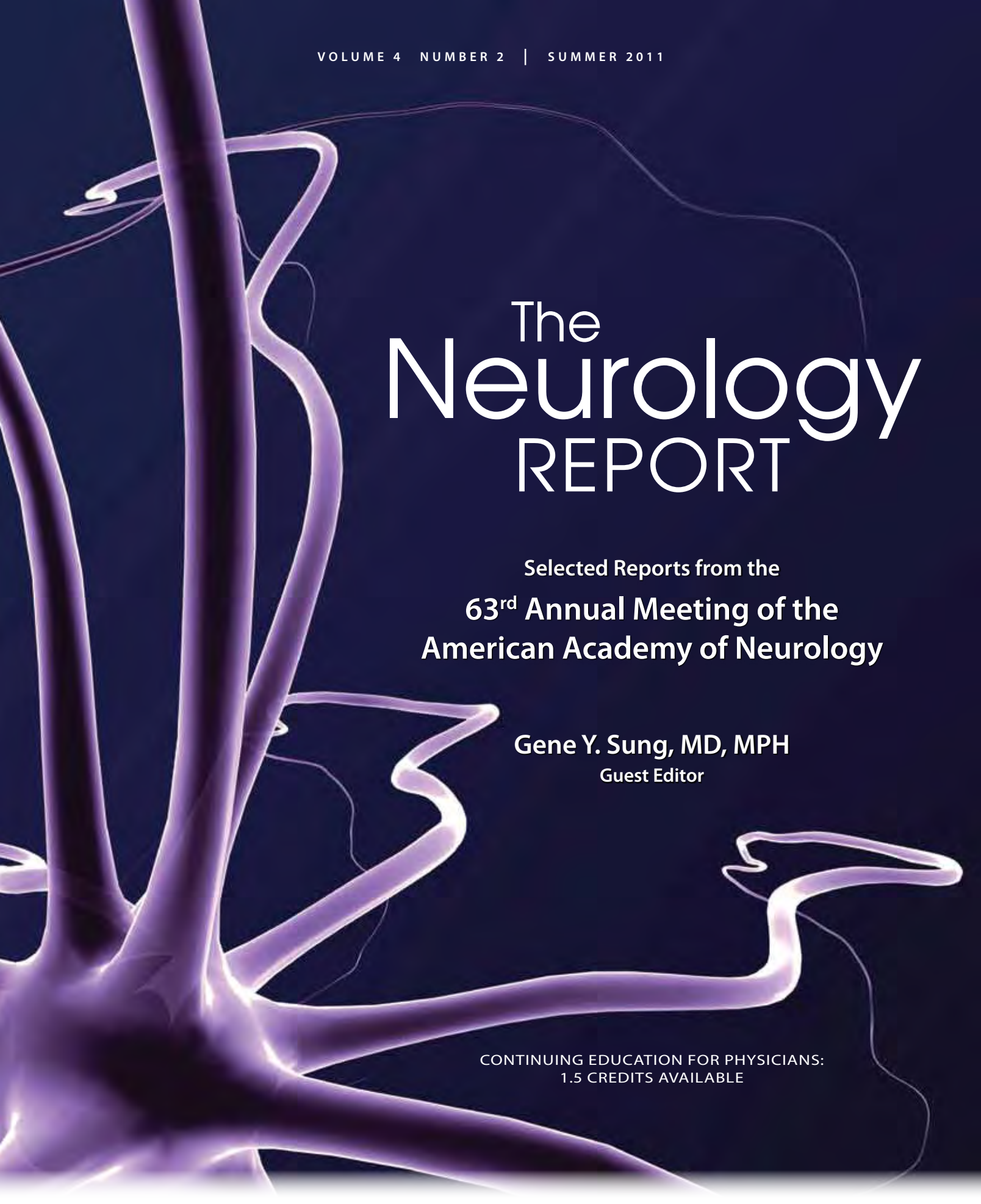
VOLUME 4 NUMBER 2 | SUMMER 2011



The Neurology REPORT

Selected Reports from the 63rd Annual Meeting of the American Academy of Neurology

Gene Y. Sung, MD, MPH
Guest Editor

CONTINUING EDUCATION FOR PHYSICIANS:
1.5 CREDITS AVAILABLE

Supported by an educational grant from Genentech, Inc.

Genentech

Guest Editor: Gene Y. Sung, MD, MPH

This publication was made possible through an educational grant from Genentech, Inc.

VOLUME 4 NUMBER 2 | SUMMER 2011

The Neurology REPORT

Selected Reports from the
63rd Annual Meeting of the
American Academy of Neurology

Gene Y. Sung, MD, MPH
Guest Editor

About This CME Activity

RATIONALE AND PURPOSE

Every minute of cerebral ischemia increases the chance that a stroke patient will lose cognitive and motor function. This simple fact haunts healthcare personnel charged with managing acute stroke patients from the time a 911 call is received. This edition of *The Neurology Report* focuses on prompt recognition of stroke, other medical conditions that may mimic this potentially devastating phenomenon, and optimal treatment strategies to prevent permanent damage and improve patient outcomes. The authors discuss the importance of emergency medical services (EMS) personnel in the triage of acute stroke patients and the challenges they face in assessment and early management of potential stroke victims, the sensitivity of stroke diagnosis by EMS workers, and recommendations for improving their skills. These reports also cover coordination of acute stroke care, medicolegal and temporal issues related to the use—or nonuse—of recombinant tissue plasminogen activator (alteplase, tPA) in stroke patients, and the value of modern telecommunications in managing patients in remote areas. Speakers discussed the development and validation of an intensity-of-care quality metric specific to intracerebral hemorrhage (ICH), which may help clinicians to standardize the care of acute stroke in different therapeutic settings. Experts also shared cutting-edge information on the medical and surgical management of acute stroke, recommendations on managing this condition more rapidly, and the results of studies investigating the many aspects of stroke care. The articles within are based upon presentations delivered during the 63rd Annual Meeting of the American Academy of Neurology, held April 9–16, 2011, in Honolulu, Hawaii.

The articles in this issue, written from the academic perspective of physicians-in-training at leading medical institutions, summarize the import of these new findings and place them into clinical context. This activity has been developed and approved by a planning committee of nationally recognized thought leaders to meet a perceived educational need to provide neurologists, neurosurgeons, and other physicians with diagnostic and therapeutic strategies to help them perform their medical roles.

LEARNING OBJECTIVES

After studying this issue of *The Neurology Report,* participants in this educational activity should be able to:

- Identify obstacles to recognizing and optimally managing acute stroke and methods for providing better emergency treatment of affected patients.
- Evaluate currently available drugs and devices intended to prevent or treat ICH, and recall temporal mandates for administering stroke therapy.
- Summarize medicolegal issues and clinical findings on the use of intravenous tPA for acute ischemic stroke.
- Interpret the results of research on an intensity-of-care, ICH-specific quality metric and the sensitivity of EMS diagnosis and early management of stroke.

TARGET AUDIENCE

Neurologists, neurosurgeons, and other physicians significantly involved in the management of patients with acute ischemic stroke should find participation in this educational activity valuable.

ACCREDITATION AND CREDIT DESIGNATION

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of the University of Cincinnati and Direct One Communications, Inc.

The University of Cincinnati is accredited by the ACCME to provide continuing medical education for physicians. The University of Cincinnati designates this educational activity for a maximum of 1.5 *AMA PRA Category 1 Credits*™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

CREDIT AVAILABILITY

Activity release date: June 29, 2011
Expiration date: June 30, 2012

METHOD OF PARTICIPATION

This self-instructional CME activity is available in print and online at **www.NeurologyReport.com** and consists of an introduction, four articles, a postactivity assessment, and an evaluation. Estimated time to complete the activity is 1.5 hours.

To receive credit, participants must read the CME information on these two pages, including the learning objectives and disclosure statements, as well as the full content of this monograph, and then complete the post test and evaluation form online at **www.NeurologyReport.com**. Upon successful completion of the post test (80% correct) and evaluation form, a CME certificate

of participation will be awarded automatically. The certificate may be printed directly from the Web site or e-mailed and printed later.

There are no fees for participating in or receiving credit for this activity.

CME REVIEWER

Rick Ricer, MD
Adjunct Professor of Family Medicine
University of Cincinnati
Cincinnati, Ohio

CME ACCREDITATION

Susan P. Tyler, MEd, CMP, CCMEP
Director, Continuing Medical Education
University of Cincinnati
Cincinnati, Ohio

FACULTY DISCLOSURES

All faculty members (or anyone else in a position to control content, such as activity planners) are required to complete a Disclosure of Commercial Interest and Resolution form and to cooperate with identified methods for resolving conflict of interest prior to participating in the activity. The University of Cincinnati requires disclosure to the learners of all relevant financial relationships and adheres strictly to the ACCME Standards for Commercial Support.

Gene Y. Sung, MD, MPH, is Associate Professor of Neurology and Chief, Division of Stroke and Neurocritical Care, University of Southern California, Los Angeles, California. Dr. Sung is on the advisory boards of Cerebrotech and Aristos; is a consultant to The Medicines Company; has received grants from the National Stroke Association, the National Institutes of Health, and Genentech; and serves on the speakers' bureaus of Bristol-Myers Squibb and Boehringer Ingelheim.

Fawad Ahmed Khan, MD, a fourth-year Adult Neurology Resident at the University of North Carolina Hospital, Chapel Hill, North Carolina, has nothing to disclose.

Kristian Barlinn, MD, a Research Fellow in the Comprehensive Stroke Center of the Department of Neurology, University of Alabama at Birmingham Hospital, Birmingham, Alabama, has nothing to disclose.

Neil F. Rosenberg, MD, a Fellow in Neurocritical Care at Northwestern Memorial Hospital, Chicago, Illinois, has nothing to disclose.

Basanagoud Mudigoudar, MD, a Child Neurology Resident at SUNY Downstate Medical Center, Brooklyn, New York, has nothing to disclose.

Rick Ricer, MD, has nothing to disclose.

Susan P. Tyler, MEd, CMP, CCMEP, has nothing to disclose.

Jacqueline Keenan and **Edwin Geffner** of Direct One Communications, Inc., have nothing to disclose.

DISCLAIMER

This activity is an independent educational activity under the direction of the University of Cincinnati. The activity was planned and implemented in accordance with the Essential Areas and Policies of the ACCME, the Ethical Opinions/Guidelines of the American Medical Association, the US Food and Drug Administration (FDA), the Office of Inspector General of the US Department of Health and Human Services, and the Pharmaceutical Research and Manufacturers of America Code on Interactions With Healthcare Professionals, thus assuring the highest degree of independence, fair balance, scientific rigor, and objectivity.

However, the planning committee, faculty, University of Cincinnati, Genentech, Inc., and Direct One Communications, Inc. shall in no way be liable for the currency of information or for any errors, omissions, or inaccuracies in this activity. The opinions and recommendations presented herein are those of the faculty and do not necessarily reflect the views of the provider, producer, or grantors.

Participants in this activity are encouraged to refer to primary references or full prescribing information resources.

DISCLOSURE OF UNAPPROVED/OFF-LABEL USE

Discussions concerning drugs, dosages, devices, and procedures may reflect the clinical experience of the planning committee or faculty, may be derived from the professional literature or other sources, or may suggest uses that are investigational and not approved labeling or indications.

In particular, Drs. Neil F. Rosenberg and Basanagoud Mudigoudar discuss the evidence for extending the time window for administering IV tPA to 4.5 hours following the onset of stroke symptoms, a use that is currently under review by the FDA. Dr. Rosenberg also briefly describes a clinical trial of the investigational thrombolytic prourokinase and research on several intra-arterial treatments for restoring perfusion, none of which is currently approved.

CONTACT INFORMATION

We would like to hear your comments regarding this or other educational activities produced by Direct One Communications, Inc. In addition, suggestions for future activities are welcome. Contact us at:

Direct One Communications, Inc.
1424 Ridge Road
Syosset, NY 11791
Phone: 516-364-1020
Fax: 516-364-4217
www.CMEdirect.net

Introduction

Gene Y. Sung, MD, MPH, *Guest Editor*

University of Southern California, Los Angeles, California

Time is a critical commodity that can be an enemy or an ally of patients experiencing an acute stroke. Unfortunately, stroke evaluation and treatment are not always as clear-cut as they may seem. During the 63rd Annual Meeting of the American Academy of Neurology, held April 9–16, 2011, in Honolulu, Hawaii, more than 11,000 neurologists and other participants from 93 countries had the opportunity to attend over 2,500 abstract presentations, lectures, and debates on the pathogenesis, diagnosis, management, and sequelae of stroke and other neurologic morbidities.

This edition of *The Neurology Report* contains articles on the prompt and effective triage and treatment of acute stroke patients contributed by senior fellows and residents in neurology. Leaders in acute ischemic stroke and its management covered specific topics related to prompt recognition of symptoms; evaluation of patient status; eligibility for thrombolytic therapy; and treatment with effective, individualized medical protocols. In addition, speakers presenting data from clinical trials and participating in panel discussions and educational sessions discussed the sensitivity and specificity of stroke diagnosis by emergency medical services (EMS) personnel, critical information and directives for nonvascular neurologists and other clinicians who treat patients presenting with signs and symptoms of an acute stroke, current recommendations for optimal treatment of this patient population, and a systems approach to accommodate the time-sensitive nature of acute stroke management.

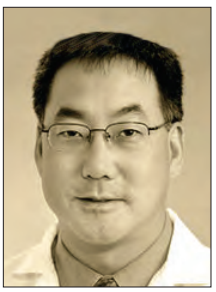
The first healthcare professional to evaluate and treat a suspected stroke patient often is an EMS worker. Fawad Ahmed Khan, MD, from the University of North Carolina Hospital in Chapel Hill, explains the crucial nature of triage before a patient reaches a hospital and summarizes the results of a study investigating the accuracy of prehospital stroke diagnosis at an urban hospital. In addition, Dr. Khan touches upon obstacles to the diagnosis of stroke and steps that EMS directors should take to optimize the care and outcomes of prospective stroke patients.

Most likely, stroke patients presenting to a hospital are evaluated by nonvascular neurologists before an expert in vascular neurology is called for a consultation. Kristian Barlinn, MD, from the University of Alabama at Birmingham Hospital, summarizes information from a panel discussion on treatment strategies available for patients who likely have experienced a stroke. Members of the panel commented on why many patients never receive intravenous (IV) recombinant tissue plasminogen activator (tPA), the only drug approved by the US Food and Drug Administration to treat acute ischemic stroke. Speakers also detailed an algorithm for emergency evaluation and management of the acute stroke patient, including administration of IV tPA and intra-arterial reperfusion methods. Finally, members of the panel itemized complications that may hamper the optimal treatment of patients who have had a stroke.

Neil F. Rosenberg, MD, from Northwestern Memorial Hospital in Chicago, reviews current information and published guidelines for preventing acute stroke and managing acute ischemic stroke with IV tPA and intra-arterial reperfusion procedures. Participants in an educational session discussed the importance of prompt tPA administration, criteria that would exclude a patient from receiving the drug, and clinical findings on the use of other drug therapies or devices in stroke patients. Accordingly, Dr. Rosenberg discusses the need for antihypertensive, hypolipidemic, anticoagulant, antiplatelet, and hypoglycemic therapy in particular situations and describes indications for surgery in patients who have experienced a stroke.

Multidisciplinary management of stroke consists of a number of healthcare professionals involved in therapeutic steps ranging from preventing the crisis to coordinating rehabilitation of the stricken patient. In describing the content of a scientific poster session, Basanagoud Mudigoudar, MD, from SUNY Downstate Medical Center in Brooklyn, New York, relays information on the effect of aspirin use before spontaneous intracerebral hemorrhage on hematoma expansion, patient disability, and mortality. In addition, Dr. Mudigoudar summarizes medicolegal considerations concerning the use of IV tPA for acute ischemic stroke and the effect of a regional health information exchange in simplifying outcomes epidemiology. This article additionally provides insight on the effectiveness of IV tPA given outside the optimal, FDA-approved 3-hour time window and the impact of a statewide telecommunications program on treating stroke patients who live far from a stroke center. Finally, Dr. Mudigoudar describes neurologic conditions that may mimic acute stroke and a metric that may help implementation of standardized care for intracerebral hemorrhage.

The authors of these reports stress the urgent nature of stroke management, beginning with the potential impact of stroke prevention measures on the delivery of urgent care to medical and surgical management in the immediate aftermath of a new or recurrent stroke. We thank them and look forward to their future contributions in this rapidly advancing—and controversial—field of neurology.



Dr. Sung is Associate Professor of Neurology and Chief, Division of Stroke and Neurocritical Care, University of Southern California, Los Angeles, California.

The Accuracy of Prehospital Diagnosis of Stroke

Fawad Ahmed Khan, MD

University of North Carolina Hospital, Chapel Hill, North Carolina

Abstract Over the past decade, clinicians have witnessed a remarkable structural transformation in acute stroke care. For patients who have an acute stroke, "time is brain." For most strokes, the clock starts ticking outside the hospital, within minutes after the onset of symptoms. The patient usually is first treated by members of emergency medical services (EMS). Prehospital triage and management by EMS workers play a crucial role in the overall care of patients and may impact overall outcomes. During the 63rd American Academy of Neurology Annual Meeting, a panel discussion on acute stroke addressed the accuracy of prehospital stroke diagnosis and recommendations for future improvement of EMS practices.

When the first symptoms of stroke occur, the race begins to recognize the onset of a stroke, evaluate the patient's condition, initiate appropriate therapy, and deliver the patient to a healthcare facility for further evaluation and treatment. Patients are usually reached first by emergency medical services (EMS) members, who perform triage and administer treatment as the patients are transferred to a hospital or stroke center. These steps seem to be obvious and mechanical in nature. However, the earliest treatment of patients suffering a stroke may dictate their odds of survival, ability to function, and quality of life for years to come.

During the 63rd Annual Meeting of the American Academy of Neurology in Honolulu, Hawaii, speakers at a scientific platform session discussed a variety of issues related to management of acute stroke. In one presentation, researchers summarized a study on the accuracy of prehospital stroke diagnosis and discussed the challenges and obstacles related to early emergency consultations and treatment of patients who apparently have suffered a stroke.

Dr. Khan is a fourth-year Adult Neurology Resident at the University of North Carolina Hospital, Chapel Hill, North Carolina.

PREHOSPITAL TRIAGE AND COURSE

About 50% of all stroke patients are transported by EMS workers to a medical facility. Patients transported by EMS arrive to the hospital sooner and are treated faster in the emergency department (ED) than are those transported by other means.[1] Rajajee and Saver[1] noted that accurate identification of stroke by EMS personnel provides the following benefits:

- Appropriate treatment (and, possibly, future use of neuroprotective agents) can be initiated in the field, and potentially inappropriate treatment may be avoided.
- The receiving hospital can be notified about patient status.
- Rapid transport of the patient can be initiated.
- Stroke patients may be diverted to dedicated stroke centers.

Furthermore, early recognition of stroke allows more effective communication between healthcare professionals and more rapid administration of thrombolytic treatment in the ED. The therapeutic benefits and favorable outcomes resulting from the use of intravenous recombinant tissue plasminogen activator (tPA; alteplase) are exquisitely time-dependent. Lees et al[2] conducted a pooled analysis of clinical trials comparing administration of alteplase with use of placebo in acute stroke patients. They reported that when compared with use of placebo, the adjusted odds of a favorable 3-month outcome were 2.55 if tPA treatment began within 0–90 minutes after the onset of stroke symptoms, 1.64 if treatment began within 91–180 minutes, 1.34 if treatment began within 181–270 minutes, and 1.22 if treatment began within 271–360 minutes.

SENSITIVITY AND SPECIFICITY OF EMS STROKE DIAGNOSIS

Adapted from a presentation by Toby L. Gropen, MD, Chairman, Department of Neurology, and Director, Stroke Center, Long Island College Hospital, Brooklyn, New York.

Previous studies of the accuracy of EMS personnel in diagnosing stroke have reported sensitivities of 44%–66%.[3–6] Many of these studies focused on barriers to ED arrival and delays in transporting patients. However, there has been little examination of factors related to poor diagnostic sensitivity by EMS workers. In this study, clinical investigators evaluated the sensitivity and specificity of stroke diagnosis by EMS workers.

Methods and Results

The researchers reviewed ambulance and hospital records for 1,138 patients transported to Long Island College Hospital by hospital-based EMS personnel

from January 1, 2009, to June 30, 2010. Patients were diagnosed with stroke, syncope, headache, altered mental status, hypoglycemia, or seizure.

The investigators primarily were interested in the sensitivity and specificity of EMS stroke diagnosis and the specific factors relating to accuracy. In addition, they examined the influence of correct EMS identification of stroke patients on subsequent ED care. In addition, they compared the EMS diagnosis with the hospital-discharge diagnosis for admitted patients and the ED diagnosis for nonadmitted patients. Stroke diagnoses, which were confirmed by vascular neurologists, included transient ischemia, cerebral infarction, intracerebral hemorrhage, and subarachnoid hemorrhage. The EMS personnel in the study received biannual education on stroke and used the Cincinnati Prehospital Stroke Scale (CPSS)[5] to evaluate symptoms of suspected stroke patients.

In all, 53 patients (4.7%) had a stroke; of them, 30 (57%) were incorrectly diagnosed by EMS workers. Stroke assessment was documented in only 17% of stroke patients (Table 1). The groups were fairly balanced with the exception of variability in sensitivity among essentially four groups—those having an NIHSS (National Institutes of Health Stroke Scale) score ≥ 4, patients having a right-sided stroke, those exhibiting motor signs, and individuals who had a documented stroke assessment (Table 2).

The investigators demonstrated that the significant predictors of a true-positive EMS diagnosis of stroke were the presence of motor signs, the identification of a right-sided lesion, and the documentation of stroke assessment (Table 3). They also showed that the severity of stroke according to NIHSS score was not significant and did not affect the odds ratio (Table 4).

TABLE 1
Stroke Diagnosis Analysis[a]

EMS diagnosis	Confirmed stroke, n	Confirmed nonstroke, n
Stroke	23	11
Nonstroke	30	1,074

EMS = emergency medical services

[a] Sensitivity was 43%; specificity was 98%; positive predictive value was 68%; negative predictive value was 97% ($P < 0.0001$, Pearson $\chi^2 = 313.45$).

TABLE 2
Factors Related to Diagnostic Sensitivity

Variable, n	Sensitivity, %	*P* value[a]
Ethnicity, white (23) vs nonwhite (30)	52 vs 37	0.259
Gender, female (31) vs male (22)	48 vs 36	0.384
EMS provider, ALS (11) vs BLS (38)	45 vs 42	0.843
Stroke type, hemorrhage (12) vs ischemia (41)	33 vs 46	0.424
NIHSS score, ≥ 4 (25) vs < 4 (24)	64 vs 29	**0.015**
Lesion side, right (27) vs left (18)	63 vs 28	**0.021**
Motor signs, present (27) vs absent (26)	59 vs 27	**0.018**
Stroke assessment documented, yes (9) vs no (44)	78 vs 36	**0.022**

EMS = emergency medical services; ALS = advanced life support; BLS = basic life support; NIHSS = National Institutes of Health Stroke Scale

[a] Values shown in bold are significant ($P < 0.05$).

TABLE 3
Predictors of True-Positive EMS Diagnosis of Stroke: Without NIHSS Score

Variable	*P* value[a]	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Motor signs present	**0.012**	6.60	1.48	38.25
Right-sided lesion identified	**0.007**	8.25	1.74	55.78
Stroke assessment documented	**0.027**	7.01	1.27	204.64

EMS = emergency medical services; NIHSS = National Institutes of Health Stroke Scale; CI = confidence interval

[a] Values shown in bold are significant ($P < 0.05$).

TABLE 4
Predictors of True-Positive EMS Diagnosis of Stroke: With NIHSS Score

Variable	*P* value[a]	Odds ratio	95% CI for odds ratio	
			Lower	Upper
Motor signs present	**0.040**	5.95	1.08	44.72
Right-sided lesion detected	**0.005**	9.11	1.85	65.81
Stroke assessment documented	**0.041**	8.45	1.09	184.03
NIHSS score obtained	0.706	2.01	0.04	85.75

EMS = emergency medical services; NIHSS = National Institutes of Health Stroke Scale; CI = confidence interval

[a] Values shown in bold are significant ($P < 0.05$).

Discussion

Increased sensitivity of EMS diagnosis in patients with motor findings may reflect the easier diagnosis of stroke in these patients and the motor-weighting of the CPSS score.

Stroke assessment was documented for only 17% of stroke patients, but it appeared to be a significant predictor of diagnostic sensitivity. Thus, false-negative diagnoses of stroke by EMS staff may partially reflect failure to consider the diagnosis and to determine a stroke scale score.

Increased sensitivity of EMS diagnosis in patients with right-sided lesions was a surprise and remains unexplained.

Conclusion

The sensitivity of EMS stroke diagnosis in this study was only 43%, which coincided with sensitivities noted in previous studies. Stroke diagnosis was missed more frequently when the stroke assessment was not documented and when patients had left-sided lesions and an absence of motor signs.

There is an ongoing need for EMS education to lower the threshold for use of prehospital stroke scales, improve stroke assessment documentation, and increase the accuracy of EMS stroke diagnosis in patients without motor signs. Ongoing research is focusing on the development and assessment of an EMS educational program and exploration of the relation-

ship between EMS diagnostic sensitivity and lesion side.

DISCUSSION

The discrepancy between left- and right-sided stroke diagnosis certainly is peculiar. Diagnosis may be challenging among those with left-sided lesions, because they present with aphasias and altered mental status and attention.

There is often significant turnover in EMS departments, and some clinicians remain concerned that such changes in staffing reflect upon the clinical skills of EMS personnel. More important than turnover, however, is the lack of quality education and didactics that renders EMS workers at a disadvantage in accurately and efficiently diagnosing stroke. EMS personnel may overcome this disadvantage by retaking educational courses. Stroke does not occur frequently enough in any one district or shift to allow EMS workers to master their skills. Thus, repeating educational and simulation learning activities allows EMS workers to practice stroke management and maintain skills for evaluating a cerebrovascular crisis.

State and county public health officials and EMS medical directors should take steps to ensure access to effective stroke care in their districts, with the goal of establishing effective regional acute stroke system coverage for all Americans.

Further studies on the outcomes of interventional educational initiatives for EMS and improvement of diagnostic accuracy for stroke patients are warranted. These studies can delineate other undiscovered barriers to effective EMS diagnosis and documentation. Educational programs for EMS workers should be incorporated into the continuing medical education activities of certified stroke centers and should include simulations, case discussions, and feedback. In addition, increased public awareness and education about the importance of prompt medical and paramedical evaluation and treatment of stroke are needed.[7]

Accurate recognition of acute stroke by EMS personnel is important to avoid "burn out" of stroke teams that are activated based on incorrect prehospital evaluations.[1] In this age of selective EMS transport of patients to stroke centers, more emphasis must be placed on correct diagnosis in the field, not just speed of transport to a medical facility for coordinated stroke care.

REFERENCES

1. Rajajee V, Saver J. Prehospital care of the acute stroke patient. *Tech Vasc Interv Radiol.* 2005;8:74–80.

2. Lees KR, Bluhmki E, von Kummer R, et al. Time to treatment with intravenous alteplase and outcome in stroke: an updated pooled analysis of ECASS, ATLANTIS, NINDS, and EPITHET trials. ECASS, ATLANTIS, NINDS and EPITHET rt-PA Study Group. *Lancet.* 2010;375:1695–1703.

3. Ramanujam P, Guluma KZ, Castillo EM, et al. Accuracy of stroke recognition by emergency medical dispatchers and paramedics—San Diego experience. *Prehosp Emerg Care.* 2008;12:307–313.

4. Smith WS, Isaacs M, Corry MD. Accuracy of paramedic identification of stroke and transient ischemic attack in the field. *Prehosp Emerg Care.* 1998;2:170–175.

5. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati Prehospital Stroke Scale: reproducibility and validity. *Ann Emerg Med.* 1999;33:373–378.

6. Kothari R, Jauch E, Broderick J, et al. Acute stroke: delays to presentation and emergency department evaluation. *Ann Emerg Med.* 1999;33:3–8.

7. Papapanagiotou P, Iacovidou N, Spengos K, et al. Temporal trends and associated factors for pre-hospital and in-hospital delays of stroke patients over a 16-year period: the Athens study. *Cerebrovasc Dis.* 2011;31:199–206.

Surviving Stroke Call: A Guide for Nonvascular Neurologists

Kristian Barlinn, MD

University of Alabama at Birmingham Hospital, Birmingham, Alabama

Abstract Stroke management is an important component of emergency medical interventions. During a panel discussion at the 2011 Annual Meeting of the American Academy of Neurology, experts in stroke management and the organization of related services stressed key points for examining and treating potential stroke patients, minimizing possible complications, and promoting a good working relationship with emergency department personnel. Panelists outlined an algorithm for the emergency evaluation and treatment of stroke, including issues related to the timing and use of intravenous thrombolysis and intra-arterial reperfusion. In addition, they covered obstacles to effective, prompt treatment and communication with patients and their families.

Approximately 795,000 people each year suffer a stroke in the United States, making it the third leading cause of death and the leading cause of long-term disability in this country.[1] Neuronal tissues are extremely sensitive to ischemia, with nearly 2 million neurons dying per minute during an acute ischemic episode.[2] Thus, stroke must be treated as a medical emergency.[2]

Hospitals that do not have comprehensive or primary stroke centers but maintain an emergency department (ED) must have efficient algorithms to rapidly identify and evaluate potential stroke patients, be aware of conditions that may mimic stroke-like symptoms, and distinguish other conditions requiring immediate imaging and intervention. However, many hospitals do not have the necessary resources and organization to meet those criteria efficiently. The results of a survey of stroke prevention and treatment facilities showed that two of three participating hospitals do not have a standardized stroke protocol, and only one of five has a rapid triage unit for patients with suspected acute stroke.[3] Further, intravenous (IV) recombinant tissue plasminogen activator (tPA) is the only treatment approved by the US Food and Drug Administration (FDA) to reverse ischemic stroke if given within 3 hours of symptom onset.[4,5]

Even though IV thrombolysis with tPA is widely available in EDs nationwide, up to 98% of patients with acute ischemic stroke still do not receive tPA.[6] Reasons for this omission include delays in presentation, contraindications for thrombolytic treatment, clinician concerns about bleeding complications, and the inability of some emergency medical systems to rapidly triage and evaluate stroke patients. These issues are further amplified by most stroke patients receiving treatment from nonvascular neurologists (ie, general neurologists) and internists.

During the 63rd Annual Meeting of the American Academy of Neurology, held April 9–16, 2011, in Honolulu, Hawaii, a panel of experts in vascular neurology, emergency medicine, and interventional neuroradiology participated in an interactive discussion regarding the evaluation and treatment of patients suspected of having suffered an acute ischemic stroke. The panel presented common pitfalls of treating this population and provided an algorithm for the emergency evaluation and treatment of stroke. The algorithm also included issues related to use of IV tPA thrombolysis and intra-arterial (IA) reperfusion procedures for treating acute ischemic stroke.

COMMON SCENARIOS AND PITFALLS DURING INITIAL STABILIZATION AND ASSESSMENT

Adapted from a presentation by Enrique C. Leira, MD, MS, Assistant Professor of Neurology, University of Iowa College of Medicine, Iowa City, Iowa, and Azeemuddin Ahmed, MD, MBA, Clinical Associate Professor of Emergency Medicine, University of Iowa College of Medicine, Iowa City, Iowa.

Pitfall #1: Inadequate airway protection

Stroke patients with decreased consciousness, inadequate gag reflexes, and frequent vomiting are at high risk of airway compromise. Thus, protection of the airway via intubation may avoid early aspiration.

The decision to intubate should be based upon clinical examination (eg, level of consciousness and the patient's ability to protect airways) rather than upon oxygenation or respiratory rate. However, the very low threshold for intubation held by an ED may confound a neurologic examination and interfere with thrombolysis. Therefore, neurologists should emphasize the need for a

Dr. Barlinn is a Research Fellow in the Comprehensive Stroke Center of the Department of Neurology, University of Alabama at Birmingham Hospital, Birmingham, Alabama.

baseline neurologic assessment and, if possible, a quick, noncontrast, computed tomography (CT) assessment of the head *before* intubation.

On the other hand, the risk of pneumonia, one of the leading complications of stroke and an important cause of clinical deterioration and death following a cerebrovascular event, may increase if an ED has a very high threshold for intubation.

Pitfall #2: Overlooking rapid serum glucose determination

Hypoglycemia may produce neurologic signs that mimic ischemic stroke in 1%–2% of cases, and hypoglycemia alone may lead to brain injury. The physician should not wait for results of serum chemistry analysis. Prompt measurement of glucose levels at the bedside and rapid correction of an abnormal arterial glucose level may have a great impact on outcomes after stroke.[7]

Pitfall #3: Inadequate blood pressure management

The management of blood pressure (BP) in patients with acute ischemic stroke is controversial, since both high and low BP levels are associated with a poor outcome.[6] An ED's overly aggressive management of BP level may lead to exacerbation of neurologic deficits due to a further compromise of the hypoperfused penumbral tissue. Treatment should not be initiated unless end-organ damage is present or the BP level exceeds the limit for tPA administration (ie, 185/110 mm Hg).

However, an ED's overly liberal BP management protocol may increase the risk of hemorrhagic transformation and end-organ damage. Upper BP thresholds should be determined, particularly when treatment with tPA is considered. In particular, the panel recommended use of IV labetalol, hydralazine, and nitroprusside for management of BP. Current clinical guidelines do not recommend use of hydralazine; instead, their second choice is a continuous nicardipine drip to achieve fast and efficient control of BP for 24 hours or longer.[7] This point is extremely important for maintaining the safety of IV tPA, and the use of nicardipine before bolus administration of tPA should not exclude patients from receiving thrombolytic therapy.

In addition, the panel emphasized that selection of each agent may be influenced by the presence of other medical conditions. For example, labetalol is contraindicated in the presence of asthma, whereas hydralazine may increase intracranial pressure and may exacerbate myocardial ischemia.

Pitfall #4: Inadequate history and physical examination

Relevant data must be collected as soon as possible after patient presentation. First, the exact time of symptom onset (ie, the last time patients were known to be at their previous baseline or symptom-free) is the most important item of information needed. In patients with neurologic symptoms that *completely* resolve (eg, crescendo transient ischemic attacks), the therapeutic clock is reset, and the time of symptom onset begins anew.

> Overly liberal management of blood pressure may increase the risk of hemorrhagic transformation and end-organ damage.

Second, the history taken should be consistent with the diagnosis of a stroke. Vertebrobasilar ischemia may be obscured by altered mental status, but other conditions, such as a seizure, complicated migraine headache, or a toxic metabolic condition, may mimic a stroke and confound the diagnosis.

Third, when deciding whether or not to use tPA, physicians should be aware of alleged improvement of symptoms (interobserver vs true fluctuations) and should consider the degree of remaining disability, rather than the absolute National Institutes of Health Stroke Scale (NIHSS) score or any improvement in the total score.

During the initial evaluation, the physician also should determine whether the patient has had a stroke and should establish potential contraindications for emergency treatment with tPA (eg, use of oral anticoagulants in patients with an INR [international normalized ratio] > 1.6). Use of IV tPA also is contraindicated in patients who have had previous recent surgery or bleeding; physicians should not hesitate to contact a patient's surgeon for information on the risk of bleeding.

Finally, neurologists should be certified in the use of the NIHSS score; a certification course is available at *http://nihss-english.trainingcampus.net/uas/modules/trees/windex.aspx* and *http://learn.heart.org/ihtml/application/student/interface.heart2/nihss.html*. Important information about the severity of stroke and prognostic issues is available at Web sites of the National Institute of Neurological Disorders and Stroke (NINDS; *http://www.ninds.nih.gov/*), the American Heart Association (AHA; *http://www.heart.org/HEARTORG/*), and the American Stroke Association (ASA; *http://www.strokeassociation.org/STROKEORG/*).

Pitfall #5: Situations that complicate stroke diagnosis

Conditions and disorders that may mimic a stroke or that may mislead physicians in diagnosing and treating this condition include vertebrobasilar symptoms, seizure, or trauma at stroke onset; intubation; symptoms present on awakening; postsurgical environment; institutionalization; headache; history of migraine; functional symptoms; and concomitant use of alcohol, drugs, or sedatives. The availability of immediate magnetic resonance imaging (MRI) scanning can aid in those situations.

Pitfall #6: ECG and cardiac enzyme interpretation

A 12-lead electrocardiogram (ECG) and cardiac enzyme tests should be a part of the initial evaluation of all stroke patients. Atrial fibrillation, an important cause of stroke, can be detected in the

acute stroke setting and may be transient.

Cardiac abnormalities are prevalent among stroke patients, and patients with suspected stroke may have an acute cardiac condition that mandates urgent treatment.[8] For example, 15% of patients with acute ischemic stroke have ECG abnormalities suggesting myocardial ischemia versus unspecific stroke-related ECG changes, and 10% have elevated troponin levels but no symptoms. However, only 3% of all patients with acute stroke have acute cardiac ischemia. The panel made specific recommendations for the interpretation of ECG and troponin changes in acute stroke patients.

Pitfall #7: Inadequate screening for aortic dissection

Acute aortic dissection, an absolute contraindication to the use of tPA, can cause ischemic stroke. The clinical diagnosis of an aortic dissection can be difficult, because the symptoms are similar to those of other conditions. Thus, corresponding diagnostic tests such as chest x-ray and chest CT with contrast should be considered in all acute ischemic stroke patients who present with additional symptoms suspicious for an aortic dissection (eg, sudden severe chest pain that radiates to the shoulder, arm, or jaw).

Pitfall #8: Premature head CT scan

Because time is critical, thrombolytic therapy with tPA should not be delayed while the physician awaits the results of the laboratory tests. The panel recommended that blood draws should be completed before patients are sent for a CT scan. Also, physicians should assess the need for sedation and airway protection immediately. Table 1 is a checklist that may be used to ensure the initial stabilization of patients with acute stroke.

Current guidelines recommend that door-to-CT completion time be no more than 20 minutes.[7]

COMMON SCENARIOS AND PITFALLS OF IV tPA USE IN ACUTE STROKE: STAY OUT OF TROUBLE!

Adapted from a presentation by Enrique C. Leira, MD, MS, and Azeemuddin Ahmed, MD, MBA.

TABLE 1
Initial Stabilization Checklist

- ☑ Airway patency: *assessed*
- ☑ Glucose level: *hypoglycemia excluded*
- ☑ Blood pressure: *need for treatment assessed*
- ☑ Focused history and time of onset: *obtained*
- ☑ NIHSS exam score: *obtained*
- ☑ ECG/history/enzymes: *MI not suspected*
- ☑ History/imaging: *aortic dissection not suspected*
- ☑ Laboratory tests (CBC, chemistries, coagulation profile): *sent*
- ☑ Need for sedation/restraint: *assessed*
- ☑ Patient now cleared to undergo a CT scan

NIHSS = National Institutes of Health Stroke Scale; ECG = electrocardiogram; MI = myocardial infarction; CBC = complete blood cell count; CT = computed tomography

Pitfall #9: Omitted screening for tPA eligibility

As many as 50% of otherwise eligible patients with acute ischemic stroke do not receive tPA.[9] Therefore, all patients with suspected ischemic stroke should be carefully screened for treatment eligibility, and physicians should document in the medical record the reasons that tPA was or was not used. Recommendations regarding IV tPA therapy are given in the current AHA/ASA Guidelines for the Early Management of Adults with Ischemic Stroke.[7]

Pitfall #10: Inadequate screening for tPA contraindications

Erroneous interpretation of tPA contraindications may result in failure to administer tPA to patients who meet eligibility requirements.[9] For example, neurologic symptoms after a seizure at stroke onset may be mistaken for Todd's paralysis, and affected patients often are not deemed to be candidates for IV tPA therapy. However, seizure at stroke onset does not constitute an absolute contraindication to tPA use, and generally it is better to treat such individuals if there is no clear evidence that the neurologic impairment is a postictal phenomenon.

Even though older age is not a proven contraindication and has not been associated with an increased risk of hemorrhagic transformation after thrombolysis, patients who are 80 years of age and older generally are treated less often with tPA than are younger patients.[9] Conversely, an interpretation of tPA exclusion criteria that is too lax may increase the likelihood for complications.

Widespread subtle signs of early ischemic changes on initial noncontrast CT scanning, such as involvement of more than one-third of the middle cerebral artery territory, are associated with a higher risk of hemorrhagic transformation after thrombolytic therapy.[7] However, neurologists' ability to reliably and reproducibly recognize early CT changes is variable. The use of scoring systems for early CT changes, such as the Alberta Stroke Program Early CT Score, may improve identification of cerebral ischemia and may provide valuable prognostic information.[10,11]

Pitfall #11: Thinking of the time window for tPA administration as a fixed "deadline"

Because of the rapid death of neuronal tissue following an acute ischemic stroke,[2] even small delays before initiating tPA therapy in eligible patients decrease the chance for a favorable outcome. Time is brain![12]

Pitfall #12: Inadequate consent for IV tPA

Written consent to administer tPA for treatment of stroke during the time window approved by the FDA is *not* necessary. However, a full discussion of the potential risks (eg, intracerebral hemorrhage in about 6% of cases) and benefits (twofold odds for a favorable outcome) of tPA therapy with family members, if possible, is recommended.[4,5,11]

Pitfall #13: Use of the wrong thrombolytic or dose

Administration of tPA at 0.9 mg/kg IV (maximum dose, 90 mg; 10% as a bolus dose, with the remaining 90% given as a 1-h infusion) is the only thrombolytic strategy proven to be effective in patients with acute ischemic stroke. Different thrombolytic agents and dosages of these drugs are used in patients with myocardial infarction.

Pitfall #14: "Wild" BP levels during and after tPA infusion

High blood pressures are associated with an increased risk of hemorrhagic transformation both during and after tPA treatment. The best methods for preventing bleeding complications are careful, close observation and monitoring of the stroke patient, with early treatment of an elevated BP. Further, a patient with a BP > 185/110 mm Hg needs rapid treatment.[7]

Pitfall #15: Not admitting a patient to an adequate hospital for post-tPA care

Specialized stroke services improve the outcomes of stroke patients. Thus, patients who received tPA are best monitored in intensive care units or dedicated stroke units providing neurosurgical/interventional capabilities. Patients may need to be transferred to a higher level of stroke care.

Pitfall #16: Inadequate recognition of hemorrhagic transformation

Hemorrhagic transformation is a serious complication of thrombolytic therapy that increases the risk of unfavorable outcome and early mortality.[7] A triad including headache, acute neurologic deterioration, and BP spikes helps physicians to identify patients who potentially suffered intracerebral bleeding complications after thrombolytic therapy.

If any one of these conditions occurs, tPA infusion has to be discontinued immediately, and BP levels should be lowered aggressively. If immediate CT findings confirm hemorrhagic transformation, an emergent neurosurgical consultation is recommended.

Pitfall #17: Inadequate recognition of angioedema

Neurologists should be aware of the potential complication of orolingual angioedema, which may occur in 5% of patients treated with tPA and can cause partial airway obstruction.[7] The treatment of choice is appropriate airway management and antihistamines/corticosteroids. Table 2 is a checklist that may be used as an algorithm for administration of tPA in acute ischemic stroke patients. The Joint Commission's Primary Stroke Center Certification requires documentation that *all* eligible stroke patients have received tPA.

TABLE 2
Treatment with IV tPA Checklist

- ☑ Consider use of IV tPA
- ☑ Expedite evaluation
- ☑ Review exclusion criteria for tPA administration
- ☑ Inform families and patients briefly, but adequately, about risks and benefits of tPA therapy
- ☑ Use correct drug (tPA [alteplase])
- ☑ Ensure that correct dose (0.9 mg/kg; total: 90 mg) is delivered (10% bolus; remainder infused over 1 h)
- ☑ Monitor BP and patient status during infusion
- ☑ Monitor for angioedema
- ☑ Check neurologic status frequently
- ☑ Admit patient to the appropriate level of care

IV = intravenous; tPA = recombinant tissue plasminogen activator; BP = blood pressure

COMMON SCENARIOS AND PITFALLS BEYOND tPA: WHEN DO I NEED AN MRI? WHEN DO I NEED A NEUROINTERVENTIONALIST?

Adapted from a presentation by Enrique C. Leira, MD, MS, and Coleman O. Martin, MD, Clinical Associate, Department of Neurology, University of Iowa Hospitals and Clinics, Iowa City, Iowa.

Pitfall #18: Inadequate consideration of interventional treatments

The panel emphasized that IA reperfusion procedures using local thrombolysis and mechanical embolectomy may improve the outcomes of selected stroke patients who have middle cerebral artery or basilar artery occlusions, are treated within 8 hours of symptom onset, are not otherwise candidates for IV tPA, or have not received benefit from IV tPA therapy (rescue therapy). The FDA has approved use of the Merci Retriever® (Concentric Medical, Inc; Mountain View, CA) and the Penumbra® System (Penumbra, Inc; Alameda, CA) for thrombectomy in acute stroke patients but not as effective stroke treatment.[7]

Pitfall #19: Delay in obtaining an MRI for potential candidates for endovascular treatment

Interventionalists often need a multimodal MRI or CT scan to identify acute ischemic stroke patients who might qualify for endovascular reperfusion procedures. A multimodal MRI provides information about the arterial patency status in the precerebral and cerebral vasculature. It also allows visualization of the irreversible infarct core (with diffusion-weighted imaging [DWI]) and areas of hypoperfusion (with perfusion-weighted imaging [PWI]). The presence of a mismatch between DWI and PWI lesions can be used to estimate the extent of the ischemic penumbra.[12]

However, delay in the initiation of IA treatment also will delay brain tissue reperfusion and may minimize the chances for beneficial outcomes. Thus, neurologists should know their hospitals' MRI capabilities. Patients may need to be transferred to a higher level of stroke care if requirements for IA treatment cannot be guaranteed.

Pitfall #20: Omission of a renal function test

A significant decline in the use of gadolinium has resulted from recent recognition of its rare complications, such as nephrogenic systemic fibrosis in patients with impaired kidney function.[13] Therefore, the patient's renal function must be assessed using a laboratory test prior to administration of gadolinium for magnetic resonance angiography (MRA) or perfusion MRI.

Pitfall #21: Uncertainty about safe use of MRI

MRI cannot be used in patients with pacemakers, programmable shunts, and certain magnetic appliances. If the required information is unobtainable (eg, the patient is aphasic or no relatives are available to supply information), the benefits of MRI should always outweigh the potential safety risks. A chest x-ray

may help to detect certain devices such as pacemakers.

Pitfall #22: Doubts of where to "spend" the dose of gadolinium contrast

Contrast-enhanced MRA (CE-MRA) and time-of-flight MRA (TOF-MRA) are the MRA techniques most frequently used to evaluate cervical and intracranial arteries in patients with acute stroke. CE-MRA may help when TOF-MRA shows patent intracranial arteries and the presence of an extracranial occlusion (eg, in the internal carotid artery) is assumed. A perfusion MRI can be useful in identifying stroke patients who might be appropriate for endovascular reperfusion procedures. In such cases, DWI-PWI mismatch may justify intervention.[12] In general, a neurointerventionalist should be consulted before ordering advanced imaging modalities.

Pitfall #23: Inability to obtain adequate MRI images due to movement agitation

The feasibility of MRI is limited in acute stroke patients. Some stroke patients cannot tolerate MRI or cooperate poorly, which may lead to movement artifacts. These patients may require anesthesia or sedation so that higher quality images may be obtained.

Pitfall #24: Interpretation of the DWI/PWI

Acute ischemic stroke patients with evidence of a large DWI-PWI mismatch may represent optimal candidates for endovascular reperfusion procedures.[12] However, the best mismatch threshold remains a matter of controversy, and the interpretation of the DWI and PWI lesions is usually performed arbitrarily (namely, by "eyeballing"). Alternatively, the DWI/clinical mismatch (ie, small DWI lesion but major neurological deficit) or DWI/MRA mismatch (ie, small DWI lesion but proximal arterial occlusion) can be used to estimate the extend of the ischemic penumbra. Nevertheless, the neurologist and the interventionalist should decide jointly whether to proceed with an endovascular intervention.

TABLE 3
Beyond IV tPA Checklist

- ☑ Consider endovascular therapy
- ☑ Check renal function
- ☑ Check for the presence of a pacemaker, programmable shunts, or metal implants
- ☑ Contact a neurointerventionalist
- ☑ Assess the need for conscious sedation
- ☑ Decide upon gadolinium use (ie, PWI vs neck MRA)
- ☑ Interpret images for DWI/PWI (or DWI/clinical, DWI/MRA mismatch)
- ☑ Decide on a course of therapy with the neurointerventionalist

IV tPA = intravenous recombinant tissue plasminogen activator; PWI = perfusion-weighted imaging; MRA = magnetic resonance angiography; DWI = diffusion-weighted imaging

Pitfall #25: Disagreement on the need for a procedure

Currently, endovascular reperfusion procedures in patients with acute ischemic stroke are not a standard of care. Rather, they are a standard of practice. Table 3 is a checklist that may be used as an algorithm for the post-tPA management of acute ischemic stroke patients.

COMMON SCENARIOS AND PITFALLS IN FAMILY/PATIENT INTERACTIONS DURING ACUTE STROKE SITUATIONS

Adapted from a presentation by Enrique C. Leira, MD, MS, and Coleman O. Martin, MD.

Pitfall #26: Patients and relatives overwhelmed with data and decisions

Stroke leaves patients and their relatives in a state of shock and disorientation, and their ability to understand and decide on courses of therapy may be limited. Thus, the message given to the patient and relatives should be crisp and succinct:

- This is what happened.
- Other things can happen.
- This is your likely outcome.
- This is what we can do.

Pitfall #27: Failure to adequately communicate the patient's initial prognosis

The prognosis and possibility of a worsened neurologic state should be discussed in depth with patients and their families. The patient's prognosis could be crucial for further decision-making processes.

The initial NIHSS score can be used to predict mortality and functional outcome 3 months after the stroke. For example, about 80% of patients with an NIHSS score of 7–10 will have a good or excellent outcome, whereas only 20% of patients with an NIHSS score ≥ 23 will have a similar outcome.[14]

Pitfall #28: Potential interference with last wishes

The neurologist must weigh the patient's wishes and overall prognosis in deciding upon a level of care. A discussion about life support (eg, intubation, resuscitation, feeding tubes) should occur early and adequately. If advance directives do not exist or uncertainties remain, the neurologist should inquire about relatives' beliefs about the patient's last wishes.

CONCLUSION

Information shared during this insightful session will be helpful to general neurologists who were not trained in vascular neurology but who face the challenges of caring for acute stroke patients. Presently, reperfusion therapies and complex interventions are provided by physicians having advanced training in vascular neurology, endovascular neurology, and neurocritical care. Attention to details and recognition of possible obstacles to efficient treatment of acute stroke patients will lead to better patient outcomes.

REFERENCES

1. Lloyd-Jones D, Adams RJ, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2010;121:e46–e215.

2. Saver JL. Time is brain—quantified. *Stroke.* 2006;37:263–266.

3. Goldstein L. North Carolina stroke prevention and treatment facilities survey. *Stroke.* 2000;31:66–70.

4. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581–1587.

5. Hacke W, Kaste M, Bluhmki E, et al. Throm-

bolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med*. 2008;359:1317–1329.

6. Kleindorfer D, Lindsell CJ, Brass L, Koroshetz W, Broderick JP. National US estimates of recombinant tissue plasminogen activator use: ICD-9 codes substantially underestimate. *Stroke*. 2008;39:924–928.

7. Adams HP Jr, del Zoppo G, Alberts MJ, et al. 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. *Circulation*. 2007;115:e478–e534.

8. Jensen JK, Kristensen SR, Bak S, et al. Frequency and significance of troponin T elevation in acute ischemic stroke. *Am J Cardiol*. 2007;99:108–112.

9. Hills NK, Johnston SC. Why are eligible thrombolysis candidates left untreated? *Am J Prev Med*. 2006;31:S210–S216.

10. Puetz V, Dzialowski I, Hill MD, Demchuk AM. The Alberta Stroke Program Early CT Score in clinical practice: what have we learned? *Int J Stroke*. 2009;4:354–364.

11. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet*. 2004;363:768–774.

12. Warach, S. Thrombolysis in stroke beyond three hours: targeting patients with diffusion and perfusion MRI. *Ann Neurol*. 2002;51:11–13.

13. Weinreb JC, Abu-Alfa AK. Gadolinium-based contrast agents and nephrogenic systemic fibrosis: why did it happen and what have we learned? *J Magn Reson Imaging*. 2009;30:1236–1239.

14. Adams HP Jr, Davis PH, Leira EC, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: a report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology*. 1999;53:126–131.

Recent Advances in Stroke Prevention and Treatment

Neil F. Rosenberg, MD

Northwestern Memorial Hospital, Chicago, Illinois

Abstract The field of acute ischemic stroke treatment and stroke prevention is rapidly advancing. Knowledge of the most recent therapeutic guidelines and developments is important for neurologists who manage patients with stroke. This article reviews the current evidence and published recommendations regarding treatment of acute stroke with intravenous thrombolysis and intra-arterial therapies, the medical and surgical management of the acute stroke patient, and practical tips for reducing delays in stroke treatment. In addition, current guidelines and new therapies in stroke prevention are presented, along with suggestions for selecting among various available therapies.

Stroke remains one of the most pressing health problems of our time. Every year, nearly 800,000 Americans have strokes, and 87% of these events are ischemic. Besides its potential for leaving a devastating neurologic aftermath, stroke is estimated to cost at least $13 billion in lost productivity and a total of about $69 billion annually.[1]

A number of therapies, including newer intra-arterial (IA) therapies, are available to treat acute stroke. In addition, our understanding of the optimal medical and surgical management of stroke patients continues to advance, representing another opportunity to improve outcomes. Finally, prevention of stroke—and, indeed, other cardiovascular disease—may offer the greatest opportunity for reducing healthcare costs. However, navigating through the maze of antiplatelet and antihypertensive agents can prove difficult. A basic familiarity with large clinical trials, recent evidence, and guidelines will help every neurologist who cares for stroke patients.

At the 2011 Annual Meeting of the American Academy of Neurology, experts reviewed current strategies for treatment of acute ischemic stroke and for optimal secondary prevention of stroke. In addition, they offered their own advice for solving some practical problems of clinical stroke care. Speakers referred to American Heart Association (AHA)/American Stroke Association (ASA) classifications for strength of evidence and recommendations; further explanation of the classification system for acute ischemic stroke can be found in the AHA/ASA guidelines.[2]

The session was chaired by Bruce I. Ovbiagele, MD, MSc, Associate Professor of Neurology at the University of California at Los Angeles and Director of the Olive View/UCLA Medical Center Stroke Program, Los Angeles, California.

EVIDENCE-BASED MANAGEMENT OF ACUTE ISCHEMIC STROKE IN 2011

Adapted from a presentation by Pooja Khatri, MD, MSc, Associate Professor, Department of Neurology, University of Cincinnati, and Director, Greater Cincinnati/Northern Kentucky Stroke Team, Cincinnati, Ohio.

Thrombolysis

Intravenous (IV) thrombolysis with recombinant tissue plasminogen activator (tPA; alteplase) remains the only US Food and Drug Administration (FDA)-approved therapy for acute ischemic stroke and the cornerstone of its treatment. Initial FDA approval for this medication was based largely on the results of a National Institute of Neurological Disorders and Stroke (NINDS) trial,[3] which demonstrated that treatment within 3 hours of symptom onset nearly doubled the odds of a favorable 3-month outcome when compared with placebo. More recently, investigators involved in the ECASS III trial[4] evaluated use of tPA in a more carefully selected population of stroke patients treated 3–4.5 hours after the onset of stroke symptoms. At 90 days, 52% of the alteplase group had a favorable functional outcome, namely, an absolute increase of 7%, when compared with placebo.

Although alteplase is presently under FDA review for administration 3–4.5 hours after the onset of symptoms, the AHA/ASA guidelines now recommend treating acute ischemic stroke patients with alteplase 0–3 hours *(Class I; Level of Evidence A)*[2] and 3–4.5 hours *(Class I; Level of Evidence B)*[5] after symptom onset.

The recommended exclusion criteria for IV thrombolysis are listed in Table 1.[2,5] In practice, there is some variability in how these exclusion criteria are applied. There are few data, for instance, regarding the highest INR (international normalized ratio) at which tPA can safely be given, and some experts suggest excluding patients with an INR > 1.4 rather than those with an INR > 1.7. The definition of mild or

Dr. Rosenberg is a Fellow in Neurocritical Care at Northwestern Memorial Hospital, Chicago, Illinois.

rapidly resolving symptoms leaves room for interpretation. Many centers use a cut-off NIHSS (National Institutes of Health Stroke Scale) score of 5, yet other centers routinely use lower scores or permit those in the lower range if the deficit would be disabling in the context of the patient's occupation. Likewise, some centers consider recent myocardial infarction (MI) a contraindication only if there is clinical or electrocardiographic evidence of pericarditis. A seizure at presentation does not preclude stroke; thrombolysis still should be considered, especially if stroke is supported by imaging, such as the presence of vascular occlusion on computed tomography (CT) angiography.

A blood glucose level < 50 mg/dL also is a contraindication for IV tPA therapy. However, thrombolysis should strongly be considered if symptoms persist after correction of glucose or if imaging supports the diagnosis of stroke.

TABLE 1
Key Exclusion Criteria for Intravenous Thrombolytic Therapy

Exclusion criteria for administration up to 3 hours
Absolute contraindications
• Stroke or head trauma within 3 months
• Gastrointestinal or urinary tract hemorrhage within 21 days
• Major surgery within 14 days
• Arterial puncture at a noncompressible site within 7 days
• History of intracranial hemorrhage
• Symptoms of subarachnoid hemorrhage
• Active bleeding or acute trauma
• Blood pressure > 185/110 mm Hg or requiring aggressive antihypertensive therapy
• Clear and large hypodensity on head computed tomography (> 0.33 of cerebral hemisphere)
• INR > 1.7, elevated aPTT, or platelet count < 100,000/mm^3
Relative contraindications
• Minor or rapidly resolving symptoms
• Myocardial infarction in the past 3 months
• Seizure at presentation
• Glucose level < 50 mg/dL
Additional exclusion criteria for administration from 3 to 4.5 hours
• History of stroke and diabetes
• National Institutes of Health Stroke Scale score > 25
• Age > 80 years
• On anticoagulation, regardless of INR

INR = international normalized ratio; aPTT = activated partial thromboplastin time
Source: Adams et al[2] and del Zoppo et al[5]

Anticoagulant Therapy

A recent clinical trial demonstrated the effectiveness of dabigatran, a direct thrombin inhibitor, in preventing stroke in patients with nonvalvular atrial fibrillation. No guidelines currently specify how prophylactic use of this drug may affect the decision to administer tPA, but the 12- to 15-hour half-life of dabigatran suggests that patients should be excluded from tPA administration if they have received dabigatran during the preceding 48 hours.

Catheter-Based Drug Delivery

The quest to recanalize large-vessel occlusions has also spurred the development of local, catheter-based drug delivery. Investigators affiliated with the Prolyse in Acute Cerebral Thromboembolism II (PROACT-II) trial randomized patients with middle cerebral artery (MCA) occlusions within 6 hours of stroke onset to receive either IV heparin plus IA prourokinase or IV heparin alone.[6] Despite a higher rate of symptomatic intracerebral hemorrhage (ICH), patients in the heparin/prourokinase treatment group had a higher rate of functional independence (40%) at 90 days than did those who had been treated with heparin alone (25%). The smaller Japanese MELT trial also found that patients treated with IA urokinase were much more likely to have minimal or no symptoms at 90 days,[7] and a recent meta-analysis supported these findings.[8] Because most studies of IA thrombolysis have used urokinase or prourokinase, the benefit of tPA has largely been inferred.

Mechanical Devices

A number of devices have been developed for use in treating acute ischemic stroke,[9] and some studies have suggested that they may more effectively recanalize occluded vessels than can IV or IA thrombolysis alone.[10] The Penumbra® System (Penumbra, Inc; Alameda, CA) uses a teardrop-shaped probe that mechanically disrupts the clot as its fragments are aspirated into the surrounding catheter.[11] A single-arm study of the device used within 8 hours of stroke onset showed an 82% recanalization rate and 25% functional independence at 90 days with complication rates similar to those of historical controls.[12] Based. in part, on these data, the FDA approved use of the device for vessel revascularization in 2008.

Rather than applying mechanical and suction forces to the proximal face of an embolus, the Merci Retriever® (Concentric Medical, Inc; Mountain View, CA) uses an elastic nickel-titanium "memory wire," which is advanced through the clot. Once deployed distally, the wire resumes a coiled, corkscrew-like shape that, when retracted, engages and entraps the clot, allowing for its withdrawal.

Single-arm trials in patients presenting within 8 hours of stroke onset have shown revascularization rates of 46%–55%, with 28%–36% of patients achieving functional independence at 90 days.[13,14] Use of the device was approved by the FDA in 2004. The Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy study (MR RESCUE; ClinicalTrials.gov NCT00389467) and the Interventional Management of Stroke (IMS) III trial

(ClinicalTrials.gov NCT00359424) will directly compare the Penumbra, Merci Retriever, and other devices.

Other investigators have attempted to use retrievable stents for thrombectomy. The self-expanding Solitaire™ FR Revascularization Device (ev3 Endovascular, Inc.; Plymouth, MN) is first deployed within the thrombus to provide temporary revascularization and then is retracted into the guide catheter with the thrombus adhered to the stent. The Solitaire FR with the Intention for Thrombectomy (SWIFT) trial (ClinicalTrials.gov NCT01054560), sponsored by ev3, sought to compare revascularization rates between the Solitaire FR and the Merci Retriever in patients presenting within 8 hours of stroke. In March 2011, the study's Data Safety Monitoring Board recommended terminating the trial early and submitting the results for FDA review.[15] No trial results have been published.

Presently, IA thrombolysis is considered a treatment option for patients presenting with occlusion of the MCA within 6 hours of onset and who are not candidates for IV tPA *(Class I; Level of Evidence B)*. This option also is considered in patients with other contraindications to IV thrombolysis, such as recent surgery *(Class II; Level of Evidence C)*.[2] The precise role of mechanical thrombectomy is not specified in the 2007 AHA/ASA guidelines, although it may be elucidated in future iterations. At present, for patients without a contraindication to IV thrombolysis, there are no large trials demonstrating patient populations for whom or circumstances for which IA therapies are best used with or in place of IV therapy. Certainly, combining IV and IA thrombolysis is feasible,[16,17] and the ongoing SYNTHESIS EXP trial (ClinicalTrials.gov NCT00640367) aims to compare the two routes directly. On the other hand, two arms of the IMS III trial will compare IV tPA with combined use of IV tPA plus IA tPA. In any case, the availability of IA thrombolysis should not delay administration of IV thrombolysis *(Class III; Level of Evidence C)*.[2]

TABLE 2
Recommended Timeline of Care for Evaluating Patients with Acute Stroke

- Patient is seen by emergency department physician within 10 minutes
- Stroke physician is notified within 15 minutes
- CT scan is completed within 25 minutes
- CT interpretation is obtained within 45 minutes
- IV tPA is initiated within 60 minutes
- Patient is mobilized for intra-arterial therapy as rapidly as possible

CT = computed tomography; IV = intravenous; tPA = recombinant tissue plasminogen activator
Source: National Institute of Neurological Disorders and Stroke

The Crucial Role of Time

Regardless of the treatment modality chosen, minimizing the time to treatment is of critical importance to salvage hypoperfused tissue (ie, the ischemic penumbra) and limit infarct extension. Among patients receiving IV tPA, a favorable outcome is more than twice as likely in patients treated 0–90 minutes after symptom onset than in those treated 180–270 minutes from onset, and the benefit of treatment approaches that of placebo in patients treated after 360 minutes.[18] Among patients receiving IA therapy, quicker recanalization has been associated with a higher odds of functional independence at 90 days, with every 30 minutes that elapse after the onset of symptoms representing an approximately 10% decrease in probability of some functional recovery.[19,20]

Ongoing trials, such as the EXTEND trial of tPA given up to 9 hours after the onset of symptoms (ClinicalTrials.gov NCT00887328), attempt to identify subsets of patients who may benefit from later therapy. However, one of the most important targets for shortening time to treatment may be countering the tendency of providers to use the full time window for treatment. In a phase IV study of tPA in routine clinical use, patients who arrived at the emergency department (ED) soon after stroke onset typically had longer delays to treatment, such that treatment clustered at 2.5–3 hours after symptom onset regardless of patient arrival time.[21]

Thrombolytic treatment of acute ischemic stroke always should be provided as quickly as possible. The recommended timeline for stroke evaluation and treatment, adapted from the NINDS recommendations, is summarized in Table 2.

In addition, several practical considerations may facilitate early treatment. For example, consider notifying a stroke specialist before the patient is sent for a CT scan. Delaying treatment while waiting for laboratory results other than glucose level may be of little benefit, since thrombocytopenia or coagulopathy is found in only 0.3%–0.4% of patients in whom there is no clinical suspicion.[22,23] Other process improvements include physically storing tPA in the ED to minimize delays in obtaining the drug from the hospital pharmacy and mixing the drug early to avoid delays resulting from calculating and preparing the proper dose. (The drug's manufacturer offers a buyback program for tPA that is mixed but not used.)

No definite data regarding the best time to prepare the patient for endovascular therapy are available. Prenotification of the endovascular team almost certainly will speed treatment, and it may be advisable to plan for transport to the endovascular suite early. Placing two large IV catheters and a urinary catheter and priming flush bags also may minimize periprocedural delays. Some experts suggest withholding sedation or using conscious sedation rather than general anesthesia to minimize treatment delays, although this action is controversial.

Treatment of Hypertension

Most stroke patients have some degree of hypertension at presentation that often reflects a history of hypertension (diagnosed or undiagnosed) but that may result from pain, nausea, or an attempt to

compensate for acutely decreased perfusion.[24,25] The optimal treatment of elevated blood pressure in the acute stroke setting is controversial. Previous studies have associated blood pressure reduction in the first 24 hours after stroke with better functional outcomes,[24,26] no benefit,[27] and infarct growth and poor outcome.[28,29] More recently, the results of one randomized trial showed that ischemic stroke patients who continued taking antihypertensive medications had an 8% absolute reduction in risk of death or dependence at 2 weeks when compared with those who stopped their medications,[30] suggesting the safety of continuing antihypertensive medications after discharge.

The current AHA/ASA guidelines recommend emergent treatment of hypertension only when blood pressure exceeds 220/110 mm Hg in patients who are not receiving thrombolytics, unless other medical conditions, such as MI, warrant tighter control *(Class I; Level of Evidence C)*. Patients who are eligible for tPA should have their blood pressure reduced below 185/110 mm Hg before receiving tPA *(Class I; Level of Evidence B)* and maintained below 180/105 mm Hg for 24 hours following thrombolysis. Neurologically stable patients with a history of hypertension should probably have their antihypertensive therapy resumed roughly 24 hours following a stroke *(Class IIa; Level of Evidence B)*.[2]

The notable exception to this strategy is patients whose symptoms clearly worsen with lowering of blood pressure. In this case, holding home antihypertensive treatment and even using vasopressors might be beneficial.

Treatment of Hyperglycemia

High blood glucose levels are common after stroke, with a prevalence exceeding 60% observed in some series.[31] This phenomenon may represent a stress response and/or diabetes/impaired glucose tolerance. Initial hyperglycemia is associated with increased long-term mortality and decreased functional independence,[32,33] although it remains uncertain whether hyperglycemia is directly detrimental or is merely a surrogate for other processes. The current AHA/ASA guidelines suggest that glucose concentrations of 140–185 mg/dL warrant insulin administration *(Class IIa; Level of Evidence C)*,[2] and most experts agree that dextrose-containing fluids should be avoided in the acute setting. The recently funded Stroke Hyperglycemia Insulin Network Effort (SHINE) trial is seeking to assess the benefit of tighter control after stroke.

Prevention of Blood Clots

Current AHA/ASA guidelines recommend initiating therapy with 325 mg of aspirin within 24–48 hours after stroke onset; the role of platelets in secondary stroke prevention is discussed in more detail below *(Class I; Level of Evidence A)*.[2] Based on large trials, this practice is likely to result in 1 fewer recurrent stroke for every 100 patients treated.[34,35] In contrast, with full-dose anticoagulation, the risk of hemorrhagic transformation seems to negate the potential treatment benefit and, therefore, is not recommended *(Class III; Level of Evidence A)*.

Surgery for MCA Infarction

A final important treatment option for some stroke patients is decompressive hemicraniectomy for space-occupying MCA infarctions. In a pooled analysis of three randomized clinical trials involving patients younger than 60 years of age who were treated within 48 hours of stroke onset, one of every two patients who underwent this procedure survived without being bedridden; at worst, patients required assistance with daily activities and walking.[36,37]

Although this procedure may be lifesaving, it may result in significant residual disability; thus, the decision to proceed with hemicraniectomy should be individualized *(Class IIa; Level of Evidence B)*.[2] The University of Cincinnati protocol calls for consideration of hemicraniectomy with even small decreases in the level of consciousness in patients aged 18–60 years with an NIHSS score >10 and an infarct involving > 50% of MCA territory when at least 6 hours has elapsed since treatment with tPA. However, protocols at some centers allow a 12-hour waiting period.

PREVENTING TWO-THIRDS OF STROKES: NEW TRIALS AND APPROACHES

Adapted from a presentation by Mark J. Alberts, MD, Professor of Neurology, Northwestern University, and Director, Stroke Program, Northwestern Memorial Hospital, Chicago, Illinois.

As illustrated by large, contemporary patient registries, more than 28% of patients with a stroke or transient ischemic attack (TIA) will go on to suffer a stroke, MI, vascular death, or rehospitalization for another vascular event over the subsequent 3 years, and 8.4% will suffer a second stroke.[38] Because cerebrovascular disease is related to atherosclerotic disease in other vascular beds, stroke prevention often is inseparable from prevention of other vascular diseases, and discussions of secondary stroke prevention should consider the effects on other vascular diseases. Lifestyle modifications (eg, smoking cessation, diet modification, and increased exercise) are important; however, a discussion of specific strategies for accomplishing this dimension of cardiovascular disease prevention is beyond the scope of this article. Several new studies have identified other important opportunities for improving secondary stroke and preventing cardiovascular morbidity.

Management of Hypertension

Results of a meta-analysis of several large trials showed that adequate blood pressure control could theoretically reduce the risk of recurrent stroke by about 24%.[39] Over longer periods, absolute blood pressure targets should be individualized *(Class IIa; Level of Evidence B)*,[40] but many experts recommend a goal of 120/80 mm Hg for most patients.[41]

The optimal drug regimen for achieving blood pressure control may depend on demographics. Treatment of hypertension with diuretics and angiotensin receptor blockers (ARBs) appears to be effective in all patients, angiotensin-converting enzyme (ACE) inhibitors seem to be more effective in whites than in other races, calcium-channel blockers appear to work best in blacks, and beta-blockers are generally less effective for preventing vascular events than are other antihy-

pertensive agents. Although the current AHA guidelines suggest that diuretics or an ACE inhibitor/diuretic combination may be useful *(Class I; Level of Evidence A),*[40] some studies suggest that patients who require combination treatment may derive more benefit from the combination of a dihydropyridine calcium-channel blocker plus either an ACE inhibitor or an ARB.[42,43]

Hypolipidemic Agents

Elevated lipid levels, particularly of low-density lipoprotein (LDL), and a low high-density lipoprotein (HDL) level have been associated with large-vessel strokes. Data suggest an LDL goal of < 100 mg/dL in those with cardiovascular risk factors, but an LDL goal of ≤ 70 mg/dL is recommended for secondary stroke prevention *(Class IIa; Level of Evidence B).*[40]

To date, the best-studied agent for secondary stroke prevention has been atorvastatin. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial randomized patients with recent stroke (ischemic or hemorrhagic) or transient ischemic attack and no known coronary artery disease to receive 80 mg of atorvastatin or placebo.[44] Over a median follow-up of 4.9 years, patients in the atorvastatin group had a 16% reduction in the risk of having a stroke. Moreover, patients had a 3.5% absolute reduction in rates of first-time major cardiovascular events. Other statins have received less attention, but they likely play a similarly important role in preventing recurrent stroke and other cardiovascular events.

Antiplatelet Agents

The current AHA guidelines for secondary stroke prevention recommend using aspirin *(Class I; Level of Evidence A),* aspirin plus extended-release dipyridamole *(Class I; Level of Evidence B),* or clopidogrel *(Class IIa; Level of Evidence B)* for initial antiplatelet therapy in stroke patients.[40]

Aspirin is a low-cost agent that offers a 15%–20% relative risk reduction for stroke. In meta-analyses, use of this drug reduced the risk of stroke, MI, or vascular death by 13% and was linked to a relatively low incidence of major bleeding (annual risk increase vs control, 0.13%).[45] However, roughly 30%–40% of ischemic strokes occur in patients already taking aspirin, which reflects the in vitro finding that 37% of stroke patients appear to have normal (noninhibited) platelet activity despite aspirin therapy.[46]

Several trials also found combined use of aspirin and extended-release dipyridamole to be effective for stroke prevention and even more effective than aspirin alone. The European Stroke Prevention Study 2 (ESPS-2)[47] found that when compared with placebo, aspirin/dipyridamole use reduced the risk of stroke by 37% and the risk of stroke or death by 24%. The ESPRIT trial,[48] which compared use of aspirin/dipyridamole with aspirin monotherapy, found a 20% lower risk of vascular death, stroke, MI, or major bleeding complication among the treatment group. Consistent with these results, a meta-analysis found an 18% reduction in relative risk of the combined endpoint of stroke, MI, or vascular death with no increase in bleeding events when compared with aspirin alone.[45] In both the ESPS-2 and ESPRIT trials, headache and gastrointestinal (GI) upset were frequent side effects and reasons for stopping the study medication.

> Clinical trial results have suggested that clopidogrel is safer and more effective than either aspirin alone or aspirin plus dipyridamole.

Clinical trial results have suggested that clopidogrel, which will be available generically in 2012, is safer and more effective than either aspirin alone or aspirin plus dipyridamole. In the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study,[49] prophylactic use of clopidogrel reduced the risk of ischemic stroke, MI, or vascular death in patients with atherosclerotic vascular disease by 8.7% when compared with aspirin alone. Although patients taking clopidogrel were more likely to suffer from severe rash, aspirin users were more likely to experience gastrointestinal upset or severe hemorrhage.

In the largest study ever done to evaluate secondary stroke prevention, the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) study group randomized 20,332 patients in a 2 × 2 factorial design to receive either aspirin/dipyridamole or clopidogrel and to either telmisartan or placebo.[50] Patients taking clopidogrel suffered no more stroke recurrence or stroke/MI/death than did those taking aspirin/dipyridamole; however, among those taking combination therapy, the odds of major hemorrhage were increased by 15% and the odds of ICH were increased by 42%. Medication discontinuation, particularly due to headache and dizziness/lightheadedness, also was more frequent with use of aspirin/dipyridamole. Of note, combining clopidogrel with aspirin may increase the risk of life-threatening bleeding without offering additional vascular disease protection.[51] The AHA/ASA guidelines currently recommend against routine use of this combination *(Class III; Level of Evidence A).*[40]

Based on this evidence, in the absence of a cause (eg, vasculitis, dissection, cardiac source of stroke) for alternative therapy, selection of an antiplatelet agent may begin with clopidogrel therapy (because of the drug's superior efficacy and fewer side effects compared with aspirin) plus dipyridamole. In patients who cannot tolerate clopidogrel or who derive no benefit from the drug, aspirin plus dipyridamole may be a reasonable next choice. To prevent side effects, providers may wish to initiate therapy gradually by administering only one capsule daily for several days before using the full dose. If patients are unable to afford other agents, aspirin is preferable to no treatment; this issue may become a less influential factor when clopidogrel becomes available in

generic form. When other regimens fail, a combination of aspirin and clopidogrel may be considered, but its use must be weighed carefully against the increased risk of bleeding.

Few guidelines dictate how long antiplatelet therapy should be used in stroke patients. Providers should consider continuing therapy indefinitely, since stroke risk tends to increase with age, and patients tend to develop other risk factors over time. Notably, cessation of aspirin therapy for weeks to months has been associated with a 40% increase in risk of stroke or TIA.[52] In the period surrounding surgery or other procedures, antiplatelet agents generally should not be withheld for more than 5 days, because most platelet activity returns within this period. Antiplatelet agents should be restarted 48 hours after a procedure or once obvious bleeding has stopped.

Anticoagulants

Warfarin has long been the standard of care for preventing stroke in patients with atrial fibrillation. In 2010, the FDA approved the use of 150 mg of dabigatran twice daily to prevent stroke in patients with nonvalvular atrial fibrillation. The onset of effect of dabigatran is 2–3 hours; use of the drug does not require routine blood monitoring, and no significant drug interactions (except with rifampin) have been reported. However, the capsule cannot be opened or crushed, and therefore the drug cannot be given via a feeding tube. Data regarding the reversal of dabigatran anticoagulation in the event of serious bleeding are limited.

In the recent Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[53] investigators randomized patients with nonvalvular atrial fibrillation and another stroke risk factor to receive dabigatran or warfarin (goal INR, 2–3). Over a median follow-up of 2 years, administration of 150 mg of dabigatran was associated with a 34% relative risk reduction in stroke or systemic embolism, with no difference in the rate of major bleeding when compared with warfarin. Although initial publication of these results showed an increase in risk of MI with dabigatran, later corrections to the study data showed the difference to be statistically insignificant.[54] A dose of 75 mg twice daily is recommended for patients with a creatinine clearance of 15–30 mL/min.

The present AHA guidelines recommend that warfarin be used for preventing stroke in patients with atrial fibrillation *(Class I; Level of Evidence A)* and aspirin in patients unable to take warfarin *(Class I; Level of Evidence A).* The inclusion of dabigatran in the guidelines is pending additional regulatory evaluation and approval.[40] Nevertheless, dabigatran remains the first viable alternative to warfarin. Recent phase III trials of other anticoagulants, such as the Factor Xa inhibitor apixaban, raise the hope that additional agents will soon be available to prevent stroke in patients with atrial fibrillation who are unable or unwilling to take warfarin.

Carotid Endarterectomy and Stenting

Carotid endarterectomy (CEA) has shown a clear benefit over medical therapy for patients with symptomatic 70%–99% stenosis, especially when performed within 2 weeks of the occurrence of symptoms. The benefit for individuals with 50%–69% stenosis is less dramatic than for patients with higher grades of stenosis.[40]

One enduring problem in stroke prevention has been delineating the roles of CEA versus stenting. The recently published CREST trial[55] randomized patients with ≥ 50% stenosis to receive either CEA or a stent. The primary outcome was the combined endpoint of periprocedural stroke, MI, and death or of ipsilateral stroke during follow-up.

During a median 2.5-year follow-up, there was no difference between groups in the primary outcome or in the incidence of ipsilateral stroke. Stenting was associated with a higher risk of periprocedural stroke (4.1% vs 2.3%) but a lower risk of periprocedural MI (1.1% vs 2.3%). In contrast, an interim analysis of the ongoing International Carotid Stenting Study (ICSS), which randomized patients with symptomatic > 50% stenosis, found a higher 120-day rate of stroke, death, or periprocedural MI among the stenting group (8.5 vs 5.2%).

CEA and stenting both appear to be effective, and more data are yet to be gathered, yet many experts believe that the weight of evidence currently favors CEA. AHA/ASA guidelines suggest CEA for symptomatic 70%–99% stenosis *(Class I; Level of Evidence A),* recommend that this procedure be accomplished within 2 weeks *(Class IIa; Level of Evidence B),* offer stenting as an alternative to endarterectomy *(Class I; Level of Evidence B),* and suggest stenting in patients who are poor surgical candidates *(Class IIb; Level of Evidence B).*[40] Regardless of the strategy chosen, these procedures should be performed only when the established periprocedural morbidity and mortality rates are < 6%.[40]

Selecting Therapeutic Targets

Clearly, many factors may influence rates of recurrent stroke and cardiovascular disease. Yet some of the highest-yield interventions may include some considered to be the most basic. One model suggested that providers could reduce the 5-year cardiovascular event risk by 80% by effectively addressing five key behaviors and risk factors: modification of diet, exercise, use of antiplatelet agents, treatment with statins, and control of blood pressure.[56] Whereas clinical reality is seldom as bright as in these quantitative models, they are nevertheless worthwhile goals.

CONCLUSION

The landscape of stroke treatment and prevention is complex and ever-changing. A number of therapies are available to treat acute ischemic stroke, and our understanding of how best to select patients for specific therapies is evolving. However, minimizing the time to treatment remains the crux of maximizing treatment benefit. In the acute setting, medical management consists of avoiding aggressive treatment of hypertension, providing modest glycemic control, and starting antiplatelet agents early. Decompressive hemicraniectomy should be offered within 48 hours for maximal benefit.

Outside of the acute setting, stroke patients are at high risk for recurrent stroke

and other cardiovascular disease. Control of risk factors should center on modifying diet, increasing exercise, using an antiplatelet agent, administering a statin, and controlling hypertension. Patients with carotid stenosis are likely to benefit from endarterectomy and, possibly, stenting. New, effective anticoagulants are available to patients with atrial fibrillation, and additional agents are in the pipeline.

REFERENCES

1. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2009;119:480–486.
2. Adams HP Jr, del Zoppo G, Alberts MJ, et al. 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. *Stroke.* 2007;38:1655–1711.
3. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med.* 1995;333:1581–1588.
4. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359:1317–1329.
5. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Stroke Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke.* 2009;40:2945–2948.
6. Furlan A, Higashida R, Wechsler L, et al. Intra-arterial prourokinase for acute ischemic stroke. The PROACT II study: a randomized controlled trial. Prolyse in Acute Cerebral Thromboembolism. *JAMA.* 1999;282:2003–2011.
7. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke: the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT) Japan. *Stroke.* 2007;38:2633–2639.
8. Lee M, Hong KS, Saver JL. Efficacy of intra-arterial fibrinolysis for acute ischemic stroke: meta-analysis of randomized controlled trials. *Stroke.* 2010;41:932–937.
9. Rosenberg N, Chen M, Prabhakaran S. New devices for treating acute ischemic stroke. *Recent Pat CNS Drug Discov.* 2010;5:118–134.
10. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta-analysis. *Stroke.* 2007;38:967–973.
11. Bose A, Gupta V, Donahue S, Hui D. System and method for treating ischemic stroke. US Patent 7931659. March 16, 2006. http://www.freepatentsonline.com/7931659.html. Accessed May 6, 2011.
12. Penumbra Pivotal Stroke Trial Investigators. The Penumbra pivotal stroke trial: safety and effectiveness of a new generation of mechanical devices for clot removal in intracranial large vessel occlusive disease. *Stroke.* 2009;40:2761–2768.
13. Smith WS, Sung G, Saver J, et al. Mechanical thrombectomy for acute ischemic stroke: final results of the Multi MERCI trial. *Stroke.* 2008;39:1205–1212.
14. Smith WS, Sung G, Starkman S, et al. Safety and efficacy of mechanical embolectomy in acute ischemic stroke: results of the MERCI trial. *Stroke.* 2005;36:1432–1438.
15. Price D. Covidien wraps Solitaire FR clinicals early in bid for quick FDA review. March 14, 2011. Mass Device Web site. http://www.massdevice.com/news/covidien-wraps-solitaire-fr-clinicals-early-bid-quick-fda-review. Accessed May 6, 2011.
16. IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke.* 2004;35:904–911.
17. IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II study. *Stroke.* 2007;38:2127–2135.
18. Hacke W, Donnan G, Fieschi C, et al. Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet.* 2004;363:768–774.
19. Khatri P, Abruzzo T, Yeatts SD, et al. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. *Neurology.* 2009;73:1066–1072.
20. Mazighi M, Serfaty JM, Labreuche J, et al. Comparison of intravenous alteplase with a combined intravenous-endovascular approach in patients with stroke and confirmed arterial occlusion (RECANALISE study): a prospective cohort study. *Lancet Neurol.* 2009;8:802–809.
21. Albers GW, Bates VE, Clark WM, Bell R, Verro P, Hamilton SA. Intravenous tissue-type plasminogen activator for treatment of acute stroke: the Standard Treatment with Alteplase to Reverse Stroke (STARS) study. *JAMA.* 2000;283:1145–1150.
22. Cucchiara BL, Jackson B, Weiner M, Messe SR. Usefulness of checking platelet count before thrombolysis in acute ischemic stroke. *Stroke.* 2007;38:1639–1640.
23. Rost NS, Masrur S, Pervez MA, Viswanathan A, Schwamm LH. Unsuspected coagulopathy rarely prevents IV thrombolysis in acute ischemic stroke. *Neurology.* 2009;73:1957–1962.
24. Sare GM, Ali M, Shuaib A, Bath PM; VISTA Collaboration. Relationship between hyperacute blood pressure and outcome after ischemic stroke: data from the VISTA collaboration. *Stroke.* 2009;40:2098–2103.
25. Leonardi-Bee J, Bath PM, Phillips SJ, Sandercock PA; IST Collaborative Group. Blood pressure and clinical outcomes in the International Stroke Trial. *Stroke.* 2002;33:1315–1320.
26. Toyoda K, Fujimoto S, Kamouchi M, Iida M, Okada Y. Acute blood pressure levels and neurological deterioration in different subtypes of ischemic stroke. *Stroke.* 2009;40:2585–2588.
27. Yong M, Kaste M. Association of characteristics of blood pressure profiles and stroke outcomes in the ECASS-II trial. *Stroke.* 2008;39:366–372.
28. Castillo J, Leira R, Garcia MM, Serena J, Blanco M, Davalos A. Blood pressure decrease during the acute phase of ischemic stroke is associated with brain injury and poor stroke outcome. *Stroke.* 2004;35:520–526.
29. Oliveira-Filho J, Silva SC, Trabuco CC, Pedreira BB, Sousa EU, Bacellar A. Detrimental effect of blood pressure reduction in the first 24 hours of acute stroke onset. *Neurology.* 2003;61:1047–1051.
30. Robinson TG, Potter JF, Ford GA, et al. Effects of antihypertensive treatment after acute stroke in the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS): a prospective, randomised, open, blinded-endpoint trial. *Lancet Neurol.* 2010;9:767–775.
31. Gray CS, Scott JF, French JM, Alberti KG, O'Connell JE. Prevalence and prediction of unrecognised diabetes mellitus and impaired glucose tolerance following acute stroke. *Age Ageing.* 2004;33:71–77.
32. Ntaios G, Egli M, Faouzi M, Michel P. J-shaped association between serum glucose and functional outcome in acute ischemic stroke. *Stroke.* 2010;41:2366–2370.
33. Ahmed N, Davalos A, Eriksson N, et al. Association of admission blood glucose and outcome in patients treated with intravenous thrombolysis: results from the Safe Implementation of Treatments in Stroke International Stroke Thrombolysis Register (SITS-ISTR). *Arch Neurol.* 2010;67:1123–1130.
34. CAST: randomised placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) Collaborative Group. *Lancet.* 1997;349:1641–1649.
35. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19,435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet.* 1997;349:1569–1581.
36. Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. *Lancet Neurol.* 2007;6:215–222.
37. Hofmeijer J, Kappelle LJ, Algra A, et al. Surgical decompression for space-occupying cerebral infarction (the Hemicraniectomy After Middle Cerebral Artery infarction with Life-threatening Edema Trial [HAMLET]): a multicentre, open, randomised trial. *Lancet Neurol.* 2009;8:326–333.
38. Alberts MJ, Bhatt DL, Mas JL, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. *Eur Heart J.* 2009;30:2318–2326.
39. Rashid P, Leonardi-Bee J, Bath P. Blood pressure reduction and secondary prevention of stroke and other vascular events: a systematic review. *Stroke.* 2003;34:2741–2748.
40. Furie KL, Kasner SE, Adams RJ, et al. Guidelines for the prevention of stroke in patients with stroke or transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.*

2011;42:227–276.

41. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA*. 2003;289:2560–2572.

42. Wang JG. A combined role of calcium channel blockers and angiotensin receptor blockers in stroke prevention. *Vasc Health Risk Manag*. 2009;5:593–605.

43. Jamerson K, Weber MA, Bakris GL, et al. Benazepril plus amlodipine or hydrochlorothiazide for hypertension in high-risk patients. *N Engl J Med*. 2008;359:2417–2428.

44. Amarenco P, Bogousslavsky J, Callahan A 3rd, et al. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med*. 2006;355:549–559.

45. O'Donnell MJ, Hankey GJ, Eikelboom JW. Antiplatelet therapy for secondary prevention of noncardioembolic ischemic stroke: a critical review. *Stroke*. 2008;39:1638–1646.

46. Alberts MJ, Bergman DL, Molner E, Jovanovic BD, Ushiwata I, Teruya J. Antiplatelet effect of aspirin in patients with cerebrovascular disease. *Stroke*. 2004;35:175–178.

47. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci*. 1996;143:1–13.

48. ESPRIT Study Group, Halkes PH, van Gijn J, Kappelle LJ, Koudstaal PJ, Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. *Lancet*. 2006;367:1665–1673.

49. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). CAPRIE Steering Committee. *Lancet*. 1996;348:1329–1339.

50. Sacco RL, Diener HC, Yusuf S, et al. Aspirin and extended-release dipyridamole versus clopidogrel for recurrent stroke. *N Engl J Med*. 2008;359:1238–1251.

51. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomised, double-blind, placebo-controlled trial. *Lancet*. 2004;364:331–337.

52. Garcia Rodriguez LA, Cea Soriano L, Hill C, Johansson S. Increased risk of stroke after discontinuation of acetylsalicylic acid: a UK primary care study. *Neurology*. 2011;76:740–746.

53. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med*. 2009;361:1139–1151.

54. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L; Randomized Evaluation of Long-Term Anticoagulation Therapy Investigators. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363:1875–1876.

55. Brott TG, Hobson RW 2nd, Howard G, et al. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med*. 2010;363:11–23.

56. Hackam DG, Spence JD. Combining multiple approaches for the secondary prevention of vascular events after stroke: a quantitative modeling study. *Stroke*. 2007;38:1881–1885.

Cerebrovascular Disease: Stroke Systems of Care

Basanagoud Mudigoudar, MD

SUNY Downstate Medical Center, Brooklyn, New York

Abstract A systems approach to stroke management involves coordination of healthcare services along the entire continuum, from primary prevention through rehabilitation. A systems approach is necessary to change stroke treatment and give patients access to the most advanced, best-equipped treatment center available to manage the critical and time-sensitive needs of stroke patients. Information recently offered by experts in stroke management focused upon improving the prevention of stroke and the treatment, rehabilitation, and outcomes of stroke patients. Presenters at a scientific poster session discussed many aspects of stroke care, including the effect of antiplatelet agents on intracerebral hemorrhage (ICH); the utility of a regional health information exchange; the medicolegal considerations of stroke management; the effect of an expanded time window on use of tissue plasminogen activator; the impact of a telestroke program on stroke care; and the development of novel, ICH-specific, intensity-of-care quality metrics.

The current approach to stroke care is fragmented in most regions of the United States because of inadequate links between facilities and coordination among health professionals who deliver the fundamental components of stroke care. Providers can reduce the devastating effects of stroke by promoting coordinated systems that improve patient management.

At a scientific poster session offered during the 63rd Annual Meeting of the American Academy of Neurology (AAN), held April 9–16, 2011, in Honolulu, Hawaii, several studies covered such different aspects of acute stroke care as the effect of premorbid aspirin use on hematoma expansion, patient disability, and death among individuals with spontaneous intracerebral hemorrhage (ICH); the medicolegal considerations related to administration of intravenous (IV) recombinant tissue plasminogen activator (tPA; alteplase) in acute stroke care; and the usefulness of a regional health information exchange to facilitate outcomes epidemiology.

Dr. Mudigoudar is a Child Neurology Resident at SUNY Downstate Medical Center, Brooklyn, New York.

Other poster presentations discussed the results of using IV tPA during and beyond the 3-hour time window and reflected upon the impact of a statewide telestroke program on different time parameters in spoke hospitals. They also reviewed the results of research concerning the diagnosis of conversion disorder mimicking acute stroke via a telecommunication program and comparing post-thrombolytic care of acute stroke patients in hub versus spoke hospitals participating in a statewide "telestroke" program.

Finally, two presenters reviewed the development and validation of a novel, ICH-specific, intensity-of-care quality metric, which represents a step toward implementing standardized care to ICH patients in different settings. Results of these studies will likely impact the delivery of stroke care in the future.

PREMORBID ASPIRIN USE ON HEMATOMA EXPANSION, DISABILITY, AND DEATH

Adapted from a poster presentation by Fazeel M. Siddiqui, MD, Southern Illinois University Health Care, Springfield, Illinois.

Aspirin (acetylsalicylic acid; ASA) is the most common antiplatelet agent used to prevent ischemic stroke and cardiovascular events. Although low doses of aspirin are generally well tolerated, their use might worsen hematoma growth and clinical outcome in patients with spontaneous ICH. Studies examining the effect of prior antiplatelet therapy on outcome in patients with spontaneous ICH have shown conflicting results.[1]

To clarify this issue, Siddiqui et al[2] performed a systematic review of previous studies to identify the relationship between prior use of antiplatelet agents and hematoma growth, patient disability, and death in individuals with spontaneous ICH. Investigators identified pertinent studies that had well-defined clinical outcomes, 20 or more ICH patients, and a proper statistical design from online publishing databases and bibliographies of selected publications. The investigators evaluated the relationship between antiplatelet therapy and both death and favorable outcome (ie, modified Rankin scale [mRS] score ≤ 3) at discharge and at 3 months for ICH patients. In addition, they scrutinized the role of antiplatelet agents in causing hematoma growth (> 33% from baseline) at 24–48 hours from admission.

Eleven studies with a total study population of 4,734 patients met the criteria. The incidence of inpatient death was higher in patients using an antiplatelet agent than in those who did not (27% vs 19%, respectively; $P = 0.002$). Prior use of antiplatelet agents was associated with a lower rate of favorable outcome at discharge when compared with no previous use of antiplatelet therapy (28% vs 37%), although statistical significance was not reached. The mortality at 3 months also was higher in patients who had prior antiplatelet use (36% vs 22%; $P = 0.029$). The incidence of hematoma expansion was higher among those using antiplatelet agents (18% vs 14%; $P = 0.255$).

This systematic review demonstrated a modest increase in hematoma expansion and intermediate-term mortality among ICH patients who used antiplatelet therapy before symptom onset. Future prospective studies are needed to further confirm these findings and to evaluate whether reversal of antiplatelet activity by platelet transfusion can modify the effect of premorbid antiplatelet therapy in this patient population.

MEDICOLEGAL CONSIDERATIONS SURROUNDING tPA USE

Adapted from a poster presentation by Archit Bhatt, MD, MPH, Spectrum Health Medical Group, Grand Rapids, Michigan.

Despite the success of the 1995 National Institute of Neurological Disorders and Stroke study[3] using IV tPA in acute stroke patients that led to the drug's marketing approval by the US Food and Drug Administration, physicians have been reluctant to use tPA because of safety and efficacy issues. Use of the drug has been associated with a high incidence of ICH and protocol violations. As a result, physicians are increasingly liable for both administering and not administering tPA for acute ischemic stroke.[4]

To understand the factors influencing litigation and to avoid future recurrence, Bhatt et al[5] performed a detailed retrospective review of medicolegal cases involving tPA administration and stroke. Investigators performed an extensive literature search for such cases using MEDLINE, Embase, Westlaw, LexisNexis, and Google Scholar.

The investigators identified 40 cases having adequate available information among 789 stroke patients involved in malpractice suits between 1996 and 2011. The most frequent claims by plaintiffs were failure to treat with tPA (70%) and failure to diagnose eligible candidates (25%). Only 5% of the claims involved complications of tPA. Emergency department (ED) physicians were involved in the majority of these cases (60%); the minority involved neurologists and multiple physicians. Although the majority of verdicts favored defendants, a significant number (30%) went in favor of plaintiffs.

Factors in favor of the defense were proper documentation, informed consent, unknown time of symptom onset, tPA protocol in the hospital, unavailability of tPA in the hospital, expert witness testimony, and patient presentation after 3 hours of symptom onset. Factors favoring plaintiffs were delay in physician evaluation and failure to treat with tPA, diagnose, transfer the patient to another facility, obtain informed consent, or maintain proper documentation.

These findings suggest that hospitals and ED physicians who administer tPA to patients with acute ischemic stroke are at an increased risk of medical litigation. Physicians are more likely to be sued for failure either to diagnose acute ischemic stroke or treat it with tPA. Improvements in documentation, communication with families, education of providers, strategic partnerships with bigger hospital systems, and telemedicine efforts may help to reduce the threat of litigation.[5]

USE OF REGIONAL HEALTH INFORMATION EXCHANGE

Adapted from a poster presentation by Brett M. Kissela, MD, MS, FAAN, Vice-Chair of Education and Clinical Services, Department of Neurology, University of Cincinnati College of Medicine, University of Cincinnati, Cincinnati, Ohio.

Health information exchange (HIE) is defined as the electronic transmission of healthcare information across organizations within a region, community, or hospital system. HIE provides this capability among disparate healthcare information systems while maintaining the integrity of the exchanged data. The goal is to facilitate access to and retrieval of clinical data to provide safer and more timely, efficient, effective, equitable, and patient-centered care.

Kissela et al[6] examined the usefulness of HIE in studying ischemic stroke outcomes in the greater Cincinnati/Northern Kentucky region (population, 1.3 million). Stroke incidence in this population is studied periodically; for example, in 2005, investigators conducted interviews of patients at 3 months to analyze outcomes following an acute ischemic stroke. In 2010, the researchers partnered with HealthBridge, a regional HIE, to potentially improve the efficiency of studying ischemic stroke outcomes.

In 2005, the quest to find ischemic stroke subjects involved screening hospital admission logs for chief complaint terms. During that period, many facilities required that investigators travel each day to examine logs on-site and then conduct medical record reviews to confirm that patients had an ischemic stroke.

In 2010, however, investigators established a secure interface to receive real-time HIE data feeds and populate a dedicated database with data from likely stroke patients for further review. They remotely accessed electronic medical records from facilities via HealthBridge to increase the likelihood that patients truly had experienced an ischemic stroke before nurses were dispatched to obtain consent from prospective subjects. Person-hours of effort from both periods were captured, and data were analyzed descriptively.

For 2005, recruiting 502 subjects required 14 coordinator-hours and 26 study nurse-hours daily on average; 42 subjects were excluded as nonstrokes after physician review. During the first 5 months of 2010, recruiting 250 subjects required 10 coordinator-hours and 21 study nurse-hours daily, and only 1 case was excluded as a nonstroke. Thus, daily person-hours were reduced by 23% in 2010, and recruitment over 5 months was 16.8% higher than expected based upon 2005 estimates.

HIE use enabled access to real-time

healthcare data across a region in a secure fashion, provided greater efficiency and accuracy of study subject identification, and improved recruitment in this pilot study when compared with traditional approaches. HIE-based approaches could greatly facilitate population-based epidemiology and outcomes studies, but further assessment of their potential is needed to confirm these results.

ADMINISTRATION OF tPA IN THE EXPANDED TIME WINDOW

Adapted from a poster presentation by Wondwossen G. Tekle, MD, Vascular Neurology/Neurocritical Care Fellow, Department of Neurology, University of Minnesota, Minneapolis, Minnesota.

The results of ECASS III, a randomized, double-blind trial, demonstrated that IV tPA administered 3–4.5 hours after the onset of symptoms significantly improved clinical outcomes in patients with acute ischemic stroke.[7] Based on these results, in May 2009, the American Stroke Association (ASA) recommended that IV tPA be used for patients presenting within 3–4.5 hours after symptom onset.[8]

To further address the effect of expanding the time window for tPA use, Tekle et al[9] retrospectively reviewed the charts of all the patients treated with IV tPA at two comprehensive stroke centers from September 2008 to July 2010. They also identified patients who arrived to the ED within 2.5–4 hours of symptom onset between January 2007 and June 2010 but received only endovascular treatment. Favorable outcome was defined as an mRS score of 0–2 at both discharge and 3-month follow-up and a National Institutes of Health Stroke Scale (NIHSS) score improvement of ≥ 4 points or 0 at discharge. Rates of favorable clinical outcome among patients treated with IV tPA 3–4.5 hours after symptom onset first were compared with those of patients given IV tPA before 3 hours and then with patients presenting in a similar time window but treated only with endovascular therapy.

Of 98 patients treated with IV tPA, 84 received treatment within 3 hours of symptom onset, and 14 were treated within 3–4.5 hours. Twelve patients received endovascular treatment only during the specified time window. Baseline characteristics, including mean admission NIHSS score, were not different between the groups. For those treated within 3–4.5 hours or 0–3 hours, no difference was seen in favorable clinical outcome at discharge (50% vs 56%, respectively; $P = 0.77$) or at 3 months (64% vs 64%; $P = 1.0$) or for NIHSS score improvement (43% vs 58%; $P = 0.38$). When outcomes of patients treated with IV tPA within 3–4.5 hours after symptom onset were compared with those of patients treated with primary endovascular treatment, there was an insignificantly higher rate of favorable outcomes at discharge (25% vs 50%, respectively; $P = 0.24$) and at 3 months (42% vs 64%; $P = 0.43$). An additional 14% received IV tPA because the treatment window was expanded from 3 to 4.5 hours.

Treatment-window expansion seems to help an additional subset of patients who present later, and outcomes are comparable to those of patients treated within 3 hours of symptom onset. These findings reinforced the conclusions of ECASS III. Thus, any acute stroke patient who presents up to 4.5 hours after symptom onset and fulfills the eligibility criteria should be a candidate for IV tPA. The shift of those patients from primary endovascular treatment does not appear to affect patient outcome adversely.

TELESTROKE PROGRAM IN ACUTE STROKE CARE

Adapted from a poster presentation by Bappaditya Ray, MD, Department of Neurology and Center for Distance Health, and Salah G. Keyrouz, MD, Assistant Professor of Neurology, University of Arkansas for Medical Sciences, Little Rock, Arkansas.

Telemedicine is the exchange of medical information from one site to another using electronic communication (eg, telephone, Internet, videoconference). The application of telemedicine for care of acute strokes, often called "telestroke," was a natural progression from general telemedicine because of a shortage of stroke neurologists and recent advances in technology. To overcome the gap in availability of and access to stroke specialists and to address the underuse of therapies for acute stroke, telemedicine techniques have been adapted to the emergency evaluation of acute stroke.[10] Several research groups have reported on the impact of telestroke programs on acute stroke care.

Impact of Number of Consultations on the Efficient Delivery of Acute Stroke Care

The Arkansas SAVES (Stroke Assistance Through Virtual Emergency Support) program is a statewide telestroke network that provides acute stroke care to patients in 22 hospitals across the state. It is funded by Arkansas Medicaid and the state Department of Human Services. Ray et al[11] compared the time parameters relating to IV thrombolysis in high-volume spoke hospitals (ie, those having a large number of consultations) of the SAVES program with those having a low volume. For the purpose of this analysis, they defined a high-volume site as one having at least two consultations per month.

The investigators reviewed the prospective database kept since inception of the program in November 2008. They compared baseline characteristics and the time parameters for door-to-brain computed tomography (CT) scale, door-to-neurologist consultation, and door-to-needle treatment (ie, with IV tPA) in the 18 spoke hospitals participating in the program for > 3 months. Data were analyzed in respect to the average number of consultations received monthly by each spoke site.

During the 3-month study period, 45 patients received IV tPA at 18 spoke hospitals. High-volume hospitals were prompt in consulting the stroke neurologist when compared with low-volume facilities (door-to-neurologist consultation [minutes], 51 ± 29 vs 66 ± 24; $P = 0.06$). They also were more efficient in administering IV tPA (door–to-needle [minutes], 117 ± 24 vs 92 ± 32; $P < 0.05$). There was no significant difference between the groups in obtaining a noncontrast brain CT scan upon a patient's arrival. Furthermore, there was no significant difference in the final outcome between the two types of spoke hospitals (mRS score ≤ 2, 1.8 ± 2.4 vs 1.88 ± 2.4; $P = 0.98$).

The use of telemedicine is effective in delivering acute stroke care in rural and underserved areas. These results suggest that using these services more frequently may lead to more efficient delivery of acute stroke care. Despite the fact that outcomes did not differ, awareness among community members and rapid response by providers in the spoke hospitals are vital for providing acute stroke care in a timely manner.

Conversion Disorder Mimicking Acute Stroke

Thrombolysis is an established therapy for acute ischemic stroke that requires accurate identification of a potential stroke on an emergent basis. Diagnosing stroke mimics is vital to avoiding unnecessary, potentially dangerous therapy. Among those mimics, conversion disorder proves difficult to distinguish, even in face-to-face encounters. The reliability of telemedicine in making this diagnosis remains unknown.

Using the SAVES program, Keyrouz et al[12] performed a retrospective study to describe the experience of their telestroke network with stroke mimics, discuss challenges encountered, and question the reliability of diagnosing conversion disorder via telemedicine. The investigators reviewed all records of patients diagnosed with conversion disorder. The diagnosis of conversion disorder was made on clinical grounds considering age, comorbid diseases, history of psychiatric illnesses and acute stressors, and findings on examination.

Of 274 patients followed for suspected acute stroke during the study period, 18 patients (7%) were diagnosed with conversion disorder. These individuals were relatively young (mean age, 47 years), and most (89%) were women. These patients had a low incidence of stroke risk factors. However, 89% of these patients had a history of a psychiatric condition or acute stressors. At least two patients who initially were believed to have suffered a stroke and who received IV tPA later eventually were diagnosed with conversion disorder, but neither had any complications.

In an acute setting, conversion disorder mimicking stroke is not uncommon. The low figures (7%) obtained during this study may not reflect the true incidence of conversion disorder in the telemedicine setting, given the conservative nature of the decision-making process. Therefore, telemedicine might not be a reliable method to diagnose this condition. Larger prospective studies are needed to better understand the specific challenges of this technology in diagnosing conversion disorder.

Post-Thrombolytic Care of Acute Ischemic Stroke

The clinical application of thrombolysis has revolutionized the care of patients with acute ischemic stroke. Hospitals should implement standardized processes and protocols for acute stroke management to guide immediate patient assessment, brain imaging, drug administration, and post-thrombolytic care.[13] Strict adherence to the prescribed protocol for the IV use of tPA and post-thrombolytic care is crucial to minimize the risk of hemorrhagic complications. However, barely any literature has addressed post-thrombolytic care in the setting of a telestroke program.

> Patients transferred to hub hospitals for post-thrombolytic care shared similar outcomes with those treated at spoke hospitals, despite differences in initial stroke severity.

Yaghi and Keyrouz[14] compared the outcomes of patients with acute stroke following IV thrombolysis in the Arkansas SAVES telestroke network who received post-thrombolytic care at a spoke or hub hospital. The investigators reviewed the prospective database kept since the inception of the program. They sought baseline demographics, including relevant medical history, time to thrombolysis, NIHSS score at presentation, and 3-month mRS score for outcome adjudication.

A total of 97 patients who received IV thrombolysis and had available 3-month mRS scores were included in the final analysis. Following thrombolysis, 22 patients (23%) remained in a spoke facility, and 75 (77%) were transferred to a hub hospital after receiving IV tPA. Both groups were comparable in age, gender, comorbid conditions, and mean time from last known time of wellness to thrombolysis. Conversely, the mean NIHSS score was higher (12 vs 8) among patients transferred to hub hospitals as compared with those who stayed at spoke hospitals ($P = 0.021$). Still, the percentage of patients with an mRS score ≤ 2 was similar among the groups.

Therefore, patients cared for at hub hospitals shared a similar outcome with those treated at spoke hospitals, despite differences in initial stroke severity. Whether this finding implies that patients treated in hub hospitals received better care remains to be confirmed. Severity of stroke could have been a factor leading stroke neurologists to encourage patients' transfer to hub hospitals for post-thrombolytic care. However, more studies on this aspect of stroke care are needed.

THE EFFECT OF DIFFERENCES IN STROKE CARE

Adapted from poster presentations by Adnan I. Qureshi, MD, Professor of Neurology, Neurosurgery, and Radiology, and Saqib A. Chaudhry, MD, Clinical Research Fellow, Zeenat Qureshi Stroke Research Center, University of Minnesota, Minneapolis, Minnesota.

ICH carries a higher risk of long-term disability and mortality than does any other form of stroke. Despite a greater understanding of ICH pathophysiology, physicians continue to have limited treatment options for this devastating condition. Moreover, a lack of a standard, universally accepted, ICH-specific, intensity-of-care quality metric has contributed to variations in management protocols and clinical trial designs.[15] ICH care can differ among centers, and previous stud-

TABLE 1
Quality Indicators Used for Measuring ICH-Specific Intensity of Care

- Emergency department evaluation
- Expedient acquisition of neuroimaging
- Intensive care unit monitoring
- Avoidance of withdrawal of care and/or do-not-resuscitate orders
- Treatment of acute hypertensive response
- Early intubation and mechanical ventilation
- Treatment of clinically significant intracranial mass effect or transtentorial herniation
- Treatment of repetitive seizures and status epilepticus (clinical)
- Treatment of repetitive seizures and status epilepticus (subclinical)
- Rapid reversal of elevated INR (international normalized ratio)
- Treatment of elevated serum glucose concentration
- Treatment of hyperpyrexia
- Prophylaxis of deep venous thrombosis
- Dysphagia screening
- Feeding (nutrition) initiation
- Gastric ulcer prophylaxis
- Treatment of persistently elevated blood pressure
- Tracheostomy for persistent intubation, or airway protection
- Treatment of hospital-acquired pneumonia

ICH = intracerebral hemorrhage
Source: Qureshi[16]

ies have demonstrated variations in ICH outcome based on differences in patient care in various settings.

Development of a Novel, ICH-Specific, Intensity-of-Care Quality Metric

Qureshi[16] designed an evidence-based dataset of elements for a new, ICH-specific, intensity-of-care quality metric. Investigators reviewed data derived from multicenter, randomized trials; selected nonrandomized or observational clinical studies; and current guidelines from the American Heart Association/ASA Stroke Council and the European Stroke Initiative Writing Committee for Management of ICH to identify quality indicators and available scientific evidence. For certain elements for which stroke-specific data were not available, data derived from other disease processes with direct relevance were used.

A total of 26 quality indicators related to 18 facets of care with thresholds for quality response were identified (Table 1). A pilot study was performed to assess and score these quality indicators. The electronic medical records of 25 randomly selected ICH patients who were admitted within 24 hours of symptom onset were jointly reviewed by two stroke researchers. Interobserver reliability was determined, and the κ value for agreement was calculated. Values of $\kappa > 0.80$ indicated excellent agreement, of 0.60–0.79 indicated good agreement, of 0.40–0.59 indicated moderate agreement, and of ≤ 0.40 indicated poor agreement. The proportion of patients meeting a quality parameter ranged from 44% to 100%, depending upon the variable. The lowest performance scores were linked to early intubation and mechanical ventilation, treatment of a significant intracranial mass effect or transtentorial herniation, and timely acquisition of neuroimaging studies. The highest performance scores were associated with treatment of any seizure within 2 weeks of admission, status epilepticus, and prevention of gastric ulcer.

The next step in developing a new, ICH-specific, intensity-of-care quality metric is validation and refinement of quality indicators and thresholds presented in the current report.

Validation of a Novel, ICH-Specific, Intensity-of-Care Quality Metric

Investigators conducting a small pilot study tested the validity of the new, ICH-specific, intensity-of-care quality metric previously described. Chaudhry et al[17] considered 26 quality indicators related to 18 facets of care. Thresholds for quality care were incorporated into a metric providing the variable and its definition (Table 1).[16] The researchers assigned a score of 1 point if the variable met the threshold of appropriate performance and of 0 points if inadequate performance was detected or adequate documentation was lacking.

The electronic medical records of 50 consecutive ICH patients admitted within 24 hours of symptom onset were reviewed by two stroke researchers. A total of 14 (28%) patients with ICH died during hospitalization. The mean score of the proposed, ICH-specific, intensity-of-care quality metric was higher among survivors than among those who died (23 ± 3 vs 21 ± 2; $P = 0.02$). Survival increased with tertiles-based higher scores on an intensity-of-care quality metric (100%, 67%, and 55%; $P = 0.017$).

Thus, performance of the new, ICH-specific, intensity-of-care quality metric correlated with in-hospital mortality in ICH patients and supported its broader use for improving and standardizing medical care among ICH patients. Future research should include selection and validation based upon a consensus of experts and an application of the system to a large series of patients with ICH. Additional studies also should assess the relationship of components in isolation and as a group to outcome after severity adjustment.

REFERENCES

1. Lacut K, Le Gal G, Seizeur R, Prat G, Mottier D, Oger E. Antiplatelet drug use preceding the onset of intracerebral hemorrhage is associated with increased mortality. *Fundam Clin Pharmacol*. 2007;21:327–333.

2. Siddiqui FM, Qureshi AI. Effect of pre-morbid aspirin use on hematoma expansion, disability and death among 4,734 patients with spontaneous intracerebral hemorrhage. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.267.

3. Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med*. 1995;333:1581–1588.

4. Weintraub MI. Thrombolysis (tissue plasminogen activator) in stroke: a medicolegal quagmire.

Stroke. 2006;37:1917–1922.

5. Bhatt A, Chaudhari D, Kassab M, et al. Medicolegal considerations with intravenous tissue plasminogen activator in stroke: a systematic review. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.268.

6. Kissela BM, Embi PJ, Alwell K, et al. Use of a regional Health Information Exchange (HIE) to facilitate outcomes epidemiology. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.269.

7. Hack W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. ECASS Investigators. *N Engl J Med*. 2008;359:1317–1329.

8. del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr; American Heart Association Strole Council. Expansion of the time window for treatment of acute ischemic stroke with intravenous tissue plasminogen activator: a science advisory from the American Heart Association/American Stroke Association. *Stroke*. 2009;40:2945–2948.

9. Tekle WG, Hassan AE, Rodriguez GJ, Chaudhry SA, Vazquez G, Qureshi AI. IV rt-PA administration in the expanded time window (3–4.5 hours) in practice: utilization and outcomes. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.270.

10. Levine SR, Gorman M. "Telestroke": the application of telemedicine for stroke. *Stroke*.1999;30:464–469.

11. Ray B, Yaghi S, Keyrouz S. Impact of number of consultations on different time parameters in spoke hospitals in a statewide telestroke program. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.271.

12. Keyrouz S, Achi E, Yaghi S. Conversion disorder mimicking acute stroke in a statewide telestroke program: experience and challenges in diagnosis. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.274.

13. Fugate JE, Giraldo EA, Rabinstein AA. Thrombolysis for cerebral ischemia. *Front Neurol*. 2010;1:139.

14. Yaghi S, Keyrouz SG. Comparison of post-thrombolysis care of acute stroke in hub versus spoke hospitals of a statewide telestroke program. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.275.

15. Qureshi AI. Intracerebral hemorrhage specific intensity of care quality metrics. *Neurocrit Care*. 2011;14:291–317.

16. Qureshi AI. Intracerebral hemorrhage specific intensity of care quality metrics. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.272.

17. Chaudhry SA, Tariq N, Fareed M, et al. Validation of a novel intracerebral hemorrhage specific intensity of care quality metrics. Presented at the 63rd Annual Meeting of the American Academy of Neurology; April 9–16, 2011; Honolulu, HI. Poster P07.273.

CME Post Test

Using this page as a worksheet, select the best answer to each question based on your reading of the articles in this issue of *The Neurology Report,* then complete the evaluation on the facing page and see the instructions below it to obtain CME credit.

1. Gropen et al determined that a significant predictor of a true-positive diagnosis of stroke by emergency medical service workers was:
   a. The presence of motor signs
   b. Identification of a left-sided lesion
   c. A National Institutes of Health Stroke Scale (NIHSS) score of 3 or higher
   d. Impaired cognition

2. Following a stroke, _____ is a leading complication and an important cause of clinical deterioration and death.
   a. Bacterial meningitis
   b. Myocardial infarction
   c. Pneumonia
   d. Hypothyroidism

3. The initial evaluation of all stroke patients should include:
   a. Urinary electrolyte levels
   b. Arterial blood gas testing
   c. Five-lead electrocardiogram
   d. Cardiac enzyme tests

4. A thrombolytic strategy proven to be effective in patients with acute ischemic stroke is administration of:
   a. 30 units of anistreplase intravenously (IV) over 2–5 minutes into a line or vein
   b. 0.9 mg/kg, up to 90 mg, of recombinant tissue plasminogen activator (tPA) IV (10% as a bolus dose, with the remaining 90% as a 1-hour infusion)
   c. 250,000 units of streptokinase IV into a peripheral vein over 30 minutes, followed by 100,000 units per hour for 24 hours
   d. Two 10-unit bolus IV injections of reteplase given over 2 minutes, with the second given 30 minutes after the first

5. Which of the following can be used to predict mortality and functional outcome 3 months after an acute stroke?
   a. Initial presence of torticollis
   b. Baseline renal function test results
   c. Initial pseudoparkinsonism
   d. Initial NIHSS score

6. Which of the following is a contraindication to the use of IV tPA for acute ischemic stroke?
   a. Blood glucose level < 50 mg/dL
   b. Blood glucose level < 75 mg/dL
   c. Seizure at presentation
   d. Recent myocardial infarction, even if pericarditis is not evident

7. A favorable outcome is _____ likely among acute stroke patients treated 0–90 minutes after symptom onset when compared with those treated 180–270 minutes from onset.
   a. Less than half as
   b. Equally
   c. More than twice as
   d. More than four times as

8. Unless other medical conditions warrant tighter control, current American Heart Association guidelines recommend emergency treatment of what level of blood pressure in patients who have had an acute stroke and are not receiving thrombolytics?
   a. > 160/90 mm Hg
   b. > 190/95 mm Hg
   c. > 200/100 mm Hg
   d. > 220/110 mm Hg

9. The results of a detailed retrospective review of medicolegal cases involving tPA administration and stroke by Bhatt et al showed that the most frequent claims by plaintiffs involved:
   a. Complications related to tPA administration
   b. Failure to treat with tPA
   c. Failure to diagnose eligible tPA candidates
   d. Failure to transport the patient to a more experienced facility

10. Results of a study comparing time parameters relating to IV thrombolysis in high-volume spoke hospitals affiliated with the Arkansas Stroke Assistance Through Virtual Emergency Support (SAVES) program with those of low-volume hospitals found that over 3 months:
   a. Consultations with a stroke neurologist were more prompt in low-volume hospitals.
   b. Noncontrast brain CT scans were obtained more promptly upon patient arrival in low-volume hospitals.
   c. IV tPA was administered more efficiently in high-volume hospitals.
   d. Fewer deaths were reported among stroke patients in high-volume hospitals.

Evaluation

Your candid and thorough completion of this evaluation will help the University of Cincinnati improve the quality of its CME activities. Thank you for your participation.

	Strongly agree	Agree	Disagree
1. As a result of this activity, I am more knowledgeable about the …			
a. Obstacles to identifying and optimally managing acute stroke and methods for providing better emergency treatment of affected patients.	❑	❑	❑
b. Current drugs and devices intended to prevent or treat intracerebral hemorrhage (ICH) and optimal timing of thrombolytic therapy.	❑	❑	❑
c. Medicolegal issues and clinical findings on the use of IV recombinant tissue plasminogen activator (alteplase, tPA) for acute ischemic stroke.	❑	❑	❑
d. Research on an intensity-of-care, ICH-specific quality metric and the sensitivity of EMS diagnosis and early management of stroke.	❑	❑	❑

	Strongly agree	Agree	Disagree
2. I found the content of this educational activity …			
a. Clearly written and well organized.	❑	❑	❑
b. Accurate and timely.	❑	❑	❑
c. Related to its overall objectives.	❑	❑	❑
d. Free from commercial bias.	❑	❑	❑
e. Relevant to my own clinical practice.	❑	❑	❑

	Yes	No	Don't know
3. Did the information you received from this CME activity:			
a. Confirm the way you currently manage your patients?	❑	❑	❑
b. Suggest new options for managing your patients that you might apply in the future?	❑	❑	❑

	Patient management	Board review	CME credit
4. I used the information in this issue for … *(check all that apply)*	❑	❑	❑

5. Approximately how long *(in minutes)* did it take you to complete this activity, including this evaluation? _____ minutes

Instructions for Obtaining CME Credit

To receive CME credit for this free educational activity and a certificate of participation from the University of Cincinnati:

- Study the educational material presented in this issue of *The Neurology Report.*
- Using page 28 as a worksheet, answer all of the post-test questions based on the content of the articles.
- Visit **www.NeurologyReport.com** on the Web by June 30, 2012, select this issue of *The Neurology Report,* and click "CME Post Test" to apply for credit online and complete the post test and evaluation.
- Complete the registration form, enter your post-test answers from the worksheet on page 28, and respond to all of the questions on the evaluation form, then click the button to submit your answers. The full text of each article may be accessed at www.NeurologyReport.com, should you need to refer to it again.
- If you answer correctly at least 8 (80%) of the 10 post-test questions, you will immediately receive credit for completing this educational activity and can access your CME certificate online by clicking the "Certificate" button at the bottom of the evaluation form. Follow the on-screen instructions to print or e-mail your certificate.