JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
© 2016 BY THE AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION
PUBLISHED BY ELSEVIER

VOL. 67, NO. 22, 2016
ISSN 0735-1097/$36.00
http://dx.doi.org/10.1016/j.jacc.2016.03.555

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

Acute Ischemic Stroke Intervention

Priyank Khandelwal, MD,[a] Dileep R. Yavagal, MD, MBBS,[b,c] Ralph L. Sacco, MD, MS[b]

ABSTRACT

Acute ischemic stroke (AIS) is the leading cause of disability worldwide and among the leading causes of mortality. Although intravenous tissue plasminogen activator (IV-rtPA) was approved nearly 2 decades ago for treatment of AIS, only a minority of patients receive it due to a narrow time window for administration and several contraindications to its use. Endovascular approaches to recanalization in AIS developed in the 1980s, and recently, 5 major randomized trials showed an overwhelming superior benefit of combining endovascular mechanical thrombectomy with IV-rtPA over IV-rtPA alone. In this paper, we discuss the evolution of catheter-based treatment from first-generation thrombectomy devices to the game-changing stent retrievers, results from recent trials, and the evolving stroke systems of care to provide timely access to acute stroke intervention to patients in the United States. (J Am Coll Cardiol 2016;67:2631–44)

Acute ischemic stroke (AIS) occurs when there is a sudden occlusion of the arterial blood supply to part of the brain, and is most commonly manifested by focal neurological deficits. More than 750,000 stroke cases occur every year in the United States, making it the fifth leading cause of death and the leading cause of disability. Strokes cost more than $70 billion annually, and have a devastating effect on the quality of life of a significant proportion of patients and their caregivers (1).

The mechanisms of ischemic stroke can be divided into embolic (artery to artery or cardioembolic), lipohyalinotic occlusion of small arteries, or in situ thrombosis over an atherostenotic plaque (atherothrombosis). Thrombolysis to recanalize the occlusion and reperfuse the brain, through either pharmacological or mechanical means, is the mainstay of treatment options for patients with AIS. Until recently, intravenous recombinant tissue plasminogen activator (IV-rtPA) was the only approved therapy for patients with AIS presenting within 0 to 4.5 h (2). Although approval of IV-rtPA was a landmark step toward treatment of AIS, more than 50% of patients receiving IV-rtPA were still either severely disabled or dead (3,4). The absolute reduction in chance of poor outcome in patients treated with IV-rtPA within 3 h is 10%, which amounts to a number needed to treat (NNT) of 10. In a 3- to 4.5-h time window, the effect is reduced further, to 7% (NNT of 14) (5,6). Delays in achieving reperfusion, inadequately complete recanalization, and hemorrhagic transformation were some of the limitations of intravenous thrombolysis. To overcome these limitations, minimally invasive endovascular approaches were developed over the last 2 decades. After initial disappointing results from trials using the first generation of mechanical thrombectomy devices, in 2015, endovascular mechanical thrombectomy with a retrievable stent (commonly called a stent retriever), along with IV-rtPA was established as the new standard of care for AIS due to large vessel occlusion (LVO) (7). In this paper, we shall review the evolution of endovascular catheter-based

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

From the [a]Department of Interventional Neuroradiology, Brigham and Women's Hospital, Boston, Massachusetts; [b]Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida; and the [c]Department of Neurosurgery, University of Miami Miller School of Medicine, Miami, Florida. Dr. Yavagal serves as a steering committee member of the SWIFT Prime clinical trial and the RECOVER-Stroke trial; serves as a consultant to Medtronic/Covidien Neurovascular and Aldagen/Cytomedix; and is a data and safety monitoring board member of the ESCAPE trial, for which he has received travel support. Dr. Sacco has received research funding from the National Institute of Neurological Disorders and Stroke, American Heart Association, and Boehringer Ingelheim. Dr. Khandelwal has reported that he has no relationships relevant to the contents of this paper to disclose. Drs. Khandelwal and Yavagal contributed equally to this work.

Manuscript received November 18, 2015; revised manuscript received March 14, 2016, accepted March 16, 2016.

ABBREVIATIONS AND ACRONYMS

AIS = acute ischemic stroke

ASPECTS = Alberta Stroke Program Early CT score

CT = computed tomography

CTA = computed tomography angiography

FIO = functionally independent outcome

IV-rtPA = intravenous recombinant tissue plasminogen activator

LVO = large vessel occlusion

mRS = modified Rankin Score

MT = mechanical thrombectomy

NIHSS = National Institutes of Health Stroke Scale

treatment of stroke, the reasoning behind the overwhelming success of recent endovascular clinical trials in AIS, and their effect on acute stroke care.

EVOLUTION OF AIS TREATMENT

INTRAVENOUS THROMBOLYSIS. IV-rtPA treatment was shown to benefit patients with AIS in the 1995 NINDS (National Institute of Neurological Disorders and Stroke) study. IV-rtPA was a major milestone in stroke treatment, as the first disease-modifying therapy for AIS (3). On the basis of the NINDS study results, in 1996, the Food and Drug Administration (FDA) approved the use of IV-rtPA for patients with AIS presenting within 3 h of symptom onset. Subsequently, in 2008, ECASS (European Cooperative Acute Stroke Study) III showed benefit of IV-rtPA over placebo among those treated within 3 to 4.5 h of symptom onset (6,8). These studies established IV-rtPA as a standard therapy for patients with AIS within 4.5 h of symptom onset. Although the FDA did not modify the original indication for use of IV-rtPA beyond 3 h, recent stroke guidelines from the American Heart Association (AHA) recommended using it up to 4.5 h from onset of symptoms in eligible patients (2). Despite this recommendation, the use of IV-rtPA is estimated to occur in <3% of patients presenting with AIS (9). The narrow therapeutic time window of 4.5 h is the most common reason that patients do not receive IV-rtPA, along with a few others (**Table 1**). Also IV-rtPA has major therapeutic limitations, including unresponsiveness of large thrombi to enzymatic digestion, resulting in a low recanalization rate (13% to 50%) in LVO stroke and a low rate of benefit in the patients having the most disabling strokes (10,11). To overcome these major limitations of IV-rtPA, endovascular approaches have been developed over the last 2 decades using catheters that are delivered intra-arterially to the site of the intracranial clot to recanalize the occluded vessel.

TABLE 1 Contraindications for IV-rtPA in AIS

1. Onset of symptoms more than 4.5 h.*
2. Significant head trauma or prior stroke in previous 3 months.
3. Any history of previous intracranial hemorrhage.
4. Acute bleeding diathesis, including platelet count <100,000, INR >1.7, or PT >17 s.
5. Arterial puncture at noncompressible site in previous 7 days.
6. Recent major surgery within 14 days and recent GI tract hemorrhage within 21 days.
7. Current use of direct thrombin inhibitors or direct factor Xa inhibitors.
8. History of previous intracranial neoplasm, arteriovenous malformation, or aneurysm.
9. CT showing early ischemic changes in more than one-third of MCA artery distribution.

*Criteria for IV-rtPA between 3 to 4.5 h: patient <80 years of age, NIHSS <25 and no prior history of DM and AIS (both), and not taking any oral anticoagulation agent.

AIS = acute ischemic stroke; CT = computed tomography; DM = diabetes mellitus; GI = gastrointestinal; INR = international normalized ratio; IV-rTPA = intravenous recombinant tissue plasminogen activator; MCA = middle cerebral artery; NIHSS = National Institute of Health Stroke Scale; PT = prothrombin time.

INTRA-ARTERIAL THROMBOLYSIS. PROACT (Prolyse in Acute Cerebral Thromboembolism Trial) was the first prospective randomized controlled trial (RCT) to investigate the safety and efficacy of intra-arterial recombinant prourokinase (IA-proUK) and heparin compared with intra-arterial heparin alone, applied within 6 h of stroke symptom onset in patients with middle cerebral artery occlusion (12). This phase II study, which randomized 46 patients, showed a significantly higher recanalization rate with IA-proUK along with a nonsignificant, but higher symptomatic hemorrhage rate. PROACT II, a phase III study of 180 patients, soon followed and showed the clear superiority of IA-proUK in achieving the primary outcome of no or slight disability, defined as a modified Rankin Scale (mRS) of 0 to 2 at 90 days, functionally independent outcome (FIO) in 60% versus 18% ($p < 0.001$) of patients, as well as a greater recanalization rate of 40% versus 25% ($p < 0.04$) compared with intra-arterial (IA) heparin alone. The improved clinical outcome occurred despite a higher symptomatic hemorrhage rate of 10% in the treatment arm compared with 2% in control subjects. Despite the success of PROACT II, the FDA did not approve IA-proUK, and soon afterward, this pharmacological agent was no longer commercially available (13). The AHA 2005 and 2013 guidelines recommended IA thrombolysis in carefully selected patients with middle cerebral artery (MCA) occlusions within 6 h who were not candidates for IV-rtPA (Class I, Level of Evidence: B), but it was not enough to make it a standard of care (14,15).

MECHANICAL THROMBECTOMY

The era of mechanical thrombectomy (MT) began with development of the "mechanical embolus removal in cerebral ischemia" (MERCI) device. The device is made of a corkscrew-shaped nitinol wire that is deployed into the thrombus in the occluded intracranial artery. Both the device and corkscrew are removed as one unit to recanalize the artery acutely. This device was tested for safety and early efficacy in the MERCI trial, a single-arm, multicenter trial of thrombectomy in patients with LVO treated within