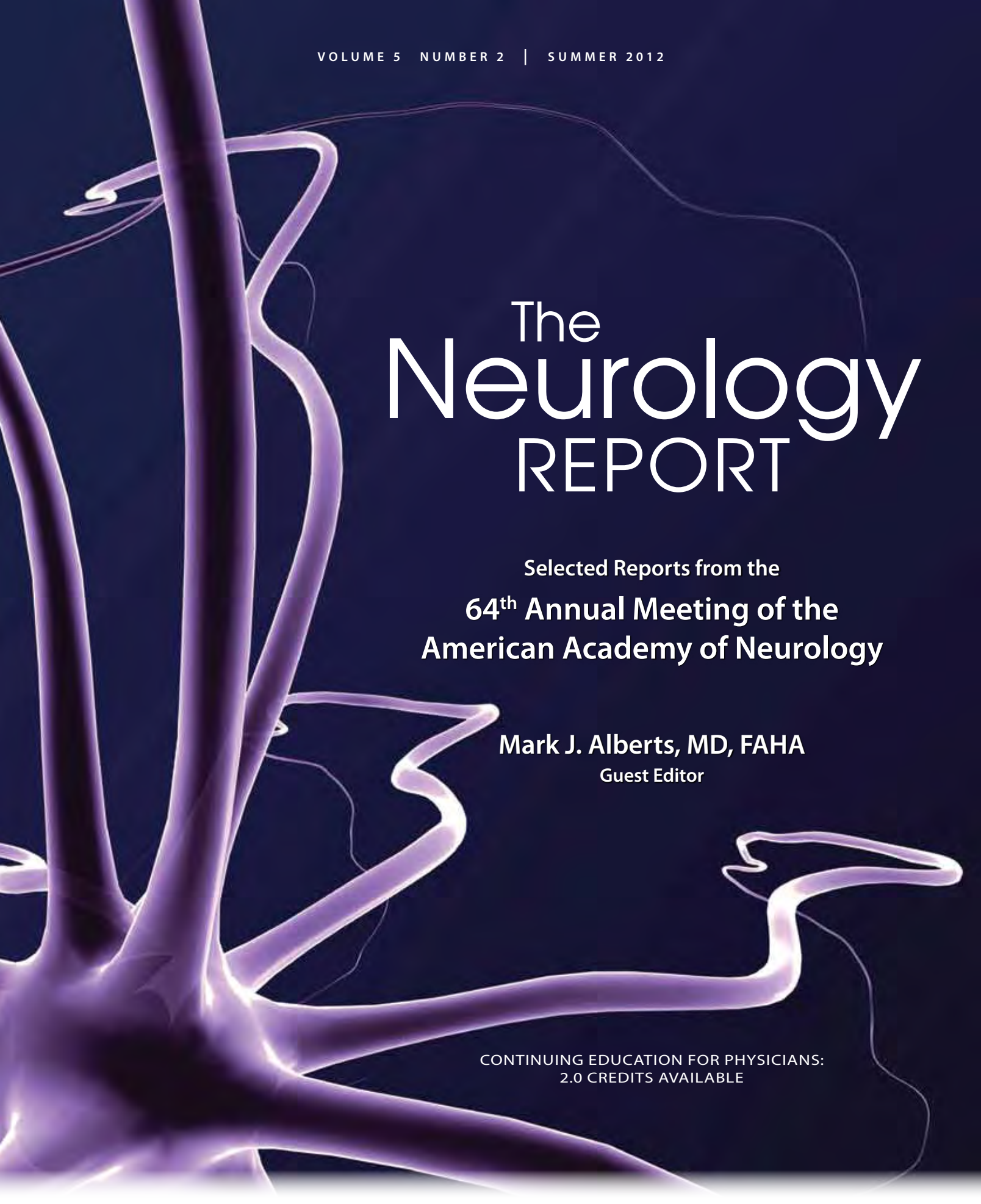
VOLUME 5 NUMBER 2 | SUMMER 2012



The Neurology REPORT

Selected Reports from the 64th Annual Meeting of the American Academy of Neurology

Mark J. Alberts, MD, FAHA
Guest Editor

CONTINUING EDUCATION FOR PHYSICIANS:
2.0 CREDITS AVAILABLE

Supported by an educational grant from Genentech, Inc.

Genentech

Guest Editor: Mark J. Alberts, MD, FAHA

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

VOLUME 5 NUMBER 2 | SUMMER 2012

The Neurology REPORT

Selected Reports from the
64th Annual Meeting of the
American Academy of Neurology

Mark J. Alberts, MD, FAHA
Guest Editor

About This CME Activity

RATIONALE AND PURPOSE

Stroke affects approximately 795,000 Americans each year and is the fourth leading cause of death behind heart disease, cancer, and lower respiratory diseases. In addition, many patients who survive a stroke have significant disability, with 15%–30% becoming permanently disabled. These patients are at high risk of having another stroke within their lifetime. Nevertheless, only a small fraction (≤ 5%) of acute ischemic stroke patients who could benefit from intravenous (IV) thrombolytic therapy are promptly treated with it.

In this edition of *The Neurology Report,* the authors provide a comprehensive overview of current trends in diagnosing, treating, and preventing acute ischemic stroke, based on selected sessions delivered during the 64th Annual Meeting of the American Academy of Neurology, held April 21–28, 2012, in New Orleans, Louisiana. Their reports range from the safety and efficacy of IV recombinant tissue plasminogen activator (tPA) therapy to predictors of outcomes following treatment for anterior circulation ischemic stroke; the pros and cons of intra-arterial (IA) thrombolysis and mechanical thrombectomy; the "drip-and-ship" treatment paradigm followed by many smaller community hospitals to transport patients safely to comprehensive stroke centers; new treatments for reducing the risk of stroke in patients with atrial fibrillation; endovascular procedures for reperfusing ischemic areas of the brain; and the potential pitfalls in assessing and managing acute stroke patients, stressing a collaborative approach among attending physicians and specialists to ward off potential problems.

The articles in this issue, written from the academic perspective of physicians-in-training at leading medical centers, 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 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:

- Summarize the actions that need to be taken by physicians when an acute stroke patient presents to the emergency department.
- Describe the rationale for and outcomes of the drip-and-ship paradigm for managing patients with acute stroke.
- Compare and contrast the benefits and risks of IV versus IA thrombolysis and the indications for mechanical thrombectomy in stroke patients.
- Discuss current trends in preventing stroke in high-risk patients.
- Review the assessment and management of medical complications associated with acute ischemic stroke.

TARGET AUDIENCE

Neurologists and other physicians significantly involved in the diagnosis, treatment, and prevention of acute ischemic stroke should find participating 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 Enduring Material Activity for a maximum of 2.0 *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: August 17, 2012
Expiration date: August 18, 2013

METHOD OF PARTICIPATION

This Enduring Material 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 2.0 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.

Mark J. Alberts, MD, FAHA, is Professor of Neurology, Northwestern University Feinberg School of Medicine, Chief of the Division of Stroke and Cerebrovascular Disease, and Director of the Stroke Program at Northwestern Memorial Hospital, Chicago, Illinois. He has served as an advisor and consultant to Boehringer Ingelheim, Bristol-Myers Squibb, Janssen, Merck, Pfizer, and sanofi-aventis; is on the speakers bureaus of Boehringer Ingelheim, Genentech, and Janssen; and has received research/grant support from Bristol-Myers Squibb, Merck, and Pfizer.

Matthew C. Smith, MD, a Vascular Neurology Fellow at the University of North Carolina School of Medicine, Chapel Hill, North Carolina, has nothing to disclose.

Karen C. Albright, DO, Clinical Instructor in Neurology in the Department of Medicine, University of Alabama School of Medicine, Birmingham, Alabama, has nothing to disclose.

Karen G. Hirsch, MD, a Fellow in Neurocritical Care in the Department of Neurology and Critical Care, University of California, San Francisco, San Francisco, California, has nothing to disclose.

Peter S. Pressman, MD, a Neurology Resident at Northwestern University Feinberg School of Medicine, Chicago, Illinois, 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 this issue of *The Neurology Report,* Drs. Smith, Albright, and Pressman refer to stroke studies in which IV tPA was administered up to 4.5 hours after symptom onset, however, the FDA has not approved the extension of tPA's therapeutic window beyond 3 hours. Dr. Smith summarizes research on the investigational use of intra-arterial thrombolytics as an alternative to IV tPA. Drs. Albright and Hirsch describe clinical trials of an investigational oral anticoagulant, apixaban, to prevent stroke in patients with atrial fibrillation. In addition, Dr. Albright mentions a trial in which stroke patients were given aspirin plus extended-release dipyridamole or clopidogrel to reduce the risk of a second stroke; however, dipyridamole is not approved by the FDA for this indication. Finally, Dr. Smith describes the off-label use of IV tPA to treat acute ischemic stroke in pediatric patients; tPA is approved by the FDA only for use in adults.

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
Website: www.CMEdirect.net

Introduction

Selected Reports from the 64th Annual Meeting of the American Academy of Neurology

Mark J. Alberts, MD, FAHA, *Guest Editor*

Northwestern University Feinberg School of Medicine, Chicago, Illinois

Although our understanding of stroke has increased considerably over the past 30 years, both the management of patients at greatest risk and the acute treatment of this potentially deadly disease remain somewhat controversial. This edition of *The Neurology Report* contains articles written by neurology fellows and one resident who attended scientific sessions at the recent 64th Annual Meeting of the American Academy of Neurology. Our goal was to provide a comprehensive overview of current trends in diagnosing, treating, and preventing stroke and many other facets of stroke care.

REPERFUSION THERAPY FOR ACUTE ISCHEMIC STROKE

Intravenous recombinant tissue plasminogen activator (IV tPA), also known as alteplase, is the gold standard for treating acute ischemic stroke, but researchers and clinicians alike continue to seek other therapeutic options for patients who cannot use this highly effective, life-saving therapy. Matthew C. Smith, MD, of the University of North Carolina at Chapel Hill, describes the treatment of stroke with intra-arterial thrombolytics and the controversies surrounding the "drip-and-ship" treatment paradigm used to initiate treatment in many smaller community hospitals. Dr. Smith also covers selection of patients for mechanical thrombectomy, use of thrombolytics in pediatric patients, and predictors of outcome following IV thrombolysis in patients experiencing acute anterior circulation ischemic stroke. Finally, he summarizes a presentation on common adverse reactions associated with IV tPA therapy in stroke patients.

Dr. Alberts is Professor of Neurology, Northwestern University Feinberg School of Medicine, Chief of the Division of Stroke and Cerebrovascular Disease, and Director of the Stroke Program at Northwestern Memorial Hospital, Chicago, Illinois.

THERAPY OF STROKE: 2012

Karen C. Albright, DO, of the University of Alabama School of Medicine, Birmingham, reviews an evidence-based approach for treating stroke and its complications. Among the topics Dr. Albright covers are methods of reducing vascular risk after acute or recent cerebral ischemia is detected and techniques for reperfusing ischemic brain areas. In addition, she compares many therapeutic options currently being used and/or tested in stroke patients, summarizing the results of studies involving novel oral anticoagulants and surgical approaches.

THE ESSENTIAL ROLE OF NEUROLOGISTS IN TREATING AND PREVENTING STROKE

"Time is brain" is an adage that resounds in the ears of neurologists and other healthcare professionals attending to stroke patients. Karen G. Hirsch, MD, of the University of California, San Francisco, offers a glimpse into cutting-edge medical therapy for cerebrovascular accidents. Dr. Hirsch condenses vital results of clinical studies testing important new medications, including rivaroxaban, apixaban, and dabigatran, against tried-and-true conventional therapies. In addition, she reviews therapeutic options that may reduce the risk of stroke for patients with symptomatic carotid artery disease and describes the neurologist's role in treating intracerebral hemorrhage.

SURVIVING STROKE CALL: A GUIDE FOR NONVASCULAR NEUROLOGISTS

Peter S. Pressman, MD, of the Northwestern University Feinberg School of Medicine in Chicago, covers an expert panel discussion on the systematic examination and treatment of individuals presenting with signs and symptoms of stroke. Considering the multiple possible complications that a stroke patient might experience, the speakers stressed the importance of collaboration among many members of an interdisciplinary medical team. Dr. Pressman also reviews the use of IV tPA, the efficacy and safety of implementing different devices and endovascular techniques, and topics that should be reviewed with stroke patients and their loved ones, even if informed consent is not required.

Presentations at medical meetings in the coming years certainly will reveal key advances in the optimal management of stroke and related conditions. The authors of the present report have contributed interesting, concise synopses of current stroke management trends for this edition of *The Neurology Report*. We thank them for their insights and look forward to their future contributions to the medical literature.

Reperfusion Therapy for Acute Ischemic Stroke

Matthew C. Smith, MD

University of North Carolina School of Medicine, Chapel Hill, North Carolina

Abstract For the past 16 years, the only FDA-approved drug available for treating acute ischemic stroke has been recombinant tissue plasminogen activator (tPA, alteplase), given intravenously (IV) within 3 hours of symptom onset. More recently, interest has grown not only in extending the therapeutic window of tPA to 4.5 hours but also in other therapeutic options for reperfusing ischemic brain tissue using intra-arterial thrombolysis and/or mechanical thrombectomy. During the 2012 Annual Meeting of the American Academy of Neurology, speakers discussed these therapeutic modalities, the pros and cons of "drip-and-ship" programs for starting IV tPA at a community hospital and then transporting patients to comprehensive stroke centers for follow-up care, and the use of IV tPA in pediatric patients. Experts also presented data on the benefits of particular imaging modalities for patient selection, the relationship between collateral blood vessel status and thrombolysis outcomes, and the risk of hemi-orolingual angioedema in insular stroke patients treated with IV tPA.

Prior to 1995, the only treatment available for patients who suffered an ischemic stroke was supportive; patient outcomes were mixed, and there was no standard of care from one hospital to the next. Following publication that year of the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study,[1] intravenous (IV) administration of recombinant tissue plasminogen activator (tPA, alteplase) within 3 hours of symptom onset became the gold standard for treating acute ischemic stroke. This trial marked the beginning of the era of acute stroke intervention instead of passive observation.

Dr. Smith is a Vascular Neurology Fellow at the University of North Carolina School of Medicine, Chapel Hill, North Carolina.

In recent years, clinical investigators have evaluated other IV thrombolytics, intra-arterial (IA) thrombolysis, and mechanical thrombectomy in acute stroke patients, but IV tPA remains the only treatment for acute ischemic stroke that has been approved by the US Food and Drug Administration (FDA). Unfortunately, in spite of many clinical trials, it is not known precisely who will benefit or be harmed by treatment with IV tPA.

During the 2012 Annual Meeting of the American Academy of Neurology (AAN), many experts in stroke and its management discussed methods to maximize the benefit of IV tPA and minimize any harm related to its use. One speaker discussed the potential of widening the therapeutic window for stroke by using IA thrombolytics. Other topics included the practice of "drip and ship" by small hospitals that lack the capability of optimally managing stroke and adherence to patient care guidelines by emergency medical services (EMS) personnel. Speakers also touched upon the best imaging modality for determining penumbra, the chances that good outcomes will correlate with the presence of good collateral blood vessels, the safety of IV tPA therapy in pediatric patients, and the risk of IV tPA side effects in treated patients.

IA THROMBOLYSIS FOR ACUTE STROKE: AN ADJUSTED META-ANALYSIS

Based on a presentation by William J. Powers, MD, H. Houston Merritt Distinguished Professor and Chair, Department of Neurology, University of North Carolina School of Medicine, Chapel Hill

One of the biggest limitations of IV tPA therapy is the narrow therapeutic window physicians have to treat patients. Because most patients do not present to the hospital in time to receive the medication, alternative treatments were investigated to pry open the time window a little more.

In 1998, the Prolyse in Acute Cerebral Thromboembolism (PROACT) I study[2] results showed the safety of using IA prourokinase within 6 hours of the onset of stroke symptoms in a specific population having known proximal middle cerebral arterial (MCA) occlusions. However, this trial did not have enough statistical power to support FDA approval for this treatment. In 1999, the PROACT II study,[3] which involved larger numbers of patients, demonstrated the superiority of IA prourokinase therapy over heparin when given within 6 hours of symptom onset to patients with large MCA occlusions.

In 2007, data from the Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial (MELT)[4] showed that urokinase therapy provided some benefit over placebo in patients with proximal MCA occlusions. However, the trial was stopped early, and the primary endpoint

of favorable outcome at 9 months did not reach statistical significance.

With all three trials showing its safety and possible benefit, use of IA thrombolytics has become an accepted alternative treatment for stroke, and specifically for proximal MCA occlusions, even though it has not been approved by the FDA.

Linearly weighted time-dependent odds ratios (ORs) derived from the IV tPA trials have illustrated the effect of the extended therapeutic window; Grotta and others[5] found that IV tPA therapy may be used in up to 15% of patients with acute ischemic stroke with a low risk of symptomatic intracerebral hemorrhage (ICH). Further, in 2008, the European Cooperative Acute Stroke Study III (ECASS III)[6] revealed that IV tPA benefits certain patients up to 4.5 hours after the onset of stroke symptoms. Proof of the efficacy and safety of this longer therapeutic window made more patients eligible for IV tPA, and the search for alternative therapies, including IA thrombolysis, became less crucial.

IV tPA versus IA tPA

Powers[7] sought to model the effect of IV tPA therapy in 130 control patients participating in these trials. He used a modified Rankin Scale (mRS) of 0–1 at 90 days as the outcome and weighted time-dependent ORs from pooled IV tPA trials.[8]

In the PROACT I and II studies,[2,3] a median of 4.5 hours elapsed before arteriography was accomplished; the model assumed that one half of the patients were treated by 3.5 hours. For MELT,[4] the principal investigator supplied hospital times for the 57 subjects. The model assumed that patients were treated 1 hour after arrival. The OR of 1.39 calculated for all 130 controls was applied to the original control data to derive an adjusted control outcome; this outcome was then compared with data from the group given IA thrombolysis.

The meta-analysis of the original data showed a statistically significant benefit for IA thrombolysis ($P = 0.03$) compared with control subjects. The adjusted meta-analysis showed no statistically significant benefit ($P = 0.32$) for IA thrombolysis when controls could have received IV tPA ≤ 4.5 hours after symptom onset (Table 1).[9] A sensitivity analysis showed that the lack of significant IA thrombolysis benefit persisted even after reducing by one half the OR for the benefit of IV tPA or the number of treated controls. The adjusted meta-analysis also considered that patients having a proximal MCA occlusion may do worse than would the pooled data set.

TABLE 1
Results of Intra-Arterial Thrombolytic Therapy for Acute Ischemic Stroke[a]

	Intervention		Control		
Study	**Events**	**Total**	**Events**	**Total**	**Odds ratio (95% CI)**
PROACT	8	26	3	14	1.63 (0.355, 7.48)
PROACT II	31	121	10	59	1.69 (0.764, 3.73)
MELT	24	57	13	57	2.46 (1.09, 5.54)
Total (original)	63	204	26	130	1.79 (1.06, 3.01)
Total (model)	63	204	32	130	1.37 (0.83, 2.25)

PROACT = Prolyse in Acute Cerebral Thromboembolism; MELT = Middle Cerebral Artery Embolism Local Fibrinolytic Intervention Trial; CI = confidence interval.

[a] Results of a meta-analysis of three randomized controlled trials of intra-arterial thrombolytic therapy within 6 hours of onset of acute ischemic stroke caused by middle cerebral artery occlusion. Original data and data after modeling the effect of intravenous recombinant tissue plasminogen activator in the control groups are shown.

Source: Powers[9]

Thus, in randomized trials, IA thrombolysis given within 6 hours of the onset of acute ischemic stroke symptoms probably would not have been more beneficial than IV tPA given within 4.5 hours of symptom onset, as shown by ECASS III.[6] It is not known whether IA thrombolysis is better than IV tPA therapy in patients eligible to receive IV tPA or better than placebo in patients who are not eligible to receive IV tPA. Further study of this question is warranted.

"DRIP AND SHIP" FOR ACUTE ISCHEMIC STROKE

Based on a presentation by Gustavo Rodriquez, MD, Assistant Professor of Neurology and Neurosurgery, University of Minnesota, Minneapolis

The term "drip and ship" denotes a practice whereby patients who present with symptoms of acute stroke are given IV tPA at an outside emergency department and then transferred, usually within 24 hours (often soon after the IV infusion is completed), to a higher level hospital for continued care. In many cases, small community hospitals refer patients to a larger comprehensive stroke center.

The drip-and-ship paradigm started in the cardiology literature in 2000[10] and then was adapted to include the use of IV tPA in stroke patients. Earlier reports on the practice mainly were case studies from individual hospitals that were first published in 2005.[11] However, relationships among hospitals, telestroke networks (geographically separated physicians who use electronic communication methods, such as videoconferencing, to exchange stroke information), and other healthcare interests could have led to substantial bias in these reports. To try to eliminate the sample bias, Qureshi et al[12] performed the first population-based study of drip and ship in Minnesota. The study was then expanded to include data from the Healthcare Cost and Utilization Project's National Inpatient Sample (2005–2008).

In 2008, the Centers for Medicare and Medicaid Services (CMS) approved a new code, V45.88 (published in the *International Classification of Diseases, 9th Revision*).[13] This code identifies patients given IV tPA at one emergency department and then transferred to a comprehensive stroke center. Tonarelli et al[14] noted that this code is 92% sensitive and 100% specific for identifying patients who received drip-and-ship treatment.

Tracking Drip-and-Ship Patterns

Using this code and the National Inpatient Sample (2005–2008), Rodriguez et al[15] obtained and analyzed comparative in-hospital outcomes for patients treated with IV tPA according to the drip-and-ship paradigm, after adjusting for potential cofounders. The investigators estimated the use of thrombolytics, costs

of hospitalization, and patterns of referral related to drip-and-ship treatment of acute stroke patients.

Over the study period, 1,564,504 acute strokes occurred. Of this number, 26,814 occurred in patients who were treated with IV tPA, and 5,144 of this group (19%) were treated using the drip-and-ship paradigm. Urban teaching hospitals received 79% of the drip-and-ship patients; 7% of affected patients received endovascular treatment at the referring facility. States in which drip and ship was more common had a higher rate of thrombolytic use (3.1%) than did states in which the practice was not commonly used (2.4%; $P < 0.001$).

The outcomes between drip-and-ship patients and those treated at the same facility were then adjusted for age, gender, hypertension, diabetes mellitus, renal failure, and hospital teaching status. The outcomes were similar among both groups in terms of self care (OR, 1.055; 95% confidence interval [CI], 0.910–1.224; $P = 0.4779$), death (OR, 0.821; 95% CI, 0.619–1.088; $P = 0.1688$), and nursing home discharge (OR, 1.023; 95% CI, 0.880–1.189; $P = 0.7659$). With drip and ship, there was a shorter hospital stay (mean ± standard error, 5.9 ± 0.18 days vs 7.4 ± 0.15 days; $P < 0.001$) and a lower cost of hospitalization (mean total charges ± standard error, $57,000 ± $3,324 vs $83,000 ± $3,367; $P < 0.001$).

> Cities, states, and regions using the drip-and-ship model are more likely to use thrombolytics and to have shorter, less costly hospital stays.

Based on these results, approximately one in five patients given IV tPA for acute ischemic stroke is treated according to the drip-and-ship paradigm, and cities, states, and regions using the drip-and-ship model are more likely to use thrombolytics and to have shorter hospital stays. Further, the practice was safe not only across a state but across regions, even when the results were adjusted for bias. However, this study was limited by the lack of an mRS and National Institutes of Health Stroke Scale (NIHSS) scores to standardize results. Further research needs to be done to ascertain the safety of the drip-and-ship paradigm in managing patients with acute ischemic stroke.

COMPLIANCE OF EMS PERSONNEL WITH ESTABLISHED GUIDELINES

Based on a presentation by Ganesh Asaithambi, MD, Fourth-year Resident and 2012 AAN Resident Research Travel Scholarship Recipient, University of Minnesota, Minneapolis

Patients treated with IV tPA at referral centers and those treated at comprehensive stroke centers have similar outcomes. To promote the safe use of IV tPA, guidelines were developed to regulate its administration, but are they followed by EMS personnel transporting patients to comprehensive stroke centers?

Guidelines Compliance During Drip and Ship

Asaithambi and colleagues[16] investigated guidelines compliance during transport of acute ischemic stroke patients given IV tPA according to the drip-and-ship paradigm. In addition, they examined the effect of this compliance on patient outcomes upon discharge. The investigators analyzed records from patients transferred to the Zeenat Qureshi Stroke Research Center in Minnesota from June 2009 to July 2011. In particular, they were interested in the frequency of blood pressure monitoring, interventions given for elevated blood pressure, and discontinuation of IV tPA if patients began to show signs and symptoms of neurologic deterioration. An mRS score ≤ 1 upon discharge was considered to show favorable outcome.

In all, 40 patients (mean age, 71.9 years; 55% male) were treated according to the drip-and-ship paradigm, with 21 given IV tPA during the entire emergency transport. Although 14 patients completed the infusion during transport, 5 patients completed receipt of the drug before being transported. A mean of 136.3 ± 56.1 minutes elapsed between symptom onset and IV tPA initiation. A total of 38 patients received hemodynamic monitoring every 10–20 minutes; 2 patients were monitored inadequately. Seven patients had at least one blood pressure reading above recommended parameters, but only one of them was treated with an antihypertensive agent. Five patients exhibited neurologic deterioration, but IV tPA use was not discontinued in any of them. The overall noncompliance rate was 30%.

Altogether, 41.7% of the noncompliance group and 35.7% of the compliance group ($P = 0.736$) had a favorable outcome. Symptomatic ICH occurred in 8.3% of the noncompliance group and in 3.6% of the compliance group ($P = 0.515$).

With the implementation of drip-and-ship treatment plans, more and more eligible patients who experience symptoms of acute ischemic stroke are receiving IV tPA. EMS personnel should be able to provide accurate hemodynamic monitoring and other interventions dictated by stroke guidelines. Tanne et al[17] noted that compliance with the stroke guidelines is around 30%; the results of the aforementioned trial were similar. The short transit time (37.7 ± 20.2 minutes) may have been a confounder that failed to show a relationship between noncompliance and adverse events. In addition, protocols were designed by local referring hospitals and not a centralized authority, which caused multiple variations in the treatment plans that were followed. Limitations of this local study included a small sample size, retrospective design, and a lack of consistent NIHSS scores. Better education via continuing medical education protocols could increase compliance among EMS workers and broaden the use of the drip-and-ship paradigm.

IMAGE-GUIDED PATIENT SELECTION AND OUTCOME

Based on a presentation by Osama Zaidat, MD, Associate Professor of Neurology and Neurosurgery, Medical College of Wisconsin, Milwaukee

Acute ischemic stroke has become a hot topic over the past decade. The use

of mechanical thrombectomy has allowed physicians to extend the treatment time window for acute stroke from 3-4.5 hours to 8 hours. The first mechanical thrombectomy device to be approved by the FDA was the Merci Retriever (Concentric Medical, Inc; Mountain View, CA) in 2004.[18] In 2008, the Penumbra System (Penumbra, Inc; Alameda, CA) was approved to remove clots within the same 8-hour therapeutic timeframe.[19]

With the therapeutic window for stroke treatment now extended, investigators turned their attention to the best candidates for mechanical thrombectomy. Multiple imaging techniques are available to visualize ischemic brain tissue, but the best way to identify patients who would benefit most from mechanical thrombectomy is unknown. An individual has to have penumbra or salvageable tissue left to reperfuse to benefit from these interventions. The Penumbra Imaging Collaborative Study (PICS) registry was developed to help identify patients having enough penumbra to salvage.

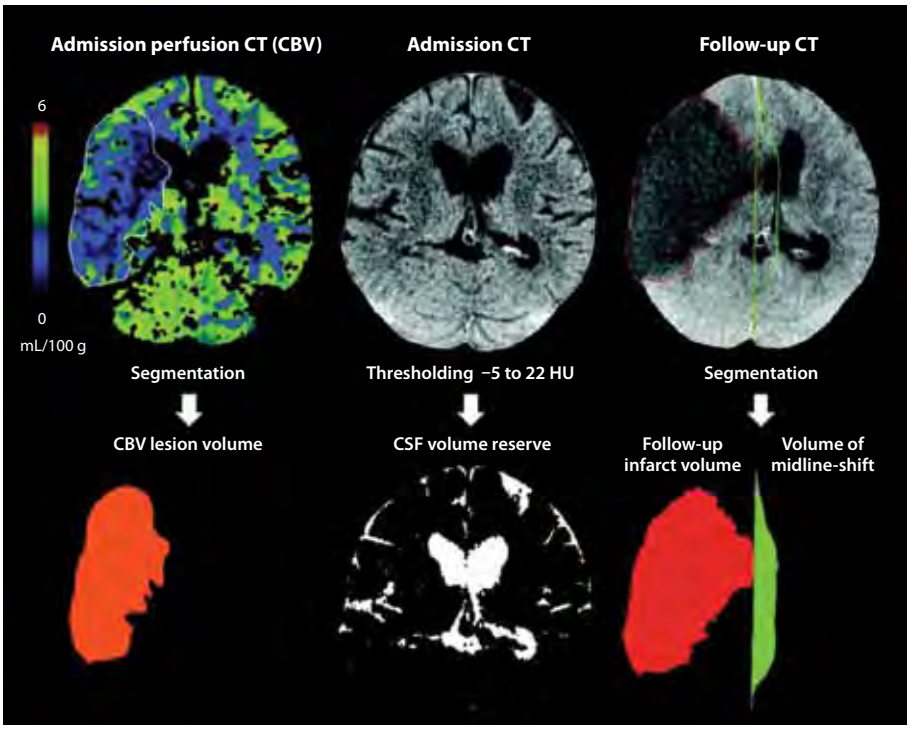


FIGURE 1 Transverse computed tomography (CT) images showing changes in cerebral blood volume (CBV) and infarct size on admission and at follow-up in a patient with acute ischemic stroke; CSF = cerebrospinal fluid. Figure courtesy of Osama Zaidat, MD.

Imaging and Patient Selection

Zaidat and others[20] used the PICS registry to investigate different imaging modalities for the triage of acute stroke patients for mechanical thrombectomy and to assess their impact on functional outcome.

Three specific imaging modalities were compared: (1) noncontrast computed tomography (NCCT), (2) computed tomography perfusion (CTP), and (3) magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) mismatch. NCCT uses the Alberta Stroke Program Early Computed Tomography Score (ASPECTS)[21] to map specific MCA regions and determine penumbra size. CTP evaluates cerebral blood volume (CBV) and flow, mean transit time (MTT), and time to peak flow in acute stroke patients.[22] MTT provides an estimate of tissue at risk for infarction, whereas CBV measures the volume of infarcted tissue (Figure 1). The ratio of MTT to CBV can provide the assumed penumbra size or area of salvageable tissue and predict infarct volume.[23] Most centers using MRI DWI mismatch agreed that the cutoff infarct volume was 60–70 cc. The Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) trial[24] was the first study to systematically measure and use MRI DWI mismatch to determine penumbra size using DWI and perfusion-weighted images (Figure 2).

There was no consensus on the mismatch size among all of the facilities involved. Investigators affiliated with the PICS registry tested all of the above methods to find out which would best determine the accurate penumbra so that outcomes could be predicted. The mRS was used to assess 90-day functional outcome.

In all, 35 centers across the United States enrolled 305 patients; 267 individuals qualified for the analysis. The mean age was 66.6 ± 15.9 years; 49% of the patients were female. The median NIHSS score was 17.0 (interquartile range, 12–21). The median time from stroke onset to presentation was 2.3 hours, and a median of 4.8 hours elapsed between the onset of symptoms to arterial puncture. The NCCT was most commonly used before mechanical thrombectomy (61.8% of patients); however, only four facilities used this technique. Infarct volume in CTP, the second most commonly used imaging modality, was employed at seven centers on 31.4% of the patients. The MRI DWI mismatch was least used; although it was available at 24 centers, it was used on just 14.2% of the patients. The time to angiography was 4.4 hours with NCCT only, 4.8 hours with infarct volume in CTP, and 6.4 hours with MRI DWI mismatch.

After treatment, 83.5% of the patients were successfully recanalized; that is, their thrombolysis in myocardial infarction score went from 0 or 1 to 2 or 3. The average number of patients with a functional independence (mRS score ≤ 2) at 90 days was 42.5% for all three imaging modalities. Functional independence at 90 days was noted among 42.5% of patients who were imaged with NCCT, 45.9% of those imaged with CTP,

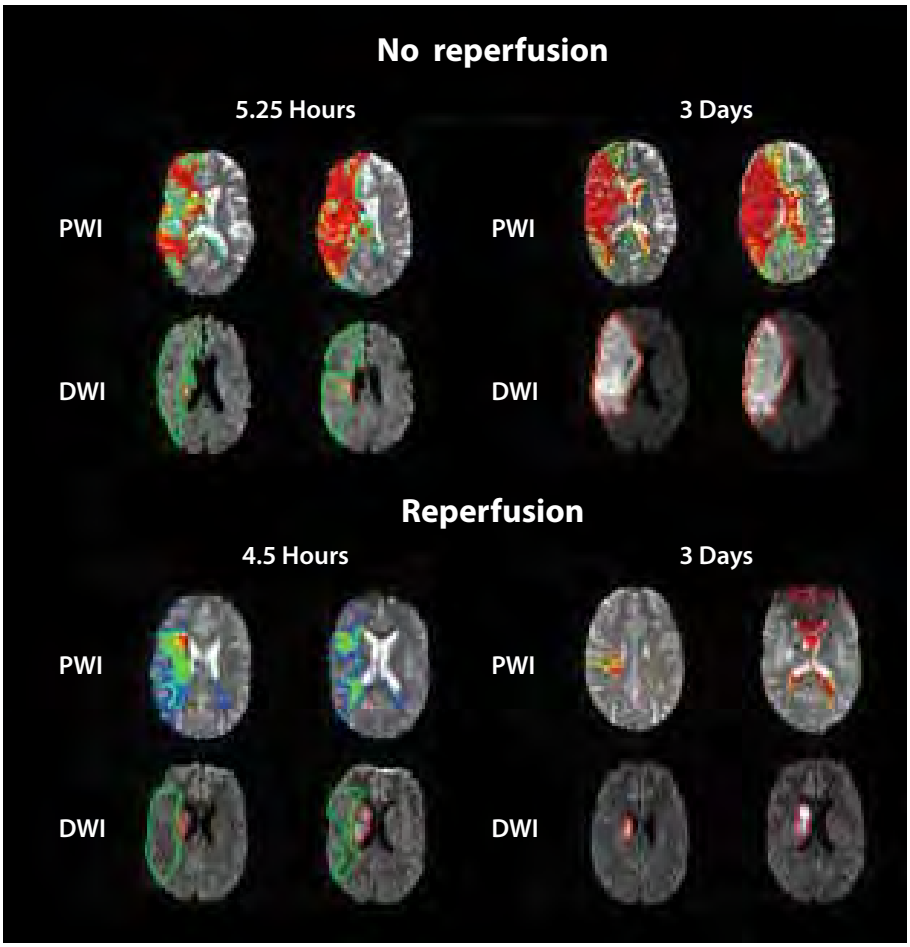


FIGURE 2 Changes over time in penumbra size, with and without reperfusion, determined by perfusion-weighted and diffusion-weighted image (PWI/DWI) mismatch. Figure courtesy of Osama Zaidat, MD.

and 42.9% of those who underwent MRI DWI imaging. For all of the modalities used, all-cause mortality was 19.9%, and the rate of symptomatic hemorrhage was 4.5%.

Of the three imaging modalities used to guide the selection of stroke patients for mechanical thrombectomy, none stands out as clearly superior. NCCT is the fastest method, but it is not as accurate as the others in predicting penumbra size. MRI DWI mismatch is the slowest, but most accurate method for predicting penumbra size. The speed and accuracy of CTP are somewhere between the other two. All of the techniques provide similar patient outcomes, suggesting that the imaging approach has little impact on functional outcome after mechanical thrombectomy.

IV THROMBOLYSIS IN PEDIATRIC STROKE PATIENTS

Based on a presentation by Amer Alshekhlee, MD, Assistant Professor of Neurology, Case Western Reserve University School of Medicine, Cleveland, Ohio

Multiple randomized clinical trials have established the safety and efficacy of IV tPA therapy for acute ischemic stroke in adults. However, no large study to date has shown that IV tPA is safe or effective when used in pediatric patients (age < 18 years) who experience an acute ischemic stroke.

Stroke in Pediatric Patients

Alshekhlee and others[25] studied children with acute ischemic stroke who were identified from the Kids' Inpatient Database (KID), the only all-payer pediatric inpatient care database in the United States, which contains data from about three million hospital stays. For this cohort, acute ischemic stroke was identified by the clinical classification software codes 109 and 110. Data from 1998 through 2009 were reviewed. A multivariate logistic regression analysis was used to assess covariates associated with hospital mortality and ICH.

A total of 9,367 children were admitted with a diagnosis of acute ischemic stroke; only 3,512 had the same diagnosis at discharge. The diagnosis in children seems to be more difficult than in adults, because seizures and migraines can mimic a stroke. Acute ischemic strokes seemed to be more common among boys and blacks and in the presence of sickle cell anemia, trauma, and prothrombotic states.

Of children initially diagnosed with acute ischemic stroke, only 75 children (0.8%) were treated with IV tPA. These children tended to be older (mean age, 12.88 ± 7.5 years compared with 8.18 ± 7.5 years among those who did not receive tPA; $P < 0.0001$) and were more likely than the rest of the cohort to have a history of diabetes mellitus and/or hypercoagulability. Four of the children treated with IV tPA developed ICH, and 12 children died. An unadjusted analysis showed that patients treated with IV tPA had a higher hospital mortality (12.0% vs 6.2%; $P = 0.03$) and rate of ICH (4.0% vs 0.38%; $P = 0.003$). An adjusted analysis showed that ICH was predictive of a higher hospital mortality but not the use of IV tPA. Thrombolysis remained predictive of ICH.

After starting out as a controversial topic, the use of IV tPA in pediatric patients appears to be coming into favor. Mortality and ICH rates following treatment of stroke with IV tPA are lower among children than the rates reported in adults. However, more data are clearly needed before the FDA will consider approving the use of IV tPA in children. It is hoped that results from the upcoming multinational Thrombolysis in Pediatric Stroke (TIPS) study (ClinicalTrials.gov NCT01591096) will help answer questions about the safety and efficacy of this treatment in pediatric patients.

GOOD COLLATERAL CIRCULATION AND FAVORABLE IV THROMBOLYSIS OUTCOMES

Based on a presentation by Leonard Yeo, MBBS, Department of Medicine (Neurology), National University Hospital, Singapore

The outcome after IV tPA varies greatly, with some patients showing marked improvement and others having none. Currently, there is no way to predict which patients will do better with IV tPA, although many studies have shown the treatment to be effective.

Collateral circulation may play a large part in the efficacy of IV tPA therapy. Variations in the circle of Willis and the intracranial collaterals may compensate for reduced cerebral perfusion (Figure 3) and may influence response to the drug.[26]

Collateral Circulation and IV Thrombolysis

Yeo and others[26] evaluated whether collaterals found during a pretreatment CT angiogram (CTA) can predict functional outcomes in acute ischemic stroke patients given IV tPA.

In this single-center, prospective study, all patients who were deemed to be IV tPA candidates by NINDS or ECASS III criteria at the National University Hospital in Singapore from 2007 to 2010 underwent CTA evaluation. Data on demographics, vascular risk factors, NIHSS scores, stroke subtypes, and pretreatment blood pressure were collected. Two independent neuroradiologists reviewed the CTAs in a blinded manner and defined them as "poor" (collaterals absent or detected in < 50% of the MCA territory) or "good" (collaterals detected in ≥ 50% of the MCA territory). Favorable outcomes were defined as an mRS score ≤ 1 at 90 days.

During the study period, 2,238 patients with acute stroke were admitted, and 240 (10.7%) received IV tPA. Only 78 (3.5%) patients underwent a CTA that showed anterior circulation occlusions before receiving IV tPA. The median age was 66 years (range, 35–89 years), and 75% of the patients were male. The median NIHSS was 19 (range, 3–29), and the median time from onset of symptoms to treatment was 130 minutes.

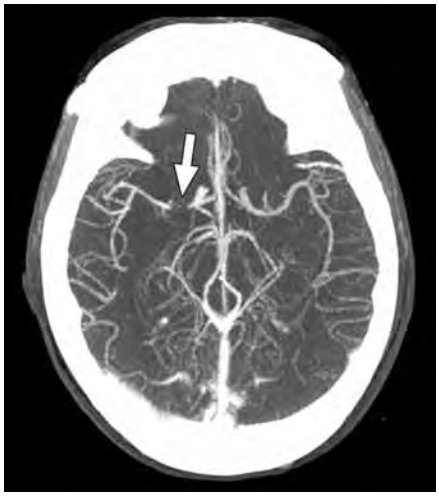


FIGURE 3 Variations in the circle of Willis and the intracranial collaterals may compensate for the reduced cerebral perfusion and may influence the response to IV tPA. Figure courtesy of Leonard Yeo, MBBS.

Good collaterals were identified in 52 patients (66.7%). Favorable outcomes were achieved in 43 patients (55.1%). Univariate analysis revealed that male gender, absence of diabetes mellitus, lower pretreatment NIHSS scores, and the presence of good collaterals were significantly associated with favorable functional outcomes. However, on multivariate logistic regression, only lower NIHSS scores (OR, 1.126 per NIHSS scale point; 95% CI, 1.016–1.247; $P = 0.023$) and good collaterals (OR, 4.859; 95% CI, 1.479–15.908; $P = 0.009$) were predictors of a favorable outcome.

Although patients who will benefit from IV tPA therapy cannot be easily determined, those with a lower NIHSS score and an mRS score ≤ 1 tend to do better than those with higher scores. Patients having good collaterals on CTA before receiving IV tPA tend to do better, as well, than those with poor collateral circulation. But should all patients be screened with CTA before receiving IV tPA? Larger studies hopefully will supply answers to this and related questions.

INSULAR STROKE AND HEMI-OROLINGUAL ANGIOEDEMA

Based on a presentation by Ralph Werner, MD, Klinik für Neurologie, Katholisches Klinikum Koblenz, Koblenz, Germany

Angioedema, a swelling beneath the skin surface with or without redness, is an allergic reaction. It often is confused with hemorrhaging under the skin that may result from the use of IV tPA. Engelter et al[27] described the occurrence of potentially life-threatening orolingual angioedema during thrombolysis in acute stroke patients. Other reports have shown angioedema to be a common adverse reaction to IV tPA in patients taking angiotensin-converting enzyme (ACE) inhibitors.[28]

Werner and Wohrle[29] investigated whether patients who experienced mid-posterior insular and frontal strokes had a higher risk of angioedema in a retrospective, single-center study from Germany. Ischemic strokes were diagnosed and localized by MRI DWI. Angioedema was reported after receipt of IV tPA in 13 of 660 patients (2.0%); most of these patients (85.7%) had acute ischemic strokes involving the mid-posterior insular region of the brain.

The authors concluded that angioedema is more common than previously believed in ischemic stroke patients treated with IV tPA and is slightly different from other causes of angioedema. They postulated that insular infarction may be an important pathophysiologic factor for developing hemi-orolingual angioedema and may be related to a catecholamine surge or other autonomic mechanism associated with insular strokes, noting that insular strokes also are associated with Takotsubo cardiomyopathy and increased autonomic dysfunction. The researchers advised that stroke patients receiving ACE inhibitors and clinical evidence of insular stroke should be monitored closely for the development of hemi-orolingual angioedema after treatment with IV tPA.

REFERENCES

1. 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.

2. Del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. *Stroke.* 1998;29:4–11.

3. Furlan A, Higashida R, Wechsler L, et al.

Intra-arterial prourokinase for acute ischemic stroke: the PROACT II study: a randomized controlled trial. *JAMA*. 1999;282:2003–2011.

4. Ogawa A, Mori E, Minematsu K, et al. Randomized trial of intraarterial infusion of urokinase within 6 hours of middle cerebral artery stroke. *Stroke*. 2007;38:2627–2628.

5. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol*. 2001;58:2009–2013.

6. 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.

7. Powers W. Intra-arterial thrombolysis for acute stroke in the post-ECASS III era: an adjusted meta-analysis. *Neurology*. 2012;78:S03.001.

8. 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. *Lancet*. 2010; 375:1695–1703.

9. Powers WJ. Thrombolysis for acute ischemic stroke: is intra-arterial better than intravenous? A treatment effects model. *J Stroke Cerebrovasc Dis*. 2012;21:401–403.

10. Chadow HL, Hauptman RE, VanAuker M, et al. Drip and ship: a new strategy for the treatment of acute coronary syndromes. *J Thromb Thrombolysis*. 2000;10:77–82.

11. Silverman IE, Beland DK, Chhabra J, McCullough LD. The "drip and ship" approach: starting IV t-PA for acute ischemic stroke at outside hospitals prior to transfer to a regional stroke center. *Conn Med*. 2005;69:613–620.

12. Qureshi AI, Chaudhry SA, Rodriguez GJ, Suri MF, Lakshminarayan K, Ezzeddine MA. Outcome of the "drip-and-ship" paradigm among patients with acute ischemic stroke: results of a statewide study. *Cerebrovasc Dis Extra*. 2012;2:1–8.

13. National Center for Health Statistics, Centers for Medicare & Medicaid Services. *International Classification of Diseases, 9th Revision*. Centers for Disease Control and Prevention Web site. http://www.cdc.gov/nchs/icd/icd9.htm. Accessed June 12, 2011.

14. Tonarelli SB, Tibbs M, Vazquez G, Lakshminarayan K, Rodriguez GJ, Qureshi Al. Accuracy of the new ICD-9-CM code for "drip-and-ship" thrombolytic treatment in patients with ischemic stroke. *J Stroke Cerebrovascular Dis*. 2012;21:121–123.

15. Rodriguez G, Tekle W, Chaudhry S, Hassan A, Suri M, Qureshi A. Thrombolytic treatment using drip and ship treatment paradigm among acute ischemic stroke patients in the United States: outcomes and impact on regional thrombolytic utilization and referral patterns. *Neurology*. 2012;78:S03.002.

16. Asaithambi G, Chaudhry S, Hassan A, Rodriguez G, Suri M, Qureshi A. Compliance to guidelines by emergency medical services in "drip and ship" patients with in-transit intravenous thrombolytic infusion. *Neurology*. 2012;78:S03.003.

17. Tanne D, Bates VE, Verro P, et al. Initial clinical experience with IV tissue plasminogen activator for acute ischemic stroke: a multicenter survey. *Neurology*. 1999;52:424–427.

18. Fisher M, Davalos A. Approval of the MERCI clot retriever: a critical view. *Stroke*. 2005;36:400–403.

19. Kulcsar Z, Bonvin C, Pereira VM, et al. Penumbra system: a novel mechanical thrombectomy device for large-vessel occlusions in acute stroke. *AJNR Am J Neuroradiol*. 2009;31:628–633.

20. Zaidat O, Meagher S, Brant-Zawadzki M, et al. Image-guided patient selection and its impact on outcome: results of the Penumbra Imaging Collaborative Study (PICS). *Neurology*. 2012:78:S03.004.

21. Pexman JH, Barber PA, Hill MD, et al. Use of the Alberta Stroke Program Early CT Score (ASPECTS) for assessing CT scans in patients with acute stroke. *AJNR Am J Neuroradiol*. 2001;22:1534–1542.

22. Wintermark M, Flanders AE, Velthuis B, et al. Perfusion-CT assessment of infarct core and penumbra: receiver operating characteristic curve analysis in 130 patients suspected of acute hemispheric stroke. *Stroke*. 2006;37:979–985.

23. Ezzeddine MA, Koroshetz WJ, Lah S, Gonzalez G, Lev MH. Hemispheric infarct volume prediction by CT perfusion imaging. *Stroke*. 2000;32:343-b.

24. Lansberg MG, Thijs VN, Hamilton S, et al. Evaluation of the clinical-diffusion and perfusion-diffusion mismatch models in DEFUSE. *Stroke*. 2007;38:1718–1719.

25. Alshekhlee A, Storkan M, Kaushal R, Meta S, Feen E, Cruz-Flores S. Thrombolysis in pediatric population from the KID database. *Neurology*. 2012;78:S03.005.

26. Yeo L, Paliwal P, Wakerley B, et al. Presence of good collateral circulation is a good predictor of favorable outcome after intravenous thrombolysis in acute anterior circulation ischemic stroke. *Neurology*. 2012;78:S03.006.

27. Engelter ST, Fluri F, Buitrago-Tellez C, et al. Life-threatening orolingual angioedema during thrombolysis in acute ischemic stroke. *J Neurol*. 2005;252:1167–1170.

28. Hill MD, Lye T, Moss H, et al. Hemi-orolingual angioedema and ACE inhibition after alteplase treatment of stroke. *Neurology*. 2003;60:1525–1527.

29. Werner R, Wohrle J. Insular stroke and hemi-orolingual angioedema. *Neurology*. 2012;78:S03.007.

Therapy of Stroke: 2012

Karen C. Albright, DO

University of Alabama School of Medicine, Birmingham, Alabama

Abstract At the 2012 Annual Meeting of the American Academy of Neurology, a panel of experts specializing in the management of acute or recent cerebral infarction discussed at length the drugs, devices, and procedures that save the lives and maintain the quality of life of patients who suffer an ischemic stroke. Along with recommendations for reducing vascular risk following a recent cerebrovascular event, the panelists discussed the current state of the art in reperfusion therapy and various clinical strategies for treating stroke patients.

The management of patients with acute or recent cerebral ischemia continues to evolve rapidly. Clinicians, and particularly generalists and physicians who do not specialize in stroke management, often find it difficult to keep abreast of advances in the field. The results of several recent clinical trials will have a substantial impact on stroke therapy, even though some conflicting data and lingering questions have led to additional controversies and uncertainty about optimal management.

At a session of the 64th Annual Meeting of the American Academy of Neurology, experts in stroke management presented an up-to-date, evidence-based approach to the comprehensive management of acute cerebral infarction. Among the topics discussed were current recommendations regarding reperfusion therapies, risk-reduction strategies following an acute or recent cerebral infarction, and clinical approaches to unclear or unproven strategies when managing patients.

MANAGEMENT OF ACUTE ISCHEMIC STROKE

Based on a presentation by Pooja Khatri, MD, MSc, Associate Professor of Neurology and Director of the Acute Stroke Program at the University of Cincinnati, Cincinnati, Ohio

Intravenous Thrombolysis

Intravenous (IV) administration of recombinant tissue plasminogen activator (tPA; alteplase) is the only pharmacologic therapy approved by the US Food and Drug Administration (FDA) to treat acute ischemic stroke. The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group's 1995 landmark publication[1,2] demonstrated that patients treated with IV tPA within 3 hours of symptom onset were 30% more likely to have little or no disability at 3 months when compared with patients given placebo *(Class I; Level of Evidence: A)*. Since that report, the results of the pooled analysis of the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS), the European Cooperative Acute Stroke Study (ECASS), the NINDS tPA stroke trials, and the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST) have confirmed these findings.[3,4] In 2008, the ECASS investigators demonstrated that IV tPA is safe and effective when given within 4.5 hours in selected patients *(Class I; Level of Evidence: B)*.[5,6] Use of IV tPA from 3 to 4.5 hours after symptom onset recently was reviewed by the FDA, which did not approve a label extension to include the 4.5-hour treatment time window.

Exclusion Criteria

Key exclusion criteria for IV tPA are listed in Table 1.[1,2,5] Treatment with IV tPA typically should not be delayed by the return of laboratory results; only 0.3% of patients have a platelet count < 100,000/μL that was not suspected when the initial history was taken.[7] Similarly, only 0.4% of patients have an unsuspected coagulopathy that would prevent thrombolysis.[8]

Use of minor or resolving symptoms as a relative contraindication for IV tPA therapy is somewhat open to interpretation; the cutoff of a National Institutes of Health Stroke Scale (NIHSS) score of 5 does not always work. The deficit would need to be considered to be nondisabling by both the doctor and the patient. A clarification statement is anticipated in the near future.

A seizure at presentation is not considered to be an absolute contraindication to IV tPA use. If a seizure occurs *in the presence of a stroke*, treatment with IV tPA should be considered. An additional relative contraindication is a blood glucose level < 50 mg/dL. If symptoms persist after correction of the glucose level or if imaging supports the diagnosis of stroke, the blood glucose level should be monitored and thrombolysis should strongly be considered.

The approval of the direct thrombin inhibitor dabigatran to prevent stroke in patients with nonvalvular atrial fibrillation has raised questions about concomitant IV tPA therapy. The 12- to 15-hour half-life of dabigatran suggests that patients should be excluded from IV tPA administration if they have received dabigatran within the past 48 hours. Presently, there is no clear way to measure the therapeutic effects of dabigatran in the acute setting; it may be reasonable to treat patients who have not taken dabigatran within 48 hours. An el-

Dr. Albright is Clinical Instructor in Neurology and a Comparative Effectiveness Research Postdoctoral Fellow in the Department of Medicine, University of Alabama School of Medicine, Birmingham, Alabama.

evated partial thromboplastin time (PTT) might be an indication that a dabigatran-induced anticoagulant effect is still present.

Additional exclusion criteria used in the ECASS III to select patients for IV tPA treatment within 3–4.5 hours of symptom onset are listed in Table 1.[1,2,5]

TABLE 1
Key Exclusion Criteriaa for IV tPA 3 Hours After Symptom Onset[a]

- Stroke or significant head trauma during the past 3 months
- Gastrointestinal/genitourinary hemorrhage in the previous 21 days
- Major surgery in prior 14 days
- Arterial puncture in noncompressible site during prior 7 days
- History of intracranial bleed (if the aneurysm has been secured, still consider treatment)
- Acute internal bleeding or acute trauma
- Systolic blood pressure < 185 mm Hg, diastolic blood pressure < 110 mm Hg
- Clear and large hypodensity on head computed tomography
- INR > 1.7 or elevated partial thromboplastin time
- Platelet count < 100,000/μL

IV tPA = intravenous recombinant tissue plasminogen activator (alteplase); INR = international normalized ratio

[a] Additional exclusion criteria used in the European Cooperative Acute Stroke Study (ECASS) III for IV tPA given 3–4.5 hours after symptom onset included age > 80 years; warfarin therapy, regardless of INR; a baseline National Institutes of Health Stroke Scale score > 25; and a history of stroke and diabetes.

Source: The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group[1]; Adams et al[2]; Hacke et al[5]

Intra-Arterial Thrombolysis (IAT)

Using a catheter to directly deliver lytic agents to the site of occlusion was first explored as a treatment for patients not eligible for IV tPA therapy. The safety and efficacy of prourokinase therapy were examined in the Prolyse in Acute Cerebral Thromboembolism (PROACT I[9] and PROACT II[10]) studies. In the PROACT II study[10] ischemic stroke patients with middle cerebral artery (MCA) occlusions who presented within 6 hours of symptom onset were randomized to receive intra-arterial (IA) prourokinase with IV heparin or to IV heparin alone. Patients receiving IA prourokinase with IV heparin had a 15% absolute benefit in functional outcome (number needed to treat = 7), despite higher symptomatic intracerebral hemorrhage (ICH) rates. Prourokinase is not commercially available in the United States.

Despite being stopped prematurely, the Japanese MCA Embolism Local Fibrinolytic Intervention Trial (MELT)[11] produced evidence that ischemic stroke patients who had occlusions of the M1 or M2 portion of the MCA, presented within 6 hours of symptom onset, and were treated with IA urokinase had improved functional outcome at 90 days when compared with the placebo group. Urokinase is no longer available in the United States. A recent meta-analysis found that endovascular treatment of acute ischemic stroke secondary to MCA occlusion led to improvements in functional endpoints.[12] However, other large studies have failed to show an overall benefit from such therapy, with about 75% of treated patients being dead or disabled.

Combined IV/IA Thrombolysis

Using catheters to directly deliver lytic agents to the site of occlusion in addition to IV tPA has also been explored. In the Interventional Management of Stroke (IMS I) and IMS II trials,[13,14] the efficacy of combination therapy (0.6 mg/kg IV tPA followed by IAT) was investigated in patients with severe stroke (eg, proximal artery occlusion, NIHSS score ≥ 10) who presented within 3 hours of symptom onset. Case series and subsequent meta-analysis examined the use of full-dose IV tPA (0.9 mg/kg) followed by IAT.[15–22] The results suggested that adding IAT to IV tPA has a reasonable safety profile accompanied by findings suggestive of improved efficacy. The IMS III trial,[23] in which patients with severe stroke were randomized to receive IV tPA alone or the IV tPA/IAT combination, was stopped due to the low likelihood of showing a 10% difference between groups. Thus, the overall applicability and efficacy of such combination therapy remain unclear at this time.

Intra-Arterial Devices

Thrombectomy. The Merci Retriever (Concentric Medical, Inc; Mountain View, CA) was the first intra-arterial device approved by the FDA. Its wire, with five helical loops, can be threaded into the thrombus for clot retrieval.

The safety and efficacy of this device were evaluated in the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) trial,[24] a prospective, single-arm, multicenter study that enrolled ischemic stroke patients within 8 hours of symptom onset. Recanalization was achieved in 46% of patients who were ineligible for IV tPA or failed to respond to IV tPA. A modified Rankin scale (mRS) score ≤ 2 was more frequent at 90 days in patients who were successfully recanalized than in those who were not.

The Multi MERCI trial[25] demonstrated that for ischemic stroke in patients presenting within 8 hours of symptom onset who were similarly excluded from thrombolytics, implantation of the second-generation Merci device was more effective in opening intracranial vessels. Recanalization rates were 57%–70%, with 36% achieving an mRS score ≤ 2.

Thromboaspiration. The second device approved by the FDA for clot removal in ischemic stroke is the Penumbra System (Penumbra, Inc; Alameda, CA). This device combines mechanical clot disruption with suction.[26]

The Penumbra Pivotal Stroke Trial,[27] a prospective, multicenter, single-arm study, showed that this device was able to recanalize 82% of occluded vessels among ischemic stroke patients presenting within 8 hours of symptom onset. Currently, the effectiveness of treating ischemic stroke using the Penumbra System, the Merci Retriever, or standard medical therapy in patients presenting within 8 hours of symptom onset is being compared with standard medical therapy in the ongoing Mechanical Retrieval and Recanalization of Stroke Clots Using Embolectomy (MR RESCUE; ClinicalTrials.gov NCT00389467) study.

Retrievable stents. More recently, high rates of recanalization have been reported with the use of retrievable stents (Stentrievers; Concentric Medical, Inc.), self-expanding stent-like devices designed to integrate the thrombus into the stent and allow for clot extraction with the removal of the unit from the vessel.[28,29]

In the multicenter, randomized, noninferiority Solitaire FR With the Intention for Thrombectomy (SWIFT) trial,[30] patients presenting within 8 hours of symptom onset received either the Solitaire FR Revascularization Device (ev3 Endovascular, Inc.; Plymouth, MN) or the Merci Retriever. This study was halted early on recommendation of the data safety monitoring board after > 60% of patients treated with Solitaire FR and 24% of those treated with the Merci Retriever achieved successful revascularization without symptomatic ICH.[30] Additionally, a higher proportion of patients randomized to receive the Solitaire FR experienced good neurologic outcome at 90 days when compared with patients randomized to receive the Merci Retriever (58% vs 33%, respectively).[31] The Solitaire FR Revascularization Device currently is being reviewed for approval by the FDA.

Classification of Recommendations and Level of Evidence for IAT

IAT is a treatment option for ischemic stroke patients with MCA occlusions who present within 6 hours of symptom onset and are not otherwise candidates for IV tPA *(Class I; Level of Evidence: B)*.[2] IAT is considered reasonable for ischemic stroke patients who have contraindications to IV tPA *(Class IIa; Level of Evidence: C)*.[2] Specific recommendations on the role of mechanical thrombectomy were not provided in the 2007 American Heart Association (AHA)/American Stroke Association guidelines. While we await the much anticipated results of IMS III, the availability of IA therapies should not delay or preclude IV tPA treatment of eligible patients *(Class III; Level of Evidence: C)*.[2]

Every Second Counts

In acute stroke, every second counts. As seen in the original NINDS trial[1] and confirmed by the pooled analysis of IV tPA trials,[3] earlier treatment with IV tPA results in improved outcome. The odds of a patient having a favorable outcome if treated with IV tPA within 90 minutes of symptom onset are twice those of patients treated within 91–180 minutes.[3] For patients receiving IV tPA within 3 hours of symptom onset, the number needed to treat to prevent one person from dependence or death is 8.[1,32] For patients treated with IV tPA from 3–4.5 hours of symptom onset, the number needed to treat is 14.[5] Similar results have been seen in patients receiving IAT. Results of the IMS I and II demonstrated a > 10% decrease in the probability of a good clinical outcome when there was a 30-minute delay in achieving reperfusion.[33]

Regardless of the acute reperfusion strategy used, treatment must be administered as rapidly as possible. Despite the NINDS timeline of care recommendations (Table 2),[34] patients who arrive in the emergency department (ED) quickly have longer door-to-needle times. Specifically, each 30-minute delay between stroke symptom onset and ED arrival was associated with a 15-minute decrease in door-to-needle time.[35] To avoid unnecessary delays, the stroke team should be activated before the head CT is obtained. As previously noted, the physician should not wait for laboratory results to come back, since glucose usually is the only test result immediately required. To ensure quick access, tPA should be stocked in the ED. Physicians should prepare the tPA for early administration and not be concerned about "wasting" unadministered tPA—the manufacturer will reimburse a facility for any tPA that is mixed but not used.

To facilitate rapid IAT, the endovascular team should be prenotified, and transport to the endovascular suite should be planned. Two large IV catheters and a urinary catheter should be placed, and flush bags should be primed. No sedation or conscious sedation should be considered in place of general anesthesia; general anesthesia may add unnecessary time delays and may increase the risk of complications.

TABLE 2
Critical Time Goals for Acute Stroke in the Emergency Department

- **Emergency department physician** should evaluate a stroke patient within *10 minutes* of arrival.
- **Stroke physician** should be available or notified within *15 minutes* of arrival.
- A **computed tomography (CT) scan** of the head should be obtained within *25 minutes* of arrival.
- The **CT scan** interpretation should be obtained within *45 minutes* of arrival.
- **Treatment with IV tPA** should be initiated within *60 minutes* of arrival.

IV tPA = intravenous recombinant tissue plasminogen activator (alteplase)
Source: NINDS recommendations[34]

The physician should resist the urge to take as much time available to initiate therapy. Every second counts. Each minute that a stroke remains untreated results in the destruction of 1.9 million neurons, 14 billion synapses, and 7.5 miles of myelinated fibers.[36]

Blood-Pressure Management

Management of elevated blood pressure (BP) in the setting of acute stroke remains controversial. A meta-regression of existing trials involving both ischemic stroke and ICH found that large decreases or increases in BP were associated with a worse outcome but suggested that modest reductions might be associated with improved outcome.[37] Unfortunately, there were insufficient data to analyze treatment effects in the hyperacute phase (ie, 6 hours).

The results from the Continue or Stop Post-Stroke Antihypertensives Collaborative Study (COSSACS),[38] a prospective, randomized clinical trial, suggested that continuation of home antihypertensive drugs was not associated with a substantial reduction in 2-week death and dependency in patients with ischemic stroke or ICH when compared with cessation of therapy. COSSACS was stopped before enrollment was completed, leaving only a 9% power to detect a 10% difference in death and dependency between the two treatment arms.

The Scandinavian Candesartan Acute Stroke Trial (SCAST),[39] a randomized,

placebo-controlled, double-blind trial, showed no beneficial effect of antihypertensive management in patients with acute stroke (ie, ischemic stroke, ICH) and elevated BP. Unfortunately, SCAST was stopped before the sample size required to adequately power the study was reached. Given the inconclusive or conflicting data, a cautious approach to treating hypertension has been recommended.[2] This might be especially true for patients with a high-grade stenosis of a major vessel, such as the internal carotid artery or basilar artery.

Current AHA guidelines for acute ischemic stroke patients not eligible for thrombolytic therapy recommend that emergency antihypertensive agents should be withheld unless the diastolic BP (DBP) is > 120 mm Hg or systolic BP (SBP) is > 220 mm Hg, unless other organ dysfunction necessitates BP reduction *(Class I; Level of Evidence: C).*[2] Patients eligible for IV tPA may have their SBP lowered to ≤ 185 mm Hg and their DBP lowered to ≤ 110 mm Hg before receiving tPA *(Class I; Level of Evidence: B);* they may be maintained at a SBP < 180 mm Hg and a DBP < 105 mm Hg for a minimum of 24 hours following IV tPA.[2] The BP recommendations for patients receiving IV tPA should also be followed in patients undergoing acute endovascular therapy *(Class I; Level of Evidence: C).*[2] Antihypertensive medications should be restarted approximately 24 hours after stroke in neurologically stable patients with preexisting hypertension *(Class IIa; Level of Evidence: B).*[2] When antihypertensive treatment is indicated, BP should be lowered cautiously, as BP lowering in hemodynamically dependent patients may lead to neurologic worsening.

Hyperglycemia Management

Despite a lack of data from randomized clinical trials to guide management, current AHA guidelines suggest that hyperglycemia should be treated in patients with acute ischemic stroke. Patients having persistent glucose concentrations > 140 mg/dL during the first 24 hours should be treated with insulin *(Class IIa; Level of Evidence: C).*[2] Further, glucose levels should be monitored closely, and insulin doses should be adjusted to avoid hypoglycemia. We await the results of the ongoing Stroke Hyperglycemia Insulin Network Effort (SHINE), a randomized clinical trial that is comparing IV insulin drip (target glucose level, 80–130 mg/dL) with standard therapy using a subcutaneous insulin sliding scale (target glucose level, < 180 mg/dL; ClinicalTrials.gov NCT01369069).

Antiplatelet Therapy

Oral administration of 325 mg of aspirin within 24–48 hours after stroke onset is recommended to treat most patients *(Class I; Level of Evidence: A);* however, the current AHA guidelines emphasize that aspirin administration should not be considered a substitute for acute stroke treatment using IV tPA *(Class III; Level of Evidence: B).*[2] Together, the results from the Chinese Acute Stroke Trial (CAST)[40] and the International Stroke Trial (IST)[41] suggest that aspirin given in the acute period prevents one death or recurrent stroke for every 100 patients. Although the administration of clopidogrel alone or with aspirin is not recommended to treat acute ischemic stroke *(Class III; Level of Evidence: C),* the current AHA guidelines express support for research testing the usefulness of emergency clopidogrel therapy to manage patients with acute stroke.[2] Outside the setting of clinical trials, the use of IV antiplatelet agents (ie, glycoprotein IIb/IIIa agents) is not recommended *(Class III; Level of Evidence: B).*

Hemicraniectomy

Malignant middle cerebral artery (MCA) infarction refers to an ischemic stroke that involves a large portion of the MCA territory. Patients with malignant MCA infarcts have high mortality rates, with nearly 80% experiencing herniation and death.[42]

In 2007, a pooled analysis of three randomized clinical trials demonstrated the efficacy of hemicraniectomy in patients with malignant MCA infarction.[43–45] Data from the pooled analysis revealed that only two patients would need to be treated with hemicraniectomy to prevent one patient from severe disability or death (mRS 5–6). Completion of the Hemicraniectomy After MCA Infarction With Life-threatening Edema Trial (HAMLET)[46] revealed that hemicraniectomy reduces mortality and poor outcome in patients treated within 48 hours of symptom onset. For patients treated within 48 hours of symptom onset, six patients would need treatment with hemicraniectomy to prevent poor outcome (mRS 3–6), two patients would need treatment to prevent severe disability or death (mRS 5–6), and two patients would need treatment to prevent death. This study did not find evidence that treatment with surgical decompression reduced poor outcome in the 48- to 96-hour period.

Surgical decompression should be considered in patients ≤ 60 years of age who show clinical or imaging signs of herniation within 48 hours of symptom onset. The University of Cincinnati decompressive hemicraniectomy protocol places any patient between 18 and 60 years of age who has an NIHSS score > 10 or an infarct on > 50% of MCA territory on "hemicrani watch." Families are extensively counseled on prognosis following hemicraniectomy. If aggressive measures are desired, a neurosurgeon should be consulted for hemicraniectomy for any patient having a subtle change in the level of consciousness or demonstrating a ≥ 4-mm increase in midline shift on head CT, provided that at least 6 hours has elapsed since treatment with IV tPA.

SECONDARY STROKE PREVENTION

Based on a presentation by Scott Kasner, MD, Professor of Neurology and Director of the Comprehensive Stroke Center at the University of Pennsylvania, Philadelphia

Each year, 795,000 strokes occur in the United States; most are ischemic. Recent data indicate that ≤ 5% of patients receive IV tPA.[47] At dedicated and well-organized stroke centers, IV tPA treatment rates approach 10%–15%. Whereas relatively few patients having ischemic strokes receive thrombolytic treatment, 100% of those experiencing ischemic strokes can benefit from secondary stroke prevention.

Ischemic stroke patients are more

TABLE 3
Comparison of $CHADS_2$ and CHA_2DS_2-VASc Scores for Risk Stratification in Atrial Fibrillation

$CHADS_2$ Score	CHA_2DS_2-VASc Score
Congestive heart failure (CHF) = 1	**C**HF or left ventricular ejection fraction ≤ 40% = 1
Hypertension = 1	**H**ypertension = 1
Age > 75 years = 1	**A**ge ≥ 75 years = 2
Diabetes = 1	**D**iabetes = 1
Stroke or TIA = 2	**S**troke/TIA/thromboembolism = 2
	Vascular disease (MI, PAD, or aortic plaque) = 1
	Age 65–74 years = 1
	Sex, female = 1

TIA = transient ischemic attack; MI = myocardial infarction; PAD = peripheral arterial disease
Source: Gage et al[51]; Lip et al[52]

likely to have another stroke than a different vascular event, such as myocardial infarction (MI).[48] Dr. Kasner's approach is first to determine the cause of the ischemic stroke and then to tailor secondary stroke prevention to the cause.

The etiologies of ischemic stroke are divided into five categories: cardioembolism, large artery disease, small vessel occlusive disease, other (eg, dissection, vasculitis, cocaine-induced), and cryptogenic type (Trial of Org 10172 in Acute Stroke Treatment [TOAST] criteria).[49]

Cardioembolism

Both persistent and paroxysmal atrial fibrillation are strong predictors of both first and recurrent stroke.[50] The stroke-risk indices $CHADS_2$ (Congestive heart failure, Hypertension, Age >75 years, Diabetes, and Stroke) and the modified CHA_2DS_2-VASc (Vascular disease, Age, Sex category) provide an estimate of stroke risk.[51] The $CHADS_2$ score combines multiple risk predictors into a seven-point scale (0–6). One point each is assigned for the presence of heart failure, hypertension, advanced age, and diabetes, whereas two points are assigned if a patient has a history of stroke or transient ischemic attack (TIA). Patients with a $CHADS_2$ score ≥ 2 should receive anticoagulant therapy. The $CHADS_2$ score was subsequently modified in an effort to address other risk factors for stroke from atrial fibrillation and to more closely examine patients with a $CHADS_2$ score of 0 or 1. Using data from the Euro Heart Survey on Atrial Fibrillation, the 10-point (0–9) CHA_2DS_2-VASc score was created.[52] As illustrated in Table 3, points are assigned for congestive heart failure or left ventricular ejection fraction ≤ 40%, hypertension, age ≥ 75 years, diabetes, stroke/TIA/thromboembolism, vascular disease (MI, peripheral arterial disease, or aortic plaque), age 65–74 years, and gender.[51,52]

A meta-analysis comparing aspirin alone with placebo or no treatment in patients with nonvalvular atrial fibrillation showed that aspirin use alone was associated with a 19% (confidence interval [CI], –1% to 35%) reduction in the incidence of stroke.[53] However, a Danish study suggested that aspirin therapy provided no benefit when compared with placebo, regardless of stroke-risk category.[54]

Another meta-analysis examining adjusted-dose warfarin compared with placebo or control in patients with nonvalvular atrial fibrillation found that warfarin therapy was associated with a 64% (95% CI, 49%–74%) reduction in stroke *(Class I; Level of Evidence: A)*.[50,53] In a randomized trial comparing rate control and rhythm control in patients with atrial fibrillation, the majority of strokes in both groups occurred in patients who had stopped taking warfarin or whose international normalized ratio (INR) was subtherapeutic.[55] There was no overall benefit between rate and rhythm control.

Anticoagulant therapy. Although warfarin therapy reduces the risk of stroke, the difficulty maintaining a therapeutic INR, the high risk of drug interactions, and concerns for bleeding remain.[56,57] These failures indicate that newer agents are needed. Such therapeutic alternatives to warfarin fall into two categories: (1) direct thrombin (factor II) inhibitors and (2) factor Xa inhibitors, which affect factor X further upstream in the coagulation pathway.

Dabigatran was the first oral direct thrombin inhibitor to be approved by the FDA to prevent stroke in patients with nonvalvular atrial fibrillation.[58] Peak plasma levels resulting in effects on its thrombin target occur about 2 hours after dosing; in contrast, warfarin can take 3–5 days to reach therapeutic efficacy. Dabigatran must be dosed twice daily due to its relatively short elimination half-life of 12–17 hours. In addition, unlike warfarin, dabigatran has few and mostly minor drug interactions.

In the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial,[59] patients with nonvalvular atrial fibrillation and a moderate-to-high risk of stroke or systemic embolism were randomized to one of three treatment groups: (1) warfarin with a target INR of 2–3, (2) 110 mg of dabigatran twice daily, or (3) 150 mg of dabigatran twice daily. RE-LY was designed primarily as a noninferiority trial to determine whether dabigatran was as efficacious as warfarin, but it also had a secondary aim as a superiority trial.

Both doses of dabigatran were noninferior to warfarin. In addition, the 150-mg dose of dabigatran was superior to warfarin in preventing stroke and systemic embolism. One half of the patients in this study were naïve to vitamin K antagonist therapy. Rates of major bleeding were similar among those using warfarin and patients taking 150 mg of dabigatran twice daily, whereas the rate was lower in patients using 110 mg of dabigatran twice daily. The relative risk of major bleeding with the 110-mg dose was 0.80 (95% CI, 0.69–0.93) when compared with the warfarin-treated group. For patients randomized to receive 150 mg of dabigatran, the relative risk of major bleeding was 0.93 (95% CI, 0.81–1.07) when compared with those using warfarin.

Thus, administration of 150 mg of dabigatran twice daily is superior to warfarin

therapy for preventing stroke. It reduces the risk of stroke or systemic embolism in patients with nonvalvular atrial fibrillation by 35%. The FDA did not approve the 110-mg dose of dabigatran for stroke prevention in patients with nonvalvular atrial fibrillation, although that dose is available outside the United States.

Rivaroxaban was the first oral factor Xa inhibitor approved by the FDA to prevent stroke in patients with nonvalvular atrial fibrillation.[60] Some experts argue that factor Xa may be a better target than thrombin and voice concern about the threat of rebound thrombin generation with use of direct thrombin inhibitors. Although the mechanism is not well understood, treatment with direct thrombin inhibitors is associated with a small increased risk of MI not noted among patients using factor Xa inhibitors.

In the double-blind, double-dummy Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF),[61] patients with nonvalvular atrial fibrillation and a high risk of stroke were randomized to receive 20 mg/d of rivaroxaban (15 mg/d for patients with a creatinine clearance of 30–49 mL/min) or warfarin (target INR, 2.0–3.0). (Some experts have argued that rivaroxaban should have been taken twice daily, given its half-life of 18–20 hours.) In a manner similar to that of the RE-LY trial, ROCKET-AF was designed primarily as a noninferiority trial to determine whether rivaroxaban was as efficacious as warfarin and secondarily as a superiority trial.

Rivaroxaban was noninferior, but not superior, to warfarin in the intention-to-treat analysis. Rates of major and nonmajor clinically relevant bleeding were similar between the rivaroxaban and warfarin groups. Conversely, patients given rivaroxaban had lower rates of fatal bleeding or bleeding from a critical anatomic site, likely due to the lower rates of hemorrhagic stroke and other intracranial bleeding seen in these patients.

Apixaban is a rapidly absorbed, direct competitive inhibitor of factor Xa that has a 12-hour half-life. It is not yet approved by the FDA for prevention of stroke in patients with nonvalvular atrial fibrillation.

The double-blind, double-dummy Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial involved patients with atrial fibrillation and at least one risk factor for stroke.[62] This trial was designed to determine whether apixaban (5 mg twice daily) was superior to aspirin (81–324 mg once daily) in patients ineligible for warfarin therapy. Apixaban reduced the risk of stroke or systemic embolism by > 50% without causing a significant increase in the risk of major bleeding when compared with aspirin.

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial[63] used a similar double-blind, double-dummy design. Patients with atrial fibrillation or flutter and at least one additional risk factor for stroke were randomized to receive apixaban (5 mg twice daily) or warfarin (titrated to a target INR of 2–3). Due to the potential for greater serum drug levels in patients who were ≥ 80 years of age, weighed ≤ 60 kg, or had a serum creatinine level ≥ 1.5 mg/dL, the dose was lowered to 2.5 mg twice daily for patients with at least two of these three factors. The study was designed to test the noninferiority hypothesis that apixaban preserves at least 50% of the relative reduction in the risk of stroke or systemic embolism associated with warfarin therapy in previous randomized, controlled trials. The results of the ARISTOTLE trial showed that when compared with warfarin therapy, treatment with apixaban significantly reduced the risk of stroke or systemic embolism by 21%, of major bleeding by 31%, and of death by 11%.

Comparing current alternatives with warfarin. None of the new oral anticoagulants has been compared directly with each other. Each study had somewhat different patient populations. Each of these new agents was either noninferior or superior to warfarin in terms of overall efficacy, and all of them were safer than warfarin in terms of cerebral hemorrhage (but with an increased rate of gastrointestinal bleeding in some cases).

A word of caution. Currently, there is no validated way to measure the therapeutic level of dabigatran, rivaroxaban, or apixaban. An elevated PTT can be an indication of the anticoagulant effects of dabigatran, and an elevated prothrombin time may indicate the effects of rivaroxaban. Oral agents that do not require frequent INR checks may extinguish the frequent patient-provider contact provided by warfarin clinics. Further, as previously stated, there have been concerns about potential rebound thrombin generation with the use of direct thrombin inhibitors.

Heart failure and low ejection fraction. The Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial[64] was a prospective, randomized study in which treated symptomatic heart failure patients in sinus rhythm who had ejection fractions ≤ 35% were randomized to receive warfarin therapy (target INR, 2.5–3.0) or double-blind antiplatelet therapy with aspirin (162 mg once daily) or clopidogrel (75 mg once daily). The results did not support the two primary hypotheses that (1) warfarin is superior to aspirin in preventing major cardiovascular outcomes and that (2) clopidogrel is superior to aspirin in this population. The findings appeared to exclude these hypotheses with a high degree of certainty. Whereas the use of warfarin rather than aspirin or clopidogrel may have resulted in reduced strokes in this trial, this benefit appeared to be offset by an increased risk from bleeding. Additionally, the low incidence of stroke among study participants complicates the interpretation of these findings.[65]

The Warfarin Versus Aspirin in Patients with Reduced Cardiac Ejection Fraction (WARCEF) study[66] was a double-blind, randomized trial of heart failure patients with an ejection fraction ≤ 35% who did not have atrial fibrillation or a prosthetic heart valve. Patients were randomized to receive either warfarin (target INR, 2.5–3) or aspirin (325 mg once daily). No overall difference in the combined primary outcome of death,

ischemic stroke, or intracranial hemorrhage was observed between the warfarin and aspirin groups. Examination of the components of the combined primary endpoint revealed a significant reduction in the occurrence of ischemic stroke among patients on warfarin as compared with those on aspirin, but this benefit was tempered by an increased risk of major hemorrhage in the warfarin group.

Large Artery Disease

The definition of "large artery disease" is based upon the TOAST criteria. Here, it specifically refers to disease related to the extracranial internal carotid and vertebral arteries (VA), the intracranial carotid siphon, MCA, anterior cerebral artery (ACA), posterior cerebral artery (PCA), and basilar artery.

Extracranial disease. Three different approaches have been compared in treating large artery disease: medical management, carotid endarterectomy (CEA), and carotid artery stenting (CAS). In randomized clinical trials, CEA was highly effective in preventing strokes in patients with 70%–99% symptomatic stenosis and only moderately beneficial in patients with 50%–69% symptomatic stenosis when compared with medical management alone.[67–70] There does not appear to be a clear benefit in patients with < 50% symptomatic stenosis, but a modest benefit has been demonstrated in patients with 60%–99% asymptomatic stenosis.[71,72]

The first study to compare carotid artery stenting and angioplasty with CEA was the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial,[73] which focused on symptomatic and asymptomatic patients with severe carotid-artery stenosis who were good candidates for either CEA or CAS and who also possessed an additional risk factor for CEA. These patients were randomized to receive CEA or stenting. In patients with at least one coexisting condition that potentially increased the risk of CEA, stenting was noninferior to CEA in the long term. Further, the results suggested that stenting may be marginally better than CEA in the short term.

CEA was again compared with CAS in the Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial.[74] This randomized, controlled trial was designed to determine whether stenting was not inferior to CEA in patients with symptomatic carotid stenosis. The results showed that in patients with symptomatic carotid disease, CEA resulted in lower rates of stroke or death when compared with stenting.

EVA-3S was followed by another trial that compared CAS with CEA in patients with symptomatic carotid stenosis, the Stent-Supported Percutaneous Angioplasty of the Carotid Artery Versus Endarterectomy (SPACE) trial.[75] In this noninferiority trial, patients with severe carotid stenosis were randomized to undergo CAS or CEA. Results of the SPACE trial failed to show carotid angioplasty with stenting to be noninferior to CEA in the short term. However, 2-year follow-up data revealed no differences between CEA and carotid angioplasty with stenting with respect to stroke prevention.[76]

> Carotid endarterectomy remains the preferred therapeutic choice for most patients with symptomatic large artery disease.

Following SPACE, the International Carotid Stenting Study (ICSS)[77] randomized patients with symptomatic carotid stenosis to receive CAS or CEA. The ICSS showed CEA to be safer than CAS in patients with symptomatic carotid artery stenosis. A meta-analysis of the three trials performed by the ICSS investigators favored CEA over CAS.[78,79]

In the Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)[79] sponsored by the National Institutes of Health, symptomatic and asymptomatic patients with carotid stenosis were randomized to undergo either CAS or CEA. The CREST study showed no significant difference in rates of the primary endpoint (composite of stroke, MI, or death) between the CAS and CEA groups (7.2% vs 6.8%, respectively). It did, however, find a higher rate of stroke in the CAS group (4.1% vs 2.3%) and higher rates of MI (1.1% vs 2.3%) in the CEA group. A recent meta-analysis incorporating the results of CREST concluded that patients undergoing CAS were at increased risk of stroke or the combined endpoint of stroke or death, whereas patients undergoing CEA were at increased risk of MI or cranial nerve injury.[80]

One variable that requires special attention in the trials comparing CAS with CEA is age. In a preplanned meta-analysis of individual patient data in the European trials, the risk of stroke or death doubled among patients ≥ 70 years with stenting as compared with CEA.[78] Patients > 70 years of age seemed to do better with CEA. A prespecified analysis of CREST demonstrated that the different efficacy of CAS when compared with CEA in various age groups primarily was a function of the increased risk of stroke with CAS in older individuals.[81]

In summary, CEA remains the preferred therapeutic choice for most patients. CAS may be worth considering in the setting of favorable anatomy (but not tortuous vessels), in younger individuals, or in patients at high risk of MI or major cranial nerve injury.

Intracranial disease. The Warfarin and Aspirin for Symptomatic Intracranial Arterial Stenosis (WASID) trial[82] is important in terms of the medical management of intracranial stenosis. In this NINDS-sponsored study, patients with intracranial stenosis were randomized to receive either warfarin (target INR, 2.0–3.0) or aspirin (650 mg twice daily or as little as 325 mg/d if dyspepsia or other side effects developed). Warfarin therapy was associated with significantly higher rates of death and major hemorrhage. Further, there was no difference in terms of ischemic stroke prevention between the two groups.

Recently, investigators published the results of the Stenting and Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) trial.[83] Patients with severe symptomatic intracranial stenosis were randomized to undergo percutaneous transluminal angioplasty and stenting (PTAS) plus aggressive medical management or aggressive medical management alone. PTAS was performed using the Wingspan Stent System (Boston Scientific; Natick, MA), the only device approved by the FDA for use in patients with atherosclerotic intracranial arterial stenosis. Aggressive medical management consisted of dual antiplatelet therapy (325 mg/d of aspirin plus 75 mg/d of clopidogrel) for 90 days, followed by aspirin alone after 90 days; BP management with a SBP goal of < 140 mm Hg; a goal low-density lipoprotein level of < 70 mg/dL using rosuvastatin; and management of secondary risk factors (diabetes, smoking, weight, exercise), using a lifestyle-modification program. Interestingly, the rate of periprocedural stroke after PTAS was higher than expected, whereas the rate of stroke among patients receiving aggressive medical management alone was lower than expected. These results demonstrated in high-risk patients with intracranial stenosis that aggressive medical therapy alone was superior to PTAS with the Wingspan stent.

Choice of antiplatelet therapy. The debate over whether aspirin, clopidogrel, or aspirin plus dipyridamole is the superior regimen for antiplatelet therapy is far from settled. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial[84] demonstrated that clopidogrel therapy provides an additional 9% relative risk reduction over and above the 25% reduction provided by aspirin use alone. The European/Australasian Stroke Prevention in Reversible Ischemia Trial (ESPRIT)[85] and the European Stroke Prevention Study 2 (ESPS 2)[86] compared the use of aspirin plus dipyridamole with aspirin therapy alone; administration of the aspirin/dipyridamole combination was more effective than taking aspirin alone in preventing recurrent vascular events.

The Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial[87] compared twice-daily administration of aspirin (25 mg) plus extended-release dipyridamole (200 mg) with once-daily use of clopidogrel (75 mg). Similar rates of recurrent stroke were observed in the two groups, and the results failed to show that either agent was superior to the other in terms of stroke prevention. Further, administration of aspirin plus extended-release dipyridamole and clopidogrel had similar effects on reducing the composite of vascular events after stroke (recurrent stroke, death from vascular causes, MI). In this comparison, clopidogrel offered the advantages of once-daily administration and being better tolerated.

An older, potentially underused antiplatelet agent, cilostazol, recently was studied in Japan for secondary stroke prevention. In the second Cilostazol Stroke Prevention Study (CSPS 2),[88] patients were randomized to receive cilostazol (100 mg twice daily) or aspirin (81 mg once daily). Cilostazol significantly lowered the risk of stroke when compared with aspirin. Cilostazol also was superior to aspirin for preventing such secondary endpoints as stroke, TIA, angina pectoris, MI, heart failure, and hemorrhage requiring hospital admission.

In summary, long-term use of dual antiplatelet therapy with aspirin and clopidogrel is not recommended. However, results from the SAMMPRIS trial raises the question of whether short-term use of this combination with close monitoring offers benefits.[83,89,90] The Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke Trial (POINT; ClinicalTrials.gov NCT00991029) currently is testing dual antiplatelet therapy in the acute setting of TIA or minor stroke. The best antiplatelet agent to select for patients at risk is still debatable, and many questions remain unanswered. What should the practitioner do for patients who do not respond to aspirin therapy? What role does genotype play in the efficacy of clopidogrel? And what role, if any, will the use of new antiplatelet agents have in secondary stroke prevention? Answers to these questions certainly will follow in the coming years.

Small Vessel Disease

Briefly, the mainstay of secondary stroke prevention in patients with small-vessel disease is antiplatelet therapy. The results of the NINDS-sponsored Secondary Prevention of Small Subcortical Strokes (SPS3) trial[91] showed no advantage of dual antiplatelet therapy (75 mg/d of clopidogrel plus 325 mg/d of aspirin) when compared with use of aspirin alone. In addition, patients on dual antiplatelet therapy had a higher bleeding rate and mortality than did those using aspirin monotherapy.

Cryptogenic Etiology

Up to 30%–40% of strokes may be cryptogenic.[92,93] Patients who experience cryptogenic strokes may suffer from undetected paroxysmal atrial fibrillation. Although 50%–90% of patients with atrial fibrillation are asymptomatic, even symptomatic patients may miss noticing subtle symptoms. The ratio of asymptomatic to symptomatic atrial fibrillation is estimated to be 12:1. In patients who present with atrial fibrillation–associated stroke, 25% have no known history of atrial fibrillation. Even in stroke patients with known paroxysmal atrial fibrillation, 50%–70% present in normal sinus rhythm.

Our ability to detect atrial fibrillation depends upon how long we monitor patients. A subgroup analysis of the TRENDS: A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics[94] found that only 3% of patients with newly diagnosed atrial fibrillation would have been identified using a single 24-hour Holter monitor, and 4% would have been identified using 48-hour Holter monitoring performed at the time of enrollment in the study. Increasing the duration of continuous Holter monitoring to 7 days would have identified 6% of patients newly diagnosed with atrial fibrillation, whereas increasing monitoring to 30 consecutive days would have identified 11%. In contrast, continuous

arrhythmia monitoring over an average of 1.1 years identified atrial fibrillation in 28% of patients with previous thromboembolic events.

A retrospective study of 56 patients with cryptogenic TIA or stroke reported that 23% had atrial fibrillation after diagnostic evaluation and mobile cardiac outpatient telemetry (MCOT; CardioNet, Inc; Conshohocken, PA) for up to 21 days.[95] Monitoring with MCOT is noninvasive. Some experts argue that we should monitor patients for longer durations. Implantable monitors that are approximately the size of a computer thumb drive can be inserted under the skin, permitting monitoring for up to 3 years. This may be a reasonable option when clinicians highly suspect that a patient has experienced a cryptogenic stroke. The Study of Continuous Cardiac Monitoring to Assess Atrial Fibrillation After Cryptogenic Stroke (CRYSTAL-AF; ClinicalTrials.gov NCT00924638) currently is evaluating the time to onset of atrial fibrillation using 6 months of continuous rhythm monitoring versus control treatment in subjects with a recent cryptogenic stroke or TIA without a history of atrial fibrillation.

In summary, we need to look more diligently for atrial fibrillation. At least 20% of cryptogenic stroke patients have occult atrial fibrillation. Clinicians should suspect atrial fibrillation in patients with cortical infarcts (especially those who have had prior "silent" cortical infarcts); in patients > 60 years of age (particularly women); in those who have had multiple strokes; and even in patients with increased left atrial diameter or increased left atrial velocity, as seen on echocardiography. As many as 90% of atrial fibrillation episodes are asymptomatic, and the detection of atrial fibrillation improves with the duration of continuous monitoring. The optimal duration of monitoring, however, has not been determined; we await the results of the CRYSTAL-AF trial for guidance on this issue. Short episodes of atrial fibrillation likely predict longer episodes. One episode lasting > 6 hours doubles a person's 1-year stroke risk. As is evident from this review, our treatment options for stroke prevention in patients with nonvalvular atrial fibrillation have greatly expanded.

Risk-Factor Modification

Regardless of stroke etiology, all stroke patients require risk-factor modification—aggressive blood pressure lowering, use of statins to lower cholesterol levels (and their presumed pleiotropic effects), and lifestyle modification. An analysis of the Organization to Assess Strategies in Acute Ischemic Syndromes (OASIS) study,[96] which enrolled over 18,000 patients with acute coronary syndrome from 41 countries, examined the influence of adhering to lifestyle modification recommendations on cardiovascular events. The OASIS study results demonstrated that the odds of a patient who continued smoking and did not adhere to diet and exercise having an MI or stroke or dying was four times that of a nonsmoker who had a modified diet and became physically active. Although the OASIS study was conducted in patients with acute coronary syndrome, these principles are likely to apply to patients with cerebrovascular disease. It is important to take time to explain to patients the importance of adhering to recommendations regarding smoking, diet, and exercise to prevent future stroke, MI, and death.

REFERENCES

1. 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.
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: the American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists. *Stroke.* 2007;38:1655–1711.
3. Hacke W, Donman 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.
4. Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet.* 2007;369:275–282.
5. Hacke W, Kaste M, Bluhmki W, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med.* 2008;359:1317–1329.
6. Del Zoppo GJ, Saver JL, Jauch EC, Adams HP Jr. 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. American Heart Association Stroke Council. *Stroke.* 2009;40:2945–2948.
7. Cucchiara BL, Jackson B, Weiner M, Mésse SR. Usefulness of checking platelet count before thrombolysis in acute ischemic stroke. *Stroke.* 2007;38:1639–1640.
8. 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.
9. del Zoppo GJ, Higashida RT, Furlan AJ, Pessin MS, Rowley HA, Gent M. PROACT: a phase II randomized trial of recombinant pro-urokinase by direct arterial delivery in acute middle cerebral artery stroke. PROACT Investigators. Prolyse in Acute Cerebral Thromboembolism. *Stroke.* 1998;29:4–11.
10. 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.
11. Ogawa A, Inoue T. MELT Japan (MCA-Embolism Local Fibrinolytic Intervention Trial Japan) [in Japanese]. *Nihon Rinsho.* 2006;64:519–523.
12. Fields JD, Khatri P, Nesbit GM, et al. Meta-analysis of randomized intra-arterial thrombolytic trials for the treatment of acute stroke due to middle cerebral artery occlusion. *J Neurointerv Surg.* 2011;3:151–155.
13. IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. *Stroke.* 2004;35:904–911.
14. IMS Study Investigators. The Interventional Management of Stroke (IMS) II Study. *Stroke.* 2007;38:2127–2135.
15. Lewandowski CA, Frankel M, Tomsick TA, et al. Combined intravenous and intra-arterial r-TPA versus intra-arterial therapy of acute ischemic stroke: Emergency Management of Stroke (EMS) Bridging Trial. *Stroke.* 1999;30:2598–2605.
16. Ernst R, Pancioli A, Tomsick T, et al. Combined intravenous and intra-arterial recombinant tissue plasminogen activator in acute ischemic stroke. *Stroke.* 2000;31:2552–2557.
17. Suarez JI, Zaidat OO, Sunshine JL, Tarr R, Selman WR, Landis DM. Endovascular administration after intravenous infusion of thrombolytic agents for the treatment of patients with acute ischemic strokes. *Neurosurgery.* 2002;50:251–259.
18. Hill MD, Barber PA, Demchuk AM, et al. Acute intravenous–intra-arterial revascularization therapy for severe ischemic stroke. *Stroke.* 2002;33:279–282.
19. Shaltoni HM, Albright KC, Gonzales NR, et al. Is intra-arterial thrombolysis safe after full-dose intravenous recombinant tissue plasminogen activator for acute ischemic stroke? *Stroke.* 2007;38:80–84.

20. Wolfe T, Suarez JI, Tarr RW, et al. Comparison of combined venous and arterial thrombolysis with primary arterial therapy using recombinant tissue plasminogen activator in acute ischemic stroke. *J Stroke Cerebrovasc Dis.* 2008;17:121–128.

21. Burns TC, Rodriguez GJ, Patel S, et al. Endovascular interventions following intravenous thrombolysis may improve survival and recovery in patients with acute ischemic stroke: a case-control study. *AJNR Am J Neuroradiol.* 2008;29:1918–1924.

22. Georgiadis Al, Memon MZ, Vazquez G, et al. Comparison of partial (.6 mg/kg) versus full-dose (.9 mg/kg) intravenous recombinant tissue plasminogen activator followed by endovascular treatment for acute ischemic stroke: a meta-analysis. *J Neuroimaging.* 2011;21:113–120.

23. Khatri P, Hill MD, Palesch YY, et al. Methodology of the Interventional Management of Stroke III Trial. *Int J Stroke,* 2008;3:130–137.

24. 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.

25. 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.

26. Bose A, Henkes H, Alfke K, et al. The Penumbra System: a mechanical device for the treatment of acute stroke due to thromboembolism. *AJNR Am J Neuroradiol.* 2008;29:1409–1413.

27. 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.

28. Jahan R. Solitaire flow-restoration device for treatment of acute ischemic stroke: safety and recanalization efficacy study in a swine vessel occlusion model. *AJNR Am J Neuroradiol.* 2010;31:1938–1943.

29. Mendonca N, Flores A, Pagiola J, et al. Trevo system: single-center experience with a novel mechanical thrombectomy device. *J Neuroimaging.* 2011 Dec 30 [Epub ahead of print].

30. Saver JL, Levy E, Jovin TG, et al. Primary results of the SOLITAIRE™ with the Intention for Thrombectomy (SWIFT) multicenter, randomized clinical trial. International Stroke Conference; February 1–3, 2012; New Orleans, LA. Abstract LB8.

31. Saver JL, Jahan R, Levy E, et al. Primary results of the SOLITAIRE™ FR with the Intention for Thrombectomy (SWIFT) multicenter, randomized clinical trial. http://my.americanheart.org/idc/groups/ahamah-public/@wcm/@sop/@scon/documents/downloadable/ucm_436233.pdf. Accessed June 3, 2012.

32. Saver JL. Number needed to treat estimates incorporating effects over the entire range of clinical outcomes: novel derivation method and application to thrombolytic therapy for acute stroke. *Arch Neurol.* 2004;61:1066–1070.

33. Khatri P, Abruzzo T, Yeatts SD, Nichols C, Broderick JP, Tomsick TA. Good clinical outcome after ischemic stroke with successful revascularization is time-dependent. IMS I and II Investigators. *Neurology.* 2009;73:1066–1072.

34. Proceedings of a National Symposium on Rapid Identification and Treatment of Acute Stroke. December 12–13, 1996. Washington, DC: National Insitute of Neurological Disorders and Stroke. http://www.ninds.nih.gov/news_and_events/proceedings/strokeworkshop.htm. Accessed June 3, 2012.

35. 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.

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

37. Geeganage CM, Bath PM. Relationship between therapeutic changes in blood pressure and outcomes in acute stroke. *Hypertension*. 2009;54:775–781.

38. 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.

39. Sandset EC, Bath PM, Boysen G, et al. The angiotensin-receptor blocker candesartan for treatment of acute stroke (SCAST): a randomised, placebo-controlled, double-blind trial. *Lancet*. 2011;377:741–750.

40. 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.

41. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet.* 1997;349:1569–1581.

42. Hacke W, Schwab S, Horn M, et al. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. *Arch Neurol.* 1996;53:309–315.

43. Vahed K, Vicaut E, Mateo J, et al. Sequential-design, multicenter, randomized, controlled trial of early decompressive craniectomy in malignant middle cerebral artery infarction (DECIMAL Trial). *Stroke.* 2007;38:2506–2517.

44. Jüttler E, Schwab S, Schmiedek P, et al. Decompressive Surgery for the Treatment of Malignant Infarction of the Middle Cerebral Artery (DESTINY): a randomized, controlled trial. DESTINY Study Group. *Stroke.* 2007;38:2518–2525.

45. Vahedi, 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. DECIMAL, DESTINY, and HAMLET investigators. *Lancet Neurol.* 2007;6:215–222.

46. Hofmeije 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. HAMLET Investigators. *Lancet Neurol.* 2009;8:326–333.

47. Adeoye O, Hornung R, Khatri P, Kleindorfer D. Recombinant tissue-type plasminogen activator use for ischemic stroke in the United States: a doubling of treatment rates over the course of 5 years. *Stroke.* 2011;42:1952–1955.

48. Dhamoon MS, Sciacca RR, Rundek T, Sacco RL, Elkind MS. Recurrent stroke and cardiac risks after first ischemic stroke: the Northern Manhattan Study. *Neurology.* 2006;66:641–646.

49. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke.* 1993;24:35–41.

50. 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, American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Clinical Cardiology, and Interdisciplinary Council on Quality of Care and Outcomes Research. *Stroke.* 2011;42:227–276.

51. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA.* 2001;285:2864–2870.

52. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest.* 2010;137:263–272.

53. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857–867.

54. Olesen JB, Lip GY, Lindharsen J, et al. Risks of thromboembolism and bleeding with thromboprophylaxis in patients with atrial fibrillation: a net clinical benefit analysis using a 'real world' nationwide cohort study. *Thromb Haemost.* 2011;106:739–749.

55. Wise DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. *N Engl J Med.* 2002;347:1825–1833.

56. Hylek EM, Singer DE. Risk factors for intracranial hemorrhage in outpatients taking warfarin. *Ann Intern Med.* 1994;120:897–902.

57. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med.* 2003;349:1019–1026.

58. FDA approves Pradaxa to prevent stroke in people with atrial fibrillation. October 19, 2010. US Food and Drug Administration Web site. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm. Accessed June 4, 2012.

59. Connolly, SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. RE-LY Steering Committee and Investigators. *N Engl J Med.* 2009;361:1139–1151.

60. FDA approves Xarelto to prevent stroke

in people with common type of abnormal heart rhythm. November 4, 2011. US Food and Drug Administration Web site. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm278646.htm. Accessed June 3, 2012.

61. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. ROCKET AF Investigators. *N Engl J Med.* 2011;365:883–891.

62. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. AVERROES Steering Committee and Investigators. *N Engl J Med.* 2011;364:806–817.

63. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992.

64. Massie BM, Krol WF, Ammon SE, et al. The Warfarin and Antiplatelet Therapy in Heart Failure trial (WATCH): rationale, design, and baseline patient characteristics. *J Card Fail.* 2004;10:101–112.

65. Massie BM, Collins JF, Ammon SE, et al. Randomized trial of warfarin, aspirin, and clopidogrel in patients with chronic heart failure: the Warfarin and Antiplatelet Therapy in Chronic Heart Failure (WATCH) trial. WATCH Trial Investigators. *Circulation.* 2009;119:1616–1624.

66. Homma S, Thompson J. Results of the Warfarin versus Aspirin in Reduced Cardiac Ejection Fraction (WARCEF) trial. WARCEF Investigators. International Stroke Conference; February 1–3, 2012; New Orleans, LA. Abstract LB12.

67. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1991;325:445–453.

68. MRC European Carotid Surgery Trial: interim results for symptomatic patients with severe (70–99%) or with mild (0–29%) carotid stenosis. European Carotid Surgery Trialists' Collaborative Group. *Lancet.* 1991;337:1235–1243.

69. Mayberg MR, Wilson SE, Yatsu F, et al. Carotid endarterectomy and prevention of cerebral ischemia in symptomatic carotid stenosis. Veterans Affairs Cooperative Studies Program 309 Trialist Group. *JAMA.* 1991;266:3289–3294.

70. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med.* 1998;339:1415–1425.

71. Chaturved, Bruno A, Feasby T, et al. Carotid endarterectomy—an evidence-based review: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2005;65:794–801.

72. Brott TG, Halperin JL, Abbara S, et al. 2011 ASA/ACCF/AHA/AANN/AANS/ACR/ASNR/CNS/SAIP/SCAI/SIR/SNIS/SVM/SVS guideline on the management of patients with extracranial carotid and vertebral artery disease: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines, and the American Stroke Association, American Association of Neuroscience Nurses, American Association of Neurological Surgeons, American College of Radiology, American Society of Neuroradiology, Congress of Neurological Surgeons, Society of Atherosclerosis Imaging and Prevention, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society of NeuroInterventional Surgery, Society for Vascular Medicine, and Society for Vascular Surgery. Writing Committee Members. *Stroke.* 2011;42:e464–e540.

73. Yadav, Wholey MH, Kuntz RE, et al. Protected carotid-artery stenting versus endarterectomy in high-risk patients. Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy Investigators. *N Engl J Med.* 2004;351:1493–1501.

74. Mas JL, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med.* 2006;355:1660–1671.

75. Ringleb PA, Allenberg J, Brückmann H, et al. 30 Day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. SPACE Collaborative Group. *Lancet.* 2006;368:1239–1247.

76. Eckstein HH, Ringleb P, Allenberg JR, et al. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol.* 2008;7:893–902.

77. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. International Carotid Stenting Study Investigators. *Lancet.* 2010;375:985–997.

78. Bonati LH, Dobson J, Algra A, et al. Short-term outcome after stenting versus endarterectomy for symptomatic carotid stenosis: a preplanned meta-analysis of individual patient data. Carotid Stenting Trialists' Collaboration. *Lancet.* 2010;376:1062–1073.

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

80. Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C.. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. *Stroke.* 2011;42:687–692.

81. Voeks JH, Howard G, Roubin GS, et al. Age and outcomes after carotid stenting and endarterectomy: the carotid revascularization endarterectomy versus stenting trial. CREST Investigators. *Stroke.* 2011;42:3484–3490.

82. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. Warfarin-Aspirin Symptomatic Intracranial Disease Trial Investigators. *N Engl J Med.* 2005;352:1305–1316.

83. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. SAMMPRIS Trial Investigators. *N Engl J Med.* 2011;365:993–1003.

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

85. 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.

86. 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. ESPRIT Study Group. *Lancet.* 2006;367:1665–1673.

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

88. Shinohara Y, Katayama Y, Uchiyama T, et al. Cilostazol for prevention of secondary stroke (CSPS 2): an aspirin-controlled, double-blind, randomised non-inferiority trial. CSPS 2 group. *Lancet Neurol.* 2010;9:959–968.

89. 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.

90. Bhatt DL, Fox KA, Jacke W, et al. Clopidogrel and aspirin versus aspirin alone for the prevention of atherothrombotic events. CHARISMA Investigators. *N Engl J Med.* 2006;354:1706–1717.

91. Benavente O. The Secondary Prevention of Small Subcortical Strokes (SPS3) trial: results of the antiplatelet intervention. International Stroke Conference; February 1–3, 2012; New Orleans, LA. Abstract LB9.

92. Foulkes MA, Wold PA, Price TR, Mohr JP, Hier DB. The Stroke Data Bank: design, methods, and baseline characteristics. *Stroke.* 1988;19:547–554.

93. Grau AJ, Welmar C, Buggle F, et al. Risk factors, outcome, and treatment in subtypes of ischemic stroke: the German stroke data bank. *Stroke.* 2001;32:2559–2566.

94. Ziegler PD, Glotzer TV, Daoud EG, et al. Incidence of newly detected atrial arrhythmias via implantable devices in patients with a history of thromboembolic events. *Stroke.* 2010;41:256–260.

95. Tayal AH, Tian M, Kelly KM, et al. Atrial fibrillation detected by mobile cardiac outpatient telemetry in cryptogenic TIA or stroke. *Neurology.* 2008;71:1696–1701.

96. Chow CK, Jolly S, Rao-Melacini P, Fox KA, Anand SS, Yusuf S. Association of diet, exercise, and smoking modification with risk of early cardiovascular events after acute coronary syndromes. *Circulation.* 2010;121:750–758.

The Essential Role of Neurologists in Treating and Preventing Stroke

Karen G. Hirsch, MD

University of California, San Francisco, San Francisco, California

Abstract The morbidity and mortality of stroke may be lowered considerably by instituting preventive interventions for patients at risk. A number of important clinical trials have compared the use of novel agents (dabigatran, rivaroxaban, and apixaban) with standard anticoagulant therapy to prevent stroke and other vascular conditions in patients with atrial fibrillation. Investigators also have studied optimal medical and surgical strategies to prevent initial and recurrent strokes in high-risk populations. Careful consideration of professional guidelines and implementation of expert recommendations may reduce the disabling and deadly ramifications of stroke.

Stroke remains a significant cause of morbidity and mortality in the United States despite recent advances in its diagnosis and treatment. Stroke affects approximately 795,000 Americans each year and is the fourth leading cause of death behind heart disease, cancer, and lower respiratory diseases.[1] Many patients who survive stroke have significant disability, with 15%–30% becoming permanently disabled.[1] Additionally, the risk of recurrent stroke is high, with 10%–20% of stroke patients 45–64 years of age suffering another incident within 5 years.[1] As such, the prevention and treatment of acute stroke are a national initiative—and neurologists stand on the front lines of these efforts.[2]

Stroke can be ischemic (87%) or hemorrhagic (10%).[1] Both types share many common risk factors (eg, hypertension, tobacco use), although unique risk factors for ischemic stroke (eg, atrial fibrillation, carotid stenosis) require special consideration.

Dr. Hirsch is a Fellow in Neurocritical Care in the Department of Neurology and Critical Care, University of California, San Francisco, San Francisco, California.

At the 2012 Annual Meeting of the American Academy of Neurology, experts reviewed recent results of clinical trials investigating stroke prevention and treatment. Some of the trials covered were the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) study,[3] the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF) trial,[4] the Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment (AVERROES) trial,[5] and the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial.[6] Speakers referred to American Heart Association (AHA)/American Stroke Association (ASA) classifications for strength of evidence and recommendations; explanation of the classes of evidence can be found in the guidelines.[7]

The session was co-chaired by Pierre Fayad, MD, Professor of Neurological Sciences and Director of the Vascular Neurology and Stroke Program at the University of Nebraska Medical Center, Omaha, and Ralph Sacco, MD, MS, FAHA, FAAN, Olemberg Family Chair in Neurologic Disorders, Chairman of the Neurology Department, and Miller Professor of Neurology, Epidemiology, and Human Genetics at the Miller School of Medicine of the University of Miami, and Chief of the Neurology Service at Jackson Memorial Hospital, Miami, Florida.

NEW OPTIONS IN ORAL ANTICOAGULATION FOR ATRIAL FIBRILLATION

Based on a presentation by Karen Furie, MD, MPH, Assistant in Neurology, Stroke Service, Massachusetts General Hospital, Boston

Atrial fibrillation is an independent risk factor for ischemic stroke.[8] Patients with atrial fibrillation have an annual stroke rate of 1%–20%. Daily use of vitamin K antagonists such as warfarin reduces the risk of ischemic stroke in patients with atrial fibrillation and is recommended for prophylaxis in patients at risk.[9,10] However, treatment with vitamin K antagonists is hampered by significant drug-drug interactions, the requirement for frequent laboratory blood testing, and the limited time that patients remain within the therapeutic range of the anticoagulant.[3] Patients with atrial fibrillation who take warfarin to prevent stroke have a target international normalized ratio (INR) of 2.0–3.0; however, as much as 30%–50% of the time their INR is not within the therapeutic range.[11] In addition to these difficulties, treatment with vitamin K antagonists increases the risk of hemorrhage, including intracerebral hemorrhage, with major bleeding occurring in 1%–5% of treated patients in most large trials.[9]

Given the significant stroke risk conferred by atrial fibrillation and the limitations of vitamin K antagonist therapy, there has been significant interest in the development of novel oral anticoagulants for patients with atrial fibrillation. Three of these novel anticoagulants (dabigatran, rivaroxaban, and apixaban) were the focus of four large randomized clinical trials that compared them with warfarin or aspirin in patients at risk.[3–6]

RE-LY Trial

Dabigatran is a prodrug that is rapidly converted into an active direct thrombin inhibitor. Its half-life is 12–17 hours, and 80% of a dose is excreted by the kidneys. Dabigatran is dosed twice daily; routine blood testing is not needed during therapy.

In the RE-LY trial,[3] dabigatran was compared with warfarin in over 18,000 patients with atrial fibrillation. The primary outcome was stroke or systemic embolization; secondary outcomes were stroke, systemic embolization, or death. The primary safety outcome was major hemorrhage. Eligible patients were randomized to treatment with 110 mg or 150 mg of dabigatran twice daily or warfarin (target INR 2.0–3.0). Patients were excluded if they had a stroke within 14 days, a severe stroke within 6 months, an increased risk of hemorrhage, a creatinine clearance rate (CCr) < 30 mL/min, or active liver disease or if they were pregnant. Twenty percent of patients continued taking aspirin in addition to the study drug.

To estimate the risk of stroke in individuals with nonrheumatic atrial fibrillation, the researchers used a clinical prediction rule known as the $CHADS_2$ score (Table 1).[12] Patients enrolled in the RE-LY trial had a mean $CHADS_2$ score of 2.1, meaning the study population in general had a relatively low risk for thrombotic events; approximately 20% of those enrolled had a previous stroke, making these findings less generalizable for secondary prevention.

The results of the RE-LY study showed that the primary outcome of stroke or systemic embolism occurred at a rate of 1.1% per year in patients receiving 150 mg of dabigatran, 1.5% per year in patients receiving 110 mg of dabigatran, and 1.7% per year in patients receiving warfarin. The 150-mg dose of dabigatran was superior to warfarin in preventing primary strokes, and the 110-mg dose of dabigatran was noninferior to warfarin. There was an increased risk of myocardial infarction (MI) and major gastrointestinal (GI) bleeding in the group receiving 150 mg of dabigatran, although overall rates of life-threatening bleeding, intracranial bleeding, and major or minor bleeding were higher with warfarin than with either dabigatran dose.

TABLE 1
$CHADS_2$ Score and Five-Year Risk of Stroke

Calculation of $CHADS_2$ score

Criterion	Points
Congestive heart failure	0 = no; 1 = yes
Hypertension	0 = no; 1 = yes
Age ≥ 75 years	0 = no; 1 = yes
Diabetes mellitus	0 = no; 1 = yes
Stroke or transient ischemic attack	0 = no; 2 = yes

Five-year risk for stroke in patients with chronic atrial fibrillation

$CHADS_2$ score	Five-year risk (%)
0	1.9
1	3.0
2	4.7
3	7.2
4	10.5
5	13.9
6	15.8

Source: Rietbrock et al[12]

After publication of this trial, dabigatran gained US Food and Drug Administration (FDA) approval in October 2010 for anticoagulation in patients with nonvalvular atrial fibrillation. Before prescribing dabigatran, physicians should consider that currently no test is available to monitor the anticoagulant effect of dabigatran during therapy, although an elevated partial thromboplastin time (PTT) may indicate the presence of a dabigatran-induced anticoagulant effect. Furthermore, no antidote is available to quickly reverse the effect in case of major bleeding or hemorrhage, although one is under development. (These same considerations also apply to rivaroxaban and apixaban.) In addition, renal function should be monitored periodically and the dosage decreased to 75 mg twice daily if the CCr falls to 15–30 mL/min.

ROCKET-AF Trial

Rivaroxaban is a direct factor Xa inhibitor with a half life of 5–9 hours. In the ROCKET-AF trial,[4] investigators compared rivaroxaban with warfarin in patients with nonvalvular atrial fibrillation. The primary endpoint was the composite risk of ischemic and hemorrhagic stroke and systemic embolism. The principal safety endpoint was a composite of major and nonmajor clinically relevant bleeding events.

The trial enrolled over 14,000 patients with nonvalvular atrial fibrillation who had a $CHADS_2$ score ≥ 2 defined by at least one stroke, transient ischemic attack (TIA), or systemic embolism or at least two of the following: ejection fraction ≤ 35%, heart failure, age ≥ 75 years, hypertension, or the presence of diabetes mellitus. Rivaroxaban was given in doses of 20 mg/d (15 mg/d for patients with a CCr = 30–49 mL/min); warfarin was dose-adjusted to achieve a target INR of 2.0–3.0. The statistical analysis involved a noninferiority design in the per-protocol population, a safety analysis once noninferiority was achieved, and then a post hoc analysis of events in the intention-to-treat (ITT) population of all randomized patients.

Data from the ROCKET-AF trial showed that the primary outcome of stroke and systemic embolism occurred at a rate of 1.7% per year in patients receiving rivaroxaban versus 2.2% per year in those given warfarin. In the ITT analysis, the primary outcome occurred at a rate of 2.1% per year in the rivaroxaban group versus 2.4% per year in the warfarin group. These results were statistically significant for the noninferiority of rivaroxaban when compared with warfarin. Rates of major bleeding were similar between the rivaroxaban and warfarin groups (3.6% and 3.4%, respectively); however, the frequency of fatal hemorrhage and intracerebral hemorrhage was lower in the rivaroxaban group.

Patients in the warfarin group had relatively little time in therapeutic range (55%), highlighting one of the challenges of warfarin therapy. In addition, there was

a transient increase in the rates of stroke and systemic embolism when rivaroxaban was discontinued (ie, when patients were transitioned to warfarin) and a significant rate of concomitant aspirin use (~35%) in the study population.

AVERROES Trial

Apixaban is a factor Xa inhibitor with a half-life of 8–15 hours; the drug is excreted through the kidneys and GI tract. AVERROES was a phase III trial evaluating the use of apixaban in patients with atrial fibrillation who were unable to take warfarin.[5] Patients were randomized to receive treatment with apixaban (5 mg twice daily) or aspirin (81–324 mg/d). The primary endpoint was stroke or systemic embolism. The trial, which enrolled 5,600 patients, was terminated early after an interim analysis revealed a > 50% reduction in the primary endpoint rate in the apixaban group when compared with the rate in the aspirin group. Stroke or systemic embolism occurred at a yearly rate of 1.7% in patients treated with apixaban and 3.9% in patients taking aspirin. Rates of major bleeding were similar between the two groups.

ARISTOTLE Trial

The second large phase III trial investigating apixaban therapy was ARISTOTLE.[6] This noninferiority study compared apixaban (5 mg twice daily) with warfarin (dose-adjusted to a target INR of 2.0–3.0). Patients had atrial fibrillation plus at least one other risk factor for stroke, including age ≥ 75 years; previous stroke, TIA, or systemic embolism; symptomatic heart failure within the previous 3 months or a left ventricular ejection fraction ≤ 40%; diabetes mellitus; or hypertension requiring pharmacologic treatment. The primary outcome was ischemic or hemorrhagic stroke or systemic embolism. In all, over 18,000 patients were enrolled.

The results of ARISTOTLE showed that the primary outcome of stroke or systemic embolism occurred at a rate of 1.27% per year in the apixaban group versus 1.60% per year in the warfarin group. This result was statistically significant for noninferiority of apixaban. Notably, the rate of major bleeding differed significantly between the two groups (2.13% per year for apixaban vs 3.09% per year for warfarin). Patients in the warfarin group were in the therapeutic range 62% of the time. These results showed that apixaban prevented ischemic stroke with an efficacy similar to that of warfarin but with a lower risk of major bleeding.

Application to Clinical Practice

Interpreting the results of these trials and applying them to clinical practice are important issues for neurologists. Despite the complex data and important results, all four trials have different limitations in their design, data analysis, and statistical power (Table 2).[13] When using these drugs, physicians must consider that there has not been a head-to-head comparison of any of the agents, there is no specific reversal agent for associated major bleeding, and there are limited means to monitor their therapeutic activity. The cost-effectiveness of the newer agents also needs to be assessed, although one analysis suggested dabigatran may be cost-effective in patients with atrial fibrillation.[14] The results of these studies shed light on a promising new era of anticoagulation for patients with atrial fibrillation, yet their applicability to clinical practice and how well and how often they will replace warfarin remain to be determined.

INTRACRANIAL ARTERY STENOSIS AND AGGRESSIVE MEDICAL THERAPY

Based on a presentation by Tanya N. Turan, MD, Assistant Professor of Neurosciences, Medical University of South Carolina, Charleston

Intracranial atherosclerotic disease that results in arterial stenosis is an important cause of ischemic stroke and is associated with a high risk of recurrent stroke.[15,16] Patients with a TIA or stroke

TABLE 2
Comparison of RE-LY, ROCKET-AF, AVERROES, and ARISTOTLE Trials

	RE-LY	ROCKET-AF	AVERROES	ARISTOTLE
Drug and dosage	Dabigatran, 110 mg bid or 150 mg bid	Rivaroxaban, 20 mg/d (15 mg/d in patients with CCr = 30–49 mL/min)	Apixaban, 5 mg bid	Apixaban, 5 mg bid
Comparator	Dose-adjusted warfarin (INR, 2.0–3.0)	Dose-adjusted warfarin (INR, 2.0– 3.0)	Aspirin, 81–324 mg/d	Dose-adjusted warfarin (INR, 2.0– 3.0)
Study design	Randomized, open-label	Randomized, double-blind, double-dummy	Randomized, double-blind	Randomized, double-blind
Number of patients	18,113	14,264	5,599	18,201
Primary endpoint: stroke and systemic embolism (rate per year)	Warfarin, 1.7%; dabigatran 110 mg, 1.5% ($P < 0.001$ for noninferiority); dabigatran 150 mg, 1.1% ($P < 0.001$ for superiority)	Warfarin, 2.4%; rivaroxaban, 2.1% (ITT analysis; $P < 0.001$ for noninferiority)	Aspirin, 3.7%; apixaban, 1.6% ($P < 0.001$)	Warfarin, 1.6%; apixaban, 1.3% ($P < 0.001$ for noninferiority)
Major bleeding (rate per year)	Warfarin, 3.4%; dabigatran 110 mg, 2.7% ($P = 0.003$); dabigatran, 150 mg, 3.1% ($P = 0.31$)	Warfarin, 3.4%; rivaroxaban, 3.6% ($P = 0.58$)	Aspirin, 1.2%; apixaban, 1.4% ($P = 0.57$)	Warfarin, 3.1%; apixaban, 2.1% ($P < 0.001$)

RE-LY = Randomized Evaluation of Long-Term Anticoagulation Therapy; ROCKET-AF = Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; AVERROES = Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment; ARISTOTLE = Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; bid = twice daily; CCr = creatinine clearance rate; INR = international normalized ratio; ITT = intention to treat

in the territory of a large intracranial vessel with severe stenosis (70%–99% of the diameter of the artery) have up to a 23% risk of recurrent stroke in that territory within the first year after the initial event.[17] Previous studies comparing aspirin with warfarin in this patient population have shown similar stroke outcomes but higher rates of hemorrhage among patients using warfarin.[16] As such, the mainstay of medical treatment for symptomatic intracranial atherosclerotic disease historically has been antiplatelet therapy. However, advances in both medical management and interventional options such as angioplasty and/or stenting have expanded the treatment options for patients with symptomatic intracranial disease.

The Stenting and Aggressive Medical Management for Preventing Recurrent Strokes in Intracranial Stenosis (SAMMPRIS) trial[18] compared aggressive medical management with percutaneous transluminal angioplasty and stenting ("stenting") in patients with symptomatic intracranial stenosis (defined as a stroke or TIA within 30 days in the territory of the vessel with 70%–99% stenosis). The findings were dramatic for two reasons. First, this trial was halted early due to the high rate of periprocedural stroke in the stenting arm, and subsequent results favored medical management. Second, aggressive medical management produced a dramatic reduction in secondary stroke when compared with historic medical management arms of similar stroke trials.

Aggressive medical management in SAMMPRIS consisted of several interventions: dual antiplatelet therapy with aspirin (325 mg/d) and clopidogrel (75 mg/d); aggressive pharmacologic management of primary risk factors (hypertension and elevated low-density lipoprotein [LDL] cholesterol levels); and management of secondary risk factors such as diabetes, smoking, and excess weight with the help of a lifestyle modification program called INTERxVENT. The goal systolic blood pressure was < 140 mm Hg; if the patient also had diabetes mellitus, it was < 130 mm Hg. The goal LDL level was < 70 mg/dL.

Using these interventions, the rate of the primary outcome of stroke or death within 30 days in the medical management arm was 5.8%. Several important and relatively simple interventions likely contributed to this significant reduction in secondary stroke. Investigators used low-cost, effective medications and followed an algorithm for titration of blood pressure medications. Rosuvastatin was used as the cholesterol medication in the trial, with a titration to clearly defined LDL goals. Overall, investigators achieved high rates of blood pressure control and reductions in LDL levels.

In her presentation, Dr. Turan stressed that physicians should implement these parameters in their practice and follow published algorithms for blood pressure control. Further, neurologists should be actively involved in ongoing risk-factor modification programs and medical management for secondary stroke prevention, especially in stroke patients with symptomatic intracranial disease who fit the profile of the SAMMPRIS patients. Significant improvements in stroke prevention can be achieved with relatively simple interventions.

> Neurologists should be actively involved in ongoing risk-factor modification programs and medical management for secondary stroke prevention.

MANAGEMENT OF CAROTID STENOSIS: THE NEUROLOGIST'S PRIMARY ROLE

Based on a presentation by Thomas G. Brott, MD, FAAN, Professor of Neurology, Eugene and Marcia Applebaum Professor of Neurosciences, and James C. and Sarah K. Kennedy Dean for Research, Mayo Clinic, Jacksonville, Florida, and Adjunct Professor of Surgery, University of Medicine and Dentistry of New Jersey, Newark

Carotid artery disease is an important cause of stroke, and treating symptomatic carotid artery disease can reduce the subsequent risk of stroke.[19,20] Historically, carotid endarterectomy and carotid artery stenting are the two unique options available to treat symptomatic carotid artery disease. Previous small trials have shown that carotid stenting may be equivalent to carotid endarterectomy,[21] but larger trials have shown a trend toward inferiority of carotid artery stenting when compared with carotid endarterectomy.[22,23] Findings from the recent Carotid Revascularization Endarterectomy Versus Stenting Trial (CREST)[24] have influenced current considerations and recommendations for treating carotid artery disease.

In the CREST study, over 2,500 patients with carotid artery stenosis were randomized to undergo either carotid endarterectomy or carotid artery stenting; the primary composite endpoint was stroke, MI, or death from any cause during the periprocedural period or any ipsilateral stroke within 4 years of follow-up. Initially, enrollment included only symptomatic patients, but it eventually was expanded to include asymptomatic patients as well. Each group had unique radiographic inclusion criteria defining the degree of vessel stenosis based on the individual imaging modality (ie, angiography vs ultrasonography vs computed tomography angiography).

The results showed no significant difference in the rates of the composite outcomes between the groups. However, in the periprocedural period, there was a higher rate of stroke in the carotid artery stenting group and a higher rate of MI in the endarterectomy group. This difference offset the primary outcome composite measure, although patients who suffered a periprocedural stroke had a decreased quality of life at 1 year when compared with those who suffered a MI. Many have argued for and against the propriety of including MI as a primary endpoint in a stroke trial.[25]

Incorporating the recent CREST data into medical practice requires evaluation of the broader landscape of trials studying the treatment of carotid artery disease. Among many other characteristics that can predict benefit from revasculariza-

tion are radiographic evidence of silent infarcts, transcranial Doppler evidence of microemboli, and carotid plaque ulceration on three-dimensional ultrasonography.

The AHA/ASA guidelines[20] recommend carotid endarterectomy for treatment of symptomatic carotid artery stenosis if the degree of narrowing is > 70% *(Level Ia evidence)* or > 50% *(Level Ib evidence)*. Carotid artery stenting may be an alternative in certain situations in symptomatic patients. Further, there is a difference in safety profiles between carotid endarterectomy and carotid artery stenting based on age and gender, where carotid endarterectomy seems to be safer in patients ≥ 64 years of age and carotid artery stenting may be safer in patients < 64 years of age and in women.

INTRACEREBRAL HEMORRHAGE: THE PRIMARY ROLE OF THE NEUROLOGIST

Based on a presentation by Michel Torbey, MD, MPH, FCCM, FAHA, Professor of Neurology and Neurological Surgery Vice Chair of Hospital Affairs, Director of the Division of Cardiovascular Diseases and Neurocritical Care, and Medical Director of the Ohio State University Neurovascular Stroke Center, Columbus

Intracerebral hemorrhage accounts for 10% of all strokes, but it has a high mortality.[1] Recent AHA/ASA guidelines focus on the management of patients with intracerebral hemorrhage.[26] Risk factors for intracerebral hemorrhage overlap significantly with those for ischemic stroke and include hypertension, alcohol and tobacco abuse, age > 55 years, and renal disease.

Intracerebral hemorrhage is a neurologic emergency, and management within the first 24 hours is critical. Approximately one third of intracerebral hemorrhages will expand within the first 24 hours, and control of blood pressure and coagulopathy are crucial during this period.[26]

Blood pressure usually is elevated in the acute setting of intracerebral hemorrhage, and blood pressure targets are somewhat controversial, given the balance between controlling blood pressure to prevent hematoma expansion and preserving cerebral perfusion, especially in the penumbra region surrounding the hemorrhage. As such, the recent AHA/ASA guidelines recommended reductions in blood pressure based on the patient's systolic blood pressure on admission.[26]

In addition to the importance of controlling blood pressure, rapid reversal of oral anticoagulant–associated coagulopathy (namely due to warfarin) is also critical in the acute setting to prevent hematoma expansion.[26]

Correction of coagulopathy with vitamin K and fresh frozen plasma or with prothrombin complex concentrates is recommended to achieve an INR < 1.4. The recent introduction of novel oral anticoagulants (eg, thrombin and factor Xa inhibitors) presents an ongoing issue in caring for intracerebral hemorrhage patients taking these agents, given the lack of proven reversal agents. However, there are some strategies that may be useful to reverse the anticoagulant effects of these new agents should significant bleeding occur.

In addition to managing patients with intracerebral hemorrhage in the acute setting, neurologists should be involved in the ongoing long-term care of patients who survive intracerebral hemorrhage. Many of the risk factors for intracerebral hemorrhage are also risk factors for ischemic stroke and carotid artery disease, leading to complex questions about management. For example, should an antiplatelet agent be given for primary or secondary prevention in patients with a history of intracerebral hemorrhage? Further, should oral anticoagulation be started or reinstituted in patients with a history of this condition?

To answer these questions, the physician must consider the etiology and type of intracerebral hemorrhage involved. For example, was the event a lobar hemorrhage (possibly due to amyloid angiopathy) or a hemorrhage in a more classic area for hypertensive hemorrhages? Dr. Torbey recommended avoiding oral anticoagulants in patients who have a history of lobar hemorrhages or have a significant cortical heme burden on their MRI, but an antiplatelet agent may be considered.

The management of intracerebral hemorrhage is complex, and early interventions are critical. Long-term complications and management issues certainly will arise in patients who survive the initial hemorrhage, and neurologists must be equipped to guide acute management decisions and modify risk factors to prevent recurrent hemorrhage.

CONCLUSION

Despite advances in the field, stroke remains a pervasive and significant health issue affecting thousands of people each year. The flurry of recent trials involving novel oral anticoagulants has yielded a large amount of data and requires medical personnel caring for patients with atrial fibrillation to stay abreast of a rapidly developing field, but warfarin certainly is no longer the sole option for stroke prevention in these patients.

The management of patients with intracranial atherosclerotic disease and extracranial carotid artery disease is equally complex, with recent data supporting aggressive medical management of intracranial disease and carotid endarterectomy over carotid artery stenting in most cases of extracranial carotid artery disease. Neurologists must be on the front lines to effectively manage medical risk factors, guide intervention decisions, and reduce the burden of recurrent stroke.

Finally, intracerebral hemorrhage accounts for a small proportion of all strokes yet causes significant morbidity and mortality. Following clinical pathways and AHA/ASA guidelines will help neurologists care for these patients.

The field of stroke continues to evolve, as important research provides vital information that will help optimize the care of stroke patients and avoid additional strokes.

REFERENCES

1. Roger VL, Go AS, Lloyd-Jones DM, et al. Heart disease and stroke statistics—2011 update: a report from the American Heart Association. *Circulation.* 2011;123;e18–e209.

2. Tomaselli GF, Harty M, Horton K, Schoeberl M. The American Heart Association and the Million Hearts Initiative: a presidential advisory from the American Heart Association. *Circulation.* 2011;124:1795–1799.

3. Connolly SJ, Ezekowitz MS, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial

fibrillation. *N Engl J Med.* 2009;36:1139–1151.

4. Patel MR, Mahaffey KW, Garg J, et al. Rivoraxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.* 2011;365:883–891.

5. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med.* 2011;364:806–817.

6. Granger CB, Alexander JH, McMurray JJV, et al. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med.* 2011;365:981–992.

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. *Stroke.* 2007;38:1655–1711.

8. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991;22:983–988.

9. Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med.* 2007;146:857–867.

10. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation—executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients with Arial Fibrillation). *J Am Coll Cardiol.* 2006;48:854–906.

11. Niespialowska-Steuden MM, Markides V, Gorog DA. Novel antithrombotic agents for atrial fibrillation. *Pharmacol Ther.* 2012;134:345–354.

12. Rietbrock S, Heeley E, Plumb J, van Staa T. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the congestive heart failure, hypertension, age >75, diabetes mellitus, and prior stroke or transient ischemic attack ($CHADS_2$) risk stratification scheme. *Am Heart J.* 2008;156:57–64.

13. Mega JL. New era for anticoagulation in atrial fibrillation. *N Engl J Med.* 2011:365:1052–1054.

14. Freeman JV, Zhu RP, Owens DK, et al. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in atrial fibrillation. *Ann Intern Med.* 2011;154:1–11.

15. Gorelick PB, Wong KS, Bae HJ, Pandey DK. Large artery intracranial occlusive disease: a large worldwide burden but a relatively neglected frontier. *Stroke.* 2008;39:2396–2399.

16. Chimowitz MI, Lynn MJ, Howlett-Smith H, et al. Comparison of warfarin and aspirin for symptomatic intracranial arterial stenosis. *N Engl J Med.* 2005;352:1305–1316.

17. Kasner SE, Chimowitz MI, Lynn MJ, et al. Predictors of ischemic stroke in the territory of a symptomatic intracranial arterial stenosis. *Circulation.* 2006;113:555–563.

18. Chimowitz MI, Lynn MJ, Derdeyn CP, et al. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med.* 2011; 365:993–1003.

19. Petty GW, Brown RD Jr, Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Ischemic stroke subtypes: a population-based study of incidence and risk factors. *Stroke.* 1999;30:2513–2516.

20. 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.

21. Ederle J, Bonati LH, Dobson J, et al. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol.* 2009;8:898–907.

22. Mas J-L, Chatellier G, Beyssen B, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med.* 2006;355:1660–1671.

23. Ederle J, Dobson J, Featherstone RL, et al. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet.* 2010;375:985–997.

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

25. Mas J, Brown MM, Ringleb PA. Stenting versus endarterectomy for carotid-artery stenosis (correspondence). *N Engl J Med.* 2010;363:1766–1768.

26. Morgenstern LB, Hemphill JC, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke.* 2010;41:2108–2129.

Surviving Stroke Call: A Guide for Nonvascular Neurologists

Peter S. Pressman, MD

Northwestern University Feinberg School of Medicine, Chicago, Illinois

Abstract Stroke management is a critical and frequently encountered problem for neurology consultants in emergency departments. During a panel discussion presented at the 2012 Annual Meeting of the American Academy of Neurology, experts in stroke neurology, emergency medicine, and interventional neuroradiology discussed important elements in the examination and treatment of people with stroke, including the use of a systematic approach, collaboration with different medical specialists, and awareness of potential problems. Topics covered included initial assessment, consideration of treatment with tissue plasminogen activator and endovascular procedures, and various issues to be discussed with patients and their loved ones.

The acute evaluation and treatment of stroke present unique challenges to the neurologist. Within a short time and in the presence of multiple distractions and, occasionally, conflicting priorities, the neurologist must make a diagnosis and decide whether a patient could benefit from costly and perhaps risky therapies, such as administration of intravenous (IV) recombinant tissue plasminogen activator (tPA). This decision, which may be made with only sparse information about patients and their symptoms, will have serious implications for the morbidity and mortality of those individuals.

Two million neurons die every minute during a period of ischemia, making stroke a medical emergency demanding immediate treatment.[1] As the medical maxim states, "Time is brain." Despite the urgency associated with stroke, very few affected patients receive necessary medical therapies.[2] Often, this problem is due to factors beyond a physician's control, such as delayed patient presentation to the emergency department (ED) or identified contraindications to available therapies. However, the physician must avoid the many opportunities for failure that will present during the evaluation and treatment of someone experiencing a stroke.[3]

Neurology consultants in the ED commonly encounter stroke. About 795,000 people suffer a stroke every year in the United States, making it the country's leading cause of long-term disability.[4] This makes it all the more important to manage the problem as effectively as possible.

During the 64th Annual Meeting of the American Academy of Neurology, a panel of experts in emergency medicine, vascular neurology, and interventional neuroradiology led a conversation about common pitfalls in diagnosing and treating stroke in the ED. The conversation was targeted to general neurologists who might be covering the ED while on call. In addition to cautioning against these potential problems, the panel recommended relying on a checklist to aid patient evaluation and management. The panelists divided each patient interaction into three parts and devised a checklist that could help in ensuring a consistent and systematic approach to patient care. Use of such checklists has proven very effective in preventing aviation disasters and has become more common in hospital operating rooms and medical wards.[5]

Experts taking part in this educational session were Coleman O. Martin, MD, Clinical Assistant Professor of Neurology at the University of Missouri at Kansas City, and, from the University of Iowa College of Medicine in Iowa City, Enrique C. Leira, MD, MS, Assistant Professor of Neurology, and Azeemuddin Ahmed, MD, MBA, Clinical Associate Professor of Emergency Medicine.

COMMON PITFALLS DURING INITIAL STABILIZATION AND ASSESSMENT

Pitfall #1: Providing inadequate airway protection

The need to evaluate the patient's neurologic status must be balanced against the patient's ability to protect the airway. A patient whose stroke has led to diminished consciousness, increased vomiting, or poor gag reflexes is at high risk for aspiration. Physicians should not rely on oxygen saturation levels as an indicator for intubation. Instead, neurologic factors, such as the patient's level of consciousness, should be used. To do otherwise increases the patient's risk of pulmonary infection.

Assessing the patient's neurologic status is critical to stroke management, and essential components of the examination may be lost after intubation. Before intubation (and sedation) is accomplished, the neurologist must communicate clearly

Dr. Pressman is a Neurology Resident at Northwestern University Feinberg School of Medicine, Chicago, Illinois.

with the staff of the ED and attempt to obtain at least a basic neurologic exam and, if possible, a noncontrast computed tomographic (CT) scan of the head

Pitfall #2: Overlooking rapid measurement of the serum glucose level

Hypoglycemia is very common, and, occasionally, it may mimic stroke.[6] In some cases, such as in patients taking β-blockers, additional signs of hypoglycemia may be absent. Rather than waiting on serum chemistry analysis, the evaluating physician should get a bedside glucose measurement. The correction of hypoglycemia may prevent brain injury and performance of unnecessary diagnostic procedures and treatments. The same is sometimes true for significant elevations in serum glucose levels.

Pitfall #3: Inadequately managing blood pressure

The management of blood pressure in patients experiencing an acute stroke is somewhat controversial, but most neurologists agree that it is best to let the blood pressure run higher than the usual thresholds for treatment. This permissive hypertension may maximize or augment cerebral perfusion. The exact threshold for blood pressure treatment in acute stroke is a matter of debate; however, members of the panel mentioned a systolic blood pressure of 185 mm Hg and a diastolic reading of 110 mm Hg as the upper limits of permitted hypertension. Furthermore, if IV tPA is not given, this threshold may be extended to as high as 220 mm Hg systolic or 120 mm Hg diastolic.[7]

If blood pressure must be managed, the three most common agents to consider prescribing are labetalol, hydralazine, and nicardipine. Each drug has potential drawbacks, however. Labetalol should not be used if the patient is already on a β-blocker, if there is concern about asthma or bradycardia, or if the patient may be a user of cocaine. Nicardipine can be slow to act; further, physicians could incorrectly perceive the initiation of too many drips as a contraindication to IV tPA administration. The panel mentioned hydralazine as a frequent drug of choice, although use of the drug carries some risk of elevated intracranial pressure.

Pitfall #4: Taking an inadequate history and/or performing an inadequate physical examination

Obtaining an appropriate history and performing a proper physical examination in the ED can be uniquely challenging. Several interruptions by ED staff may occur, and the patient may be whisked off to undergo various diagnostic procedures. In addition, time is limited, and the patient may suffer from severe impediments to communication, such as aphasia or dysarthria.

To overcome these challenges, the neurologist must be both focused and flexible and should obtain only a relevant history. Important information that must be determined quickly includes the time elapsed since the patient was last "normal" and any possible history of anticoagulant use, recent stroke, myocardial function, and surgeries. If neurologists are uncertain whether a recent procedure is a contraindication to IV tPA use, they should at least attempt to contact the surgeon or the relevant medical department. Apparent improvement in the patient's condition should not dissuade the neurologist from administering IV tPA unless significant deficits have been avoided. Further, neurologists should be fluent in the use of the National Institutes of Health Stroke Scale (NIHSS; http://nihss-english.trainingcampus.net/uas/modules/trees/windex.aspx; http://learn.heart.org/ihtml/application/student/interface.heart2/nihss.html).

Obtaining an appropriate history and performing a proper physical examination in the emergency department can be uniquely challenging.

Pitfall #5: Situations that can make the diagnosis of stroke difficult

A number of different situations can complicate the diagnosis of stroke, including vague vertebrobasilar symptoms (eg, dizziness, blurred vision), seizure or trauma at stroke onset, concomitant use of alcohol or drugs, a history of migraine headaches, or functional symptoms. Use of immediate magnetic resonance imaging (MRI) may be helpful in these situations, but necessary equipment frequently is unavailable.

Neurologists probably underutilize IV tPA and other interventions in patients who are experiencing an acute stroke.[8] The expert panel encouraged more aggressive use of thrombolytics. For example, treatment may be advisable even if a seizure occurred at symptom onset. Patients with seizures apparently were excluded from the National Institute of Neurological Disorders and Stroke (NINDS) trial for methodologic rather than safety reasons.[9] Further, the NIHSS score may not be particularly high in someone who has suffered an obvious vertebrobasilar stroke, yet administration of IV tPA may be considered if the disorder has a classic vascular distribution, such as a lateral medullary syndrome. When in doubt, it also is probably better to treat patients who present with acute neurologic deficits even if they also have a history of migraine or functional symptoms, because the use of IV tPA rarely causes significant problems under those conditions.[10]

Pitfall #6: Misinterpreting cardiac screening tests

The electrocardiogram (ECG), a part of the initial evaluation of all stroke patients, screens for atrial fibrillation and myocardial ischemia. If the patient is suffering from a concomitant myocardial infarction (MI), acute stroke care may be affected, as ST elevation classically is a contraindication for IV tPA (although tPA is indicated for this condition).

The ECG and cardiac enzyme levels must be interpreted in the clinical con-

text. Some 15% of stroke patients have ECGs that suggest ischemia; these findings could be secondary to the stroke or could be primarily cardiac in etiology. About 10% of these patients have high troponin levels, and just 3% have acute cardiac ischemia.[11] If an MI occurred very recently, IV tPA administration may be beneficial. If there is any concern about cardiac disease, close discussion with a cardiologist is advisable.

Pitfall #7: Inadequately screening for aortic dissection

Aortic dissection, an absolute contraindication to IV tPA administration, represents a difficult diagnosis. A chest x-ray film may not be sufficient to characterize aortic dissection. If a patient presents with symptoms suggesting the presence of aortic dissection, such as chest pain or numbness, but has a normal chest x-ray, the neurologist should not hesitate to order a CT scan.

Pitfall #8: Sending the patient for a head CT scan before he/she is ready

A CT scanner is a bad place for a patient to experience any type of medical emergency. Before a CT scan is accomplished, the physician must ascertain that the airway is clear, a physical examination has been performed, and a basic history and any laboratory tests required for IV tPA initiation have been obtained. If the patient requires sedation for the CT scan, the risks and benefits of performing the test at the cost of a detailed physical examination must be considered.

Table 1 provides a checklist for initial stabilization and assessment of stroke patients.

TABLE 1
Initial Patient 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

Source: Coleman O. Martin, MD, Enrique Leira, MD, MS, and Azeemuddin Ahmed, MD, MBA

COMMON PITFALLS OF IV tPA THERAPY IN ACUTE STROKE: STAY OUT OF TROUBLE!

Pitfall #9: Not screening the patient for eligibility for IV tPA

Currently, many eligible patients are not receiving IV tPA despite strong evidence of the drug's potential benefits. Even if IV tPA is not administered, a clear explanation of the physician's rationale should be documented. Physicians should ensure that European Cooperative Acute Stroke Study III (ECASS III) treatment protocols are well understood when treating patients who present 3–4.5 hours after they have begun experiencing symptoms of stroke.[12] (The US Food and Drug Administration [FDA] recently declined to approve IV tPA for stroke in the 3.0–4.5 hour therapeutic window.) Again, managing physicians should not hesitate to contact someone more knowledgeable about IV tPA administration if they have any questions about the details of eligibility criteria, such as whether having a particular procedure (eg, recent placement of a cardiac pacemaker) makes use of the drug too risky.

Pitfall #10: Not adequately screening the patient for IV tPA contraindications

Physicians must be aggressive with IV tPA administration and rely on their judgment about the appropriateness of individual treatment plans. On the other hand, bending the rules can lead to increased complications.

The balance between following guidelines and the needs of individual patients has led to often vigorous conversations among physicians, especially when the guidelines are unclear. For example, what qualifies as "major surgery" or "aggressive" blood pressure management? In patients with fluctuating symptoms, what qualifies as an improvement significant enough to exclude IV tPA administration? According to CT scan results, how should you determine whether more than one third of the hemisphere has been involved in the stroke—which would contraindicate thrombolytic treatment? These questions often have no clear answer.

How guidelines are used changes with evolving professional opinions and new medical developments. For example, as previously noted, the guidelines for not giving IV tPA to people who have experienced a seizure at the onset of symptoms have relaxed somewhat among some vascular neurologists. More widespread use of new drugs, such as the direct thrombin inhibitor dabigatran, raises questions about contraindications, since the extent to which this medication increases the risk of hemorrhagic transformation remains unknown. For now, many physicians rely on a normal partial thromboplastin time as a sign that IV tPA may be safely given, but no consensus guidelines yet exist on this issue.

Pitfall #11: Thinking of the IV tPA time treatment window as a fixed "deadline"

People naturally think in terms of deadlines. During the ED evaluation of someone who has experienced a stroke in the ED, medical professionals may comment about still having a certain amount of time "left in the window." However, this line of thinking misses the point that even within the window, people who are treated earlier tend to do better. Once again, time is brain. Delays in administering IV tPA, even within the therapeutic window, will negatively impact patient outcome.[13]

Pitfall #12: Not obtaining adequate consent for IV tPA therapy

Formal consent for IV tPA administration usually is unnecessary, but at least a verbal consent should be obtained to respect patient autonomy. Since a patient with stroke may not be able to grant consent, the physician may need to discuss the need for the drug with a family member

or other surrogate decision-maker. Such conversations should not delay treatment, however. The message should be succinct and objective and focus on the benefits of IV tPA therapy versus its risks. Administration of IV tPA can double the odds of a good functional outcome; however, it is associated with a 6.4% risk of intracranial hemorrhage, with no significant difference in mortality.[12] Community-based registry data on the use of IV tPA in stroke have shown rates of symptomatic cerebral hemorrhage that are more in the range of 3.5%[14] to 4.5%.[15]

Pitfall #13: Using the wrong thrombolytic or dose

Currently, the only thrombolytic approved by the FDA for use in patients experiencing acute stroke is tPA, or alteplase. In the future, other thrombolytics, such as tenecteplase, may be approved, but none is available at this time. Some hospitals may store different thrombolytics that are intended to treat only MI.

The recommended dose of alteplase for acute stroke is 0.9 mg/kg IV (maximum dose, 90 mg IV), with 10% of the dose given as a bolus and the remaining 90% administered as a 1-hour infusion.

Pitfall #14: Letting blood pressure "run wild" during and after infusion of IV tPA

Higher blood pressure levels after the administration of IV tPA are associated with a higher risk of intracerebral hemorrhage. Blood pressure must be monitored very closely during and after IV tPA administration. A patient must be treated immediately if any systolic blood pressure reading over 185 mm Hg or any diastolic reading over 110 mm Hg is detected during or for 24 hours after the IV infusion of tPA.

Pitfall #15: Not admitting the patient to an appropriate hospital setting for post-tPA care

Stroke patients treated with IV tPA in either an intensive care unit or a dedicated stroke unit have less morbidity and mortality. Nurses in such units receive special training to manage stroke patients, and neurosurgical/interventional capabilities are more likely to be readily available.[16]

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

Source: Coleman O. Martin, MD, Enrique Leira, MD, MS, and Azeemuddin Ahmed, MD, MBA

Pitfall #16: Not recognizing hemorrhagic transformation

In a patient who has recently received or is actively receiving IV tPA, signs and symptoms such as a headache, a deterioration in the level of consciousness, worsening neurologic deficits, or a change in blood pressure should herald the possibility of hemorrhagic transformation. Unfortunately, these findings are sometimes misinterpreted as being related to the original ischemic stroke. If the patient develops these symptoms during IV tPA use, the infusion must be stopped immediately. The airway should be reassessed, and blood pressure should be lowered aggressively before obtaining an immediate head CT scan. A neurologic consultation and administration of fresh frozen plasma also may be considered.

Pitfall #17: Not recognizing angioedema

Angioedema, a potential complication that affects up to 5% of all patients treated with IV tPA, commonly affects the mouth and tongue, leading to worsening slurring of speech, which can impair patient communication. The symptoms can be unilateral, so this symptom could be mistaken for dysarthria (or worsening dysarthria) caused by the initial stroke. Steps should be taken to protect the airway while treating the patient with diphenhydramine or corticosteroids.[17]

Table 2 provides a checklist for IV tPA therapy in stroke patients.

PITFALLS BEYOND IV tPA: WHEN DO I NEED AN MRI? IS A NEUROINTERVENTIONALIST NEEDED?

Pitfall #18: Not considering interventional treatments

Mechanical thrombectomy devices, such as the Merci Retriever (Concentric Medical, Inc; Mountain View, CA) and the Penumbra System (Penumbra, Inc; Alameda, CA), have been approved by the FDA to remove clots from arteries.[18] An additional stent-based mechanism, the Solitaire FR Revascularization Device (ev3 Endovascular, Inc., Plymouth, MN), is expected to be available in the United States within the next few months.[19] In addition, in some cases, intra-arterial (IA) tPA can be administered more directly to the site of a thrombus.

Patients with large occlusions may benefit particularly from endovascular procedures. Neurointervention is most often considered when a patient presents outside the therapeutic window for receiving IV tPA. Guidelines for interventional endovascular treatments are not well established, but such a strategy should be considered if the patient presents within 6–8 hours after symptom onset. In addition, although still considered experimental, a neuroendovascular procedure may be considered if the patient does not rapidly improve following IV tPA administration. (The Interventional Management of Stroke III Trial (IMS III), which was investigating the value of endovascular therapy in stroke patients who had been given IV tPA or a combination of IV and IA tPA, was recently stopped by the trial's independent Data Safety Monitoring Board and the NINDS due to a futility analysis. How this will affect other ongoing trials investigating such

"bridging therapy" is currently unclear.)

When needed, it is helpful to get a neurointerventionalist involved as soon as possible. Patient stabilization and medical issues must be addressed before any endovascular procedure is accomplished. The decision to go forward with a procedure will depend on conversations between the neurologist, the interventionalist, ED staff, and the patient.

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

To decide whether someone is a potential candidate for endovascular treatment, neurointerventionalists often need to obtain an MRI/magnetic resonance angiogram (MRA) or CT perfusion scan to detect evidence of a salvageable penumbra. The decision about interventional therapy may depend on whether there is a mismatch between diffusion and perfusion. In addition, the vascular system must be evaluated for arterial occlusion.

To avoid delays in diagnostic imaging, neurologists must recognize a facility's capabilities. Depending on location, the patient may need to be transferred to another hospital.

Pitfall #20: Not ordering a renal function test

To avoid complications such as renal failure and nephrogenic systemic fibrosis, a patient's renal function must be assessed before a contrast medium is administered.[20] Laboratory testing to calculate the glomerular filtration rate must be ordered as soon as possible to obtain any imaging that will guide decision-making.

Pitfall #21: Questioning the safety of MRI

The potential dangers of introducing certain metals to the strong magnetic field of an MRI machine are well known. However, an aphasic or extremely dysarthric patient may not be able to reliably answer the questions in a standardized MRI screening protocol. An x-ray examination may be able to detect some metals, such as those present in a pacemaker.

It is also not uncommon for a patient to be uncertain about the compatibility of a device (eg, pacemaker, aneurysm clip) with MRI or MRA. It is best to try to contact relatives or the medical staff involved with the procedure. If data cannot be obtained, the risks and benefits of imaging will have to be weighed carefully.

TABLE 3
Beyond IV tPA Checklist

- ☑ Consider endovascular therapy
- ☑ Check renal function
- ☑ Check for the presence of a pacemaker, programmable shunt, or metal implant
- ☑ 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

Source: Coleman O. Martin, MD, Enrique Leira, MD, MS, and Azeemuddin Ahmed, MD, MBA

Pitfall #22: Having doubts as to where to spend the dose of gadolinium contrast

Both MRA and a perfusion scan require contrast. Whereas MRA of the head can be accomplished without contrast, MRA of the neck is best done with contrast for adequate visualization. However, a patient can only receive a limited dose of gadolinium within a certain period. When in doubt, it may be best to order the perfusion first along with a time-of-flight image for the neck vessels. If the MRA of the head shows no occlusion, closer imaging of the neck can be done at a later time. In other situations, however, such as when there is concern for carotid dissection, priorities may differ. It is a good idea to discuss these decisions with the interventionalist as well.

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

Many stroke patients lose their ability to make rational decisions and cannot hold still in an MRI machine. The resulting images are highly contaminated by motion artifact. Sedating the patient can improve the quality of the imaging; however, sedation poses risks to the patient, and many aspects of the neurologic examination may be lost. In extreme cases, an anesthesiologist may need to be involved.

Pitfall #24: Interpreting diffusion- and perfusion-weighted images (DWI/PWI)

These imaging protocols are used to identify patients with large perfusion deficits in which actual ischemic damage, as evidenced by DWI, is small. This mismatch has been associated with better outcomes after endovascular reperfusion therapy; however, the evidence has been questioned, and the optimal threshold remains controversial.[21] Discussion with the neurointerventionalist is essential.

Pitfall #25: Disagreeing with the interventional radiology team regarding the need for a procedure

The neurologist and interventional radiology team may disagree about whether or not a procedure is necessary. Endovascular reperfusion procedures may benefit a patient, but they are not widely considered to be standard of care. When possible, a consensus should be reached. Ultimately, interventionalists cannot be pushed out of their comfort zone for a procedure. Similarly, neurologists cannot be forced to recommend a procedure that they do not think would be in their patient's best interest.

Table 3 provides a checklist for reviewing factors beyond IV tPA therapy in stroke patients.

FAMILY AND PATIENT INTERACTION—EFFECTIVE COMMUNICATION AND DOCUMENTATION

Pitfall #26: Overwhelming patients and relatives with data and decisions

Stroke can cause a state of psychologic shock in patients and their loved ones, which limits their ability to absorb new information. Retention of this informa-

tion is probably limited to just the first few sentences spoken by a physician. Repetition will likely be essential. Information should be delivered crisply, succinctly, and accurately. The focus should be on stating what happened, briefly describing what might happen in the near future, discussing likely outcomes, and recommending a course of action.

Pitfall #27: Failing to communicate the initial prognosis of a patient

The severity of a patient's condition might be obvious to medically trained individuals, but the understanding of the patient and family might be quite different. They may be surprised to see the patient getting worse. It may be helpful to remind them that the best data available involve time periods 3 months after treatment rather than immediately after therapy begins.

Pitfall #28: Potentially interfering with a patient's last wishes

Sometimes, even with aggressive medical care, the prognosis for meaningful recovery might be grim. In these situations, it is important to understand and respect what the patient would have wanted. A discussion of intubation, resuscitation, thrombolysis, feeding tubes, and other issues might be necessary. The patient may have an advanced directive, but such documents rarely are specific to the situation at hand, as neurologic deficits vary.

CONCLUSION

Use of guidelines and checklists can help to ensure a systematic, thorough, and efficient approach to treating stroke in the ED. The panel also pointed out the limitations of these tools. Ultimately, every case is unique, and each will call on the neurologist's judgment. Along with attending to details, neurologists must be flexible enough to know how to work as part of a team and, when necessary, must not hesitate to ask for help. By recognizing potential impediments to optimal patient care, and by being both methodical and flexible, medical professionals may supply optimal, state-of-the art care to patients with acute stroke.

REFERENCES

1. Saver JL. Time is brain—quantified. *Stroke.* 2006;37:263–266.
2. 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.
3. Hills NK, Johnston SC. Why are eligible thrombolysis candidates left untreated? *Am J Prev Med.* 2006;31:S210–S216.
4. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart disease and stroke statistics—2010 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation.* 2010;121:e46–e215.
5. Livingston EH Solutions for improving patient safety. *JAMA.* 2010;303:159–161.
6. Wallis WE, Donaldson I, Scott RS, Wilson J. Hypoglycemia masquerading as cerebrovascular disease (hypoglycemic hemiplegia). *Ann Neurol.* 1985;18:510–512.
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. *Circulation.* 2007;115:e478–e534.
8. The Paul Coverdell Prototype Registries Writing Group. Acute stroke care in the US: results from 4 pilot prototypes of the Paul Coverdell National Acute Stroke Registry. *Stroke.* 2005;36:1232–1240.
9. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med.* 1995;333:1581–1587.
10. Chernyshev OY, Martin-Schild S, Albright KC, et al. Safety of tPA in stroke mimics and neuroimaging-negative cerebral ischemia. *Neurology.* 2010;74:1340–1345.
11. 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.
12. 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.
13. Marler JR, Tilley BC, Lu M, et al. Early stroke treatment associated with better outcome: the NINDS rt-PA stroke study. *Neurology.* 2000;55:1649–1655.
14. Palumbo V, Boulanger JM, Hill MD, Inzitari D, Buchan AM; CASES Investigators. Leukoaraiosis and intracerebral hemorrhage after thrombolysis in acute stroke. *Neurology.* 2007;68:1020–1024.
15. Grotta JC, Burgin WS, El-Mitwalli A, et al. Intravenous tissue-type plasminogen activator therapy for ischemic stroke: Houston experience 1996 to 2000. *Arch Neurol.* 2001;58:2009–2013.
16. Stroke Unit Trialists' Collaboration. Collaborative systematic review of the randomised trials of organised inpatient (stroke unit) care after stroke. *BMJ.* 1997;314:1151–1159.
17. Rafii MS, Koenig M, Ziai WC. Orolingual angioedema associated with ACE inhibitor use after rtPA treatment of acute stroke. *Neurology.* 2005;65:1906.
18. Tenser MS, Amar AP, Mack WJ. Mechanical thrombectomy for acute ischemic stroke using the MERCI retriever and penumbra aspiration systems. *World Neurosurg.* 2011;76:S16–S23.
19. Roth C, Papanagiotou P, Behnke S, et al. Stent-assisted mechanical recanalization for treatment of acute intracerebral artery occlusions. *Stroke.* 2010;41:2559–2567.
20. 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.
21. Schellinger PD, Bryan RN, Caplan LR, et al. Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology evidence-based guideline: the role of diffusion and perfusion MRI for the diagnosis of acute ischemic stroke: report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology.* 2010;75:177–185.

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 page 36 and see the instructions below it to obtain CME credit.

1. Which of the following clinical trials showed that intravenous (IV) recombinant tissue plasminogen activator (tPA) was safe and effective when given within 4.5 hours of stroke onset in selected patients?
   a. SITS-MOST
   b. ATLANTIS
   c. ECASS III
   d. ARISTOTLE

2. Which of the following statements about the "drip-and-ship" model is *true?*
   a. In states in which the drip-and-ship model is followed, acute stroke patients have shorter hospital stays.
   b. In states in which the drip-and-ship model is followed, acute stroke patients are less likely to be given thrombolytics.
   c. Approximately two of five patients given IV tPA for acute ischemic stroke are treated according to the drip-and-ship model.
   d. The drip-and-ship model has been shown to be a safe practice when patients are transported within a state but not when they are transported across a region.

3. The slowest, but most accurate, method for predicting penumbra size in acute stroke patients is:
   a. Computed tomography (CT) with a contrast medium
   b. MRI diffusion-weighted imaging
   c. CT perfusion-weighted imaging
   d. Noncontrast computed tomography

4. In the PROACT II study, ischemic stroke patients with middle cranial artery occlusions given intra-arterial prourokinase with IV heparin showed a _____ absolute benefit in functional outcome when compared with IV heparin alone.
   a. 1%
   b. 5%
   c. 10%
   d. 15%

5. According to American Heart Association guidelines, which of the following is recommended for treating patients with acute ischemic stroke?
   a. Patients with a persistent glucose level > 110 mg/dL during the first 24 hours after the onset of stroke symptoms should be treated with insulin.
   b. Emergency antihypertensive agents should be withheld from patients ineligible for thrombolytic therapy unless the diastolic blood pressure is > 120 mm Hg or the systolic blood pressure is > 220 mm Hg.
   c. Antiplatelet therapy with aspirin may be substituted for acute stroke treatment with IV tPA.
   d. Clopidogrel may be given alone or with aspirin.

6. The first oral direct thrombin inhibitor approved by the US Food and Drug Administration to prevent stroke in patients with nonvalvular atrial fibrillation was:
   a. Rivaroxaban
   b. Ximelagatran
   c. Dabigatran
   d. Apixaban

7. The AVERROES trial compared the use of aspirin with that of apixaban in preventing stroke or embolism; the results showed:
   a. Patients taking apixaban had half the rate of stroke or systemic embolism compared with aspirin.
   b. Patients using aspirin had four times the rate of stroke or systemic embolism compared with apixaban.
   c. Patients taking aspirin had three times the rate of major bleeding compared with apixaban.
   d. None of the study patients using apixaban experienced major bleeding.

8. In the periprocedural period of the CREST trial, patients who underwent carotid endarterectomy had a higher rate of _____ than did those who underwent carotid stenting.
   a. Death
   b. Stroke
   c. Myocardial infarction
   d. Seizure

9. Before administering IV tPA, blood pressure should be reduced below:
   a. 180/110 mm Hg
   b. 160/90 mm Hg
   c. 220/120 mm Hg
   d. 140/95 mm Hg

10. Angioedema may occur in up to _____ of acute stroke patients receiving IV tPA.
   a. 1%
   b. 2%
   c. 5%
   d. 7.5%

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. Actions that need to be taken by physicians when an acute stroke patient presents to the emergency department.	❑	❑	❑
b. Rationale for and outcomes of the drip-and-ship paradigm for managing patients with acute stroke in the community hospital setting.	❑	❑	❑
c. Benefits and risks of intravenous versus intra-arterial thrombolysis and the indications for mechanical thrombectomy in stroke patients.	❑	❑	❑
d. Trends now taking place in medicine to prevent stroke in high-risk patients.	❑	❑	❑
e. Assessment and management of medical complications associated with acute ischemic 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 hours)* did it take you to complete this activity, including this evaluation? _____ hours

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 35 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 August 18, 2013, select this issue of *The Neurology Report,* and click "CME Credit" 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 35, 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.