	None	Paion*	None
Robert L. Grubb	Washington University	None	None	None	None	None	None
Randall T. Higashida	University of California at San Francisco Medical Center	Concentric Medical*	None	None	None	Concentric Medical*	None
Edward C. Jauch	University of Cincinnati College of Medicine	Biosite*	None	Boehringer Ingelheim*	None	AstraZeneca*; Biosite*; Genentech*; Johnson & Johnson*; Novo Nordisk*	None
Chelsea Kidwell	Washington Hospital Center Stroke Center	None	None	None	None	Bristol-Myers Squibb†; GlaxoSmithKline*; Millenium Pharmaceuticals*; S. Daiichi Arbio Pharmaceuticals*; Sanofi*	None
Patrick D. Lyden	University of California at San Diego Stroke Center	AstraZeneca*; Bayer*; Merck*; Yamanouchi*	None	None	None	Merck*; Mitsubishi*	None
Lewis B. Morgenstern	University of Michigan	None	None	AstraZeneca*; Novo Nordisk*	None	Merck*	None
Adnan I. Qureshi	University of Minnesota, Minneapolis	Centocor Therapeutic†; ESP Pharma*	None	Bristol-Myers Squibb*; Sanofi Pharmaceuticals*	None	Pfizer*; Protein Design Laboratories*	None
Robert H. Rosenwasser	Thomas Jefferson University	None	None	None	None	None	None
Phillip A. Scott	University of Michigan	None	None	None	None	AstraZeneca*	None
Eelco F.M. Wijdicks	Mayo Clinic	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire that all members of the writing group are required to complete and submit. A relationship is considered to be "Significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.

*Modest.

†Significant

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
S. Claiborne Johnston	University of California at San Francisco	Sanofi Aventis/Bristol-Myers Squibb†	None	None	None	None	Boehringer Ingelheim for Secondary Stroke Prevention Trials†	None
Ralph Sacco	Columbia University	NINDS grants for stroke research†	None	None	None	None	None	None
Stanley Tuhim	Mount Sinai Medical Center	None	None	None	None	None	None	None

This table represents the relationships of reviewers that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire that all reviewers are required to complete and submit. A relationship is considered to be "Significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "Modest" if it is less than "Significant" under the preceding definition.

†Significant.

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APPENDIX I



RANDEE PARSONS and PEGGY PARSONS, Plaintiffs - Appellants, v. SISTERS OF CHARITY OF LEAVENWORTH HEALTH SYSTEMS INC., a Kansas corporation; et al., Defendants - Appellees.

No. 11-35693

UNITED STATES COURT OF APPEALS FOR THE NINTH CIRCUIT

2012 U.S. App. LEXIS 15375

July 11, 2012, Argued and Submitted, Seattle, Washington
July 25, 2012, Filed

NOTICE: PLEASE REFER TO *FEDERAL RULES OF APPELLATE PROCEDURE RULE 32.1* GOVERNING THE CITATION TO UNPUBLISHED OPINIONS.

SUBSEQUENT HISTORY: Petition for certiorari filed at, 12/03/2012

PRIOR HISTORY: [*1]

Appeal from the United States District Court for the District of Montana. D.C. No. 1:10-cv-00047-RFC. Richard F. Cebull, Chief District Judge, Presiding. *Parsons v. Sisters of Charity of Leavenworth Health Sys.*, 832 F. Supp. 2d 1222, 2011 U.S. Dist. LEXIS 57958 (D. Mont., 2011)

DISPOSITION: AFFIRMED.

COUNSEL: For RANDEE PARSONS, PEGGY PARSONS, Plaintiffs - Appellants: Neel Hammond, Jr., Esquire, Attorney, Hammond Law, PLLC, Missoula, MT.

For SISTERS OF CHARITY OF LEAVENWORTH HEALTH SYSTEMS INC., a Kansas corporation, Defendant - Appellee: William Anderson Forsythe, MOULTON BELLINGHAM PC, Billings, MT.

For BLUE CROSS AND BLUE SHIELD OF KANSAS CITY, a Missouri corporation, BLUE CROSS AND BLUE SHIELD OF SOUTH CAROLINA FOUNDATION, a South Carolina corporation, Defendants - Appellees: Bernard F. Hubley, Attorney, Michael F. McMahon, Attorney, Stefan T. Wall, Attorney, MCMAHON, WALL & HUBLEY PLLC, Helena, MT.

JUDGES: Before: REINHARDT, KLEINFELD, and M. SMITH, Circuit Judges.

OPINION

MEMORANDUM *

* This disposition is not appropriate for publication and is not precedent except as provided by 9th Cir. R. 36-3.

Plaintiffs-Appellants appeal from an order granting summary judgment in favor of Sisters of Charity of Leavenworth Health Systems, Inc., BlueCross BlueShield of Kansas City, and BlueCross BlueShield of South Carolina. We have jurisdiction under 28 U.S.C. § 1291. [*2] We review the grant of summary judgment de novo. *Johnson v. Buckley*, 356 F.3d 1067, 1071 (9th Cir. 2004).

The benefit plan declined to cover Randee Parsons for participating in a clinical trial for autologous bone marrow transplant (ABMT) with Dr. Richard Burt because the trial was "experimental and investigational," and therefore not covered by the plan. We need not decide whether the district court should have reviewed the denial of coverage de novo or for abuse of discretion, or what law applies, because regardless, there is no genuine issue of fact as to whether this ABMT procedure was "experimental and investigational" under the plan.

A procedure is experimental and investigational under the plan if it: (1) has not received required final approval to market from appropriate government bodies; (2) is one about which the peer-reviewed medical literature does not permit conclusions concerning its effect on health outcomes; (3) is not demonstrated to be an estab-

lished alternative; (4) has not been demonstrated to improve net health outcomes; or (5) is one in which the improvement claimed is not demonstrated to be obtainable outside the experimental and investigational setting.

Here, [*3] the procedure has only been approved by the FDA for the clinical trial phase. It has not received FDA final approval. The only legible peer reviewed literature submitted, coauthored by Dr. Burt, discusses a "pilot study" of twelve patients, and says a "randomized study will be needed to confirm the efficacy of this therapy." In his deposition, Dr. Burt stated that he

had not yet completed the randomized trial. No improvements have been obtained, so far as the record shows, outside the experimental and investigational setting. The consent form signed by Randee Parsons describes this as an experimental procedure.

Accordingly, the Parsons failed to raise a genuine issue of material fact that this procedure is not experimental and investigational under the plan. The remaining arguments lack any outcome-changing force.

AFFIRMED.