THE UNREACHABLE STAR, BUT NOT THE IMPOSSIBLE DREAM

Antonio Culebras, MD, FAAN, FAHA, Seemant Chaturvedi, MD, FAAN, FAHA, American Academy of Neurology Stroke Section, Minneapolis: The vision of thrombolysis for reversal of acute ischemic stroke (AIS) was launched in 1958, but it was not until 1995 that 2 landmark studies, one in Europe and the other in the United States, established IV administration of tissue plasminogen activator (tPA) as an effective treatment for AIS. The National Institute of Neurological Disorders and Stroke study, with a 3-hour treatment window from onset of symptoms to vein puncture, showed more efficacy and had fewer safety concerns than the original European Cooperative Acute Stroke Study (ECASS) trial that had designated 6 hours from symptom onset as the limit for IV infusion of tPA. Since 1995, the administration of IV tPA to reverse the ravages of AIS has become the standard and only validated form of treatment. So much has been published, discussed, commented, editorialized and publicly aired about IV tPA in AIS that one would assume that IV tPA is a universally available form of treatment. In a recent poster presentation at the 65th annual meeting of the American Academy of Neurology (AAN), a group of investigators from the United States reported the global use of IV tPA for AIS by country, income group, and country-level health expenditure per capita. The researchers conducted a systematic review in PubMed from 1997 to 2012. Each country’s publications in any language were reviewed and the results were startling. Of 214 countries and independent territories, 54 (25%) reported use of IV tPA for AIS. In relation to income status, the study revealed IV tPA usage in 3% (1/36) of low-income countries, 13% (7/54) of lower-middle-income countries, 28% (15/54) of upper-middle-income countries, and 44% (31/70) of high-income countries. The authors concluded that IV tPA for AIS has limited use globally, is available to patients in only one-quarter of countries in the higher income brackets, and that barriers to IV tPA use for countries at different income levels must be understood to be overcome. Ironically, stroke incidence might be increasing in lower-income countries as traditional risk factors for stroke become increasingly prevalent in those countries.

We embarked on a tour of the world with the purpose of understanding how IV tPA is used in the 5 continents and what challenges and limitations restrict its administration. A compilation of facts, even though informal, could spearhead development of appropriate remedies. We asked the following question: What is the standard approach to assessment and implementation of therapeutic strategies for acute stroke within the tPA therapeutic window in your country and what affects this standard approach? We also asked that consideration be given to the cost of treatment, professional reimbursement, concerns about patients in rural communities, and variability of treatment throughout the different countries.

In Australia, Graeme J. Hankey and Christopher Levi report for IV tPA administration a therapeutic window of 4.5 hours from onset of symptoms. Protocols are in place to receive early notification of stroke cases, concede high-priority transportation and triage, implement rapid referral to the stroke team, and activate immediate access to brain imaging under the umbrella of a multidisciplinary approach. However, execution of protocols remains suboptimal due to the geography of the country and the population scatter. In addition, lack of adequate financial...
support and fragmentation of efforts among health care providers have created uncertainties. Telemedicine, a logical remedy, remains underdeveloped.

In Finland, Turgut Tatlisumak, also reports a high level of population scatter that has forced the development of telemedicine. Treatment protocols and practice guidelines are organized under the umbrella of a strong public health system that provides free care to all inhabitants. Many patients receive IV tPA “off-label” with no particular safety concerns relative to age, low or high NIH Stroke Scale score, or complete hemiplegia, based on the assumption that several lines of evidence suggest that thrombolysis is reasonably safe under conditions that were regarded as contraindications before. Adequate organization of health services allows for IV thrombolysis rates of up to 31% for hospital-admitted patients. Patient awareness remains a challenge as many patients arrive late after stroke symptom onset.

In China, Yongjun Wang reports that IV tPA is recommended as first-line treatment for AIS within 4.5 hours of symptom onset. Urokinase is administered to patients up to 6 hours from onset of symptoms. Intra-arterial thrombolysis is also available. Only a scarcity of patients are treated due to prehospital delay, in-hospital delay, lack of basic infrastructure, and lack of readiness for stroke thrombolysis of treating clinicians or patients and their families. Poor public knowledge about stroke and ineffective emergency medical systems to deliver stroke patients to capable hospitals remain significant limitations.

In Brazil, Ayrton R. Massaro reports that a few stroke centers began to treat stroke patients with tPA as far back as 1996. Despite efforts by the Brazilian Academy of Neurology and interested neurologists, the delivery of IV tPA remains unequal due to a huge socioeconomic divide. In response, the Brazilian Ministry of Health has undertaken the ambitious task of providing acute stroke care to all Brazilians with a National Stroke Program. Another challenge is the need of rehabilitation to improve functional outcome since the majority of acute stroke patients are discharged from the hospital to their homes.

In Egypt, Nabil Kitchener reports that a Stroke Awareness program recommending the use of IV tPA for treatment of AIS was started in 2009. However, the number of neurologists remains low and therefore incapable of assisting the large population. Other limitations are lack of patient awareness of disease symptoms, crowded traffic impeding transportation to the hospital, a requirement that patients pay the whole cost of tPA, which is a major barrier for its use, inadequate number of stroke units, and paucity of resources. In the absence of IV tPA, neurologists are using antiplatelet loading in acute stroke as well as heparinization for progressive strokes. They are hoping to validate these approaches with a multicenter study assessing the efficacy and safety of heparinization within a defined therapeutic window in AIS.

In the United States, Julius Latorre reports a well-developed system for administration of emergency treatments to patients with AIS. This includes IV tPA and a variety of as yet unproven endovascular procedures. Stroke center certification has standardized the approach to management of patients with AIS but variability continues to exist in availability of services and clinical outcomes. Geographical conditions and temporal factors (weekend vs weekdays) are some of the challenges cited. Development of telemedicine based on the spoke system is advancing quickly and continued expansion of organized stroke care with the recent introduction of comprehensive stroke center certification shows promise in reducing the current variability.

The remedies for implementation of universal acute stroke treatment may not be at hand, but some solutions are already available. Vast population scatters, as reported in Australia and in the United States, may be overcome with telestroke, a branch of telenurology and of telemedicine that is advancing fast. The AAN has recently published a revealing position paper on the status of telenurology. The answer to socioeconomic divides like in Brazil rests in the creation of a strong public health system as reported in Finland. Development of certified stroke centers, like those in the United States, will harmonize and homogenize acute stroke care as new forms of pharmacologic and interventional treatment of acute stroke are added to the armamentarium. None of these treatment modalities would work if the population is not educated in recognizing a stroke. The entire course of action of acute stroke treatment starts the
moment that the patient or caregiver suspects a stroke and contacts the transportation system or rushes to the hospital. Public education is thus the key ingredient in the process that starts with early recognition of stroke and ends in rehabilitation with a favorable outcome. Like Don Quixote, stroke medicine has embarked on a quest based on the belief that timely delivery of IV tPA to patients with AIS in low-income countries or execution of effective endovascular interventions in more advanced societies may be for now an unreachable star, but not an impossible dream.

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UNITED STATES

Julius Gene S. Latorre, MD, Cerebrovascular Division, Department of Neurology, Upstate Medical University, Syracuse, NY: A 63-year-old hypertensive, diabetic man called 911 at 8:00 PM complaining of right-sided weakness that started at 6:30 PM after dinner. The ambulance arrived at the patient’s house at 8:05 PM and he was brought to the nearest stroke center. While en route, the paramedic alerted the stroke center emergency department. The patient arrived at the emergency room at 8:30 PM and was immediately evaluated by the physician. A stroke code was called and the neurologist was at the bedside at 8:40 PM. An 18-gauge IV was inserted by the nurse and blood test for basic metabolic panel, complete blood count, coagulopathy panel, and lipid profile were sent. The NIH Stroke Scale was performed, showing a total score of 10. The time of onset was verified with the patient’s wife, who witnessed the event. A noncontrast CT was done at 8:50 PM and officially read at 8:55 PM, showing absence of signs of hemorrhage or acute infarct. After reviewing the inclusion and exclusion criteria, the patient was deemed eligible for thrombolysis and IV tissue plasminogen activator (tPA) was ordered. The IV tPA was initiated at 9:15 PM, 45 minutes from the time the patient entered the emergency room door, 2 hours and 45 minutes from symptom onset. This scenario is increasingly becoming a routine exercise in many primary stroke centers across the United States.

In the United States, patients with measurable deficit are treated with IV tPA within 3 hours of symptoms. Since 2008, many stroke neurologists have extended the treatment window for
IV tPA to 4.5 hours as long as the patient fulfills additional criteria as used in the European Cooperative Acute Stroke Study 3 trial, despite lack of approval by the Food and Drug Administration (FDA). In addition to IV tPA, patients in comprehensive stroke centers are evaluated further using multimodality imaging using CT or MRI to locate the stenosis or occlusion (CT or MRI angiography of the head and neck) and to quantify the infarct and estimate the size of the ischemic penumbra (CT or MRI perfusion). These additional imaging techniques are incorporated in the emergency imaging of acute stroke patients and done immediately after the noncontrast CT, while the patient is receiving IV tPA. Whether perfusion imaging is useful in clinical decision-making is uncertain. Carefully selected patients with acute occlusion or severe stenosis of intracranial vessels are immediately sent for diagnostic catheter angiography for mechanical thrombectomy or intraarterial thrombolysis. Three devices are currently FDA-approved for intracranial reperfusion: MERCI (2004), Penumbra (2007), and Solitaire (2012). Patients with stroke onset within 8 hours (longer for posterior circulation strokes) are considered for endovascular intervention if large ischemic penumbra is seen on perfusion imaging (at least 20% perfusion mismatch) especially if the infarct core/volume is less than 100 mL.

Blood pressure (BP) medications are typically withheld in the acute phase of stroke, and no intervention is done unless systolic BP goes over 185 mm Hg in patients receiving IV tPA or 220 mm Hg in patients not receiving IV tPA. Acute IV anticoagulation with heparin is not done except in some patients with extracranial arterial dissection. Patients are admitted to the stroke unit if stable, or to the neurocritical care unit if hemodynamically unstable or requiring ventilator support. Antiplatelet medications are started within 24 hours or after 24 hours of IV tPA. Patients are discharged on oral anticoagulation without bridging if atrial fibrillation is diagnosed. Diabetic education and medications are given as necessary with goal glycosylated hemoglobin (HBA1C) of <7%. High-dose statin is given to keep low-density lipoprotein under 100 mg/dL (<70 if the patient has diabetes or coronary artery disease).

The availability of emergency notification using the 911 telephone system (which covers over 96% of the US population) and the proliferation of certified stroke centers across the country (approximately 1 out of 4 acute care hospitals in the United States in 2010 were certified stroke centers, and more than 80% of the US population were within 1 hour’s drive from the nearest stroke center) has helped in increasing the use of IV tPA among eligible patients (currently about 75% of eligible patients receive IV tPA). Certified stroke centers are evaluated based on established performance measures including strict time targets for every segment of emergency stroke management. The current goal is for all eligible stroke patients to be treated with IV thrombolysis within 60 minutes from arrival to the emergency room. Key time targets in the process include performance of patient evaluation by physician within 10 minutes, stroke code activation within 15 minutes, performance of CT or MRI scan within 25 minutes, and interpretation of brain imaging within 45 minutes of patient presentation.

Ambulances transporting acute stroke patients may bypass the nearest hospital to a certified stroke center if the patient can arrive within 2 hours from symptom onset. Some states even have laws mandating this process. Some hospitals without primary stroke center certification have established transfer agreement and referral system with the nearest stroke center either via telemedicine or regular phone consultation with variable capability for remote imaging review by consultant stroke neurologist.

The standard approach in acute stroke management is relatively uniform for hospitals that have received stroke center certification in either rural or urban hospital settings. Due to increased reimbursement rate for patients treated with thrombolysis, there is financial incentive for hospitals to have stroke center certification and avoid being bypassed by ambulances with potential stroke patients. More importantly, patients admitted to stroke centers have improved outcome in terms of reduced 30-day risk of mortality, greater use of thrombolytics, and higher adherence to accepted treatment guidelines.

Despite significant advancement in standardization of acute stroke therapy, variability continues to exist in availability of services and clinical outcome geographically (Stroke Belt) and
temporal factors (weekend vs weekday) as well as IV tPA use. Continued development of organized stroke care with the recent introduction of comprehensive stroke center certification is showing promise in reducing this variability.5

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FINLAND

Turgut Tatlisumak, MD, PhD, Department of Neurology, Helsinki University Central Hospital, Helsinki, Finland: Finland has a relatively large surface area (130,000 square miles) but a small population (5.4 million) and, except the Greater Helsinki region, it is scarcely populated, which brings special challenges to organization of acute stroke care. Finland, similar to other Nordic countries, has a population-based public health system that is practically free to all inhabitants and financed with high revenue rates. All 5 university hospitals have 24/7 neurologists on-call, but local hospitals have neurologists only during office times. Therefore, stroke patients are handled by neurologists at all times in university hospitals and during the daytime in most local hospitals, but by internal medicine residents otherwise. A specialty in emergency medicine will be established soon, but acute stroke care will likely remain neurologist-led in the future.

A patient presenting with symptoms and signs suggestive of stroke must always be transferred to an emergency room with 24/7 expertise in acute stroke care including imaging and laboratory facilities, capability of delivering thrombolysis, and having a stroke unit where available. In underserved areas, the patient is transferred to the nearest hospital. Vital parameters are monitored in the ambulance and a prenotification call alerts the emergency room staff. Reviewing electronic patient records in the hospital and simultaneously checking for blood sugar, blood pressure, body temperature, and heart rhythm, as well as inserting a large-bore IV line during the ambulance ride, saves time. When the patient arrives, a quick clinical evaluation is followed by laboratory testing, noncontrast CT imaging, and a rapid decision whether the patient is eligible for thrombolysis or intra-arterial procedures. IV thrombolysis is usually started on the CT table and when necessary further imaging, i.e., CT angiography and perfusion, are performed after thrombolysis is initiated. If the patient’s condition deteriorates during tissue plasminogen activator infusion, the infusion must be stopped and the patient undergoes a stat CT scan. With appropriate evaluations, stroke mimics are rare and thrombolysis is rather safe in these cases.1 Further, precise etiologic evaluation is not necessary in most cases before thrombolysis, e.g., well-addressed safety in case of cervical artery dissections.2 Door-to-needle times approximating 20 minutes are feasible if the acute care pathway is well-organized.3 Earlier initiation of treatment reduces disability significantly4,5 and should be preferred instead of having more precise data with pretreatment detailed imaging and laboratory testing leading to another 20–30 minutes of delay. After acute treatments are given, the patient is
transferred to the observation room in the stroke unit for at least 24 hours. Admission NIH Stroke Scale (NIHSS) and Glasgow Coma Scale are routine procedures for patient assessment. NIHSS is repeated immediately following thrombolysis and at 24 hours. Recently, the DRAGON⁶ and SEDAN⁷ scores are incorporated to acute evaluation, helping in early prognostics and decision-making for intra-arterial procedures. Although intra-arterial procedures are not evidence-based, they are widely applied in carefully selected cases. We apply highly strict criteria for intra-arterial procedures and carefully review our own results.⁸ Only a minimum diagnostic workup should be done before thrombolysis and everything that can be done later should be deferred. For instance, only blood sugar and quick international normalized ratio (INR) are sufficient among laboratory parameters if patient history and clinical examination do not indicate otherwise.

Criteria for delivering IV thrombolysis differ between countries and institutions. Many present official contraindications stem from randomized controlled trials where safety was a major concern. Half of the thrombolized stroke patients in Helsinki were treated “off-label” with the most common cause for off-label treatment being age over 80 years with no particular safety concerns.⁹ Young age,¹⁰ old age,⁹ sole visual field defect with low NIHSS,¹¹ or complete hemiplegia with high NIHSS¹² alone are not contraindications per se. Currently, several lines of evidence suggest that thrombolysis is reasonably safe in most conditions regarded as contraindications before.

Patients brought to local hospitals in underserved regions have a clear disadvantage in access to adequate stroke care. Therefore, we established a national telestroke network with the Helsinki University Central Hospital being the only hub. The number of spokes reached 11 lately covering a population of 1.2 million. Our preliminary analyses showed that IV thrombolysis is equally safe and effective when given at our emergency room or given through the telestroke video consultation system.¹³

Every institution should have written guidelines for stroke care and maintain a structured training system. We prepared the first written institutional guidelines (the “Red Book”) in 1993 and revise them regularly. Our guidelines are adapted nationwide. We recently demonstrated that when following guidelines carefully, it does not matter whether IV thrombolysis is delivered during the daytime or on-call times or whether delivered by experienced stroke neurologists or neurology residents.¹⁴ Additionally, we established a simulation training program for physicians and emergency room nursing staff and later extended it to medical student education.¹⁵

Adequate organization of health services allows for IV thrombolysis rates up to 31% for hospital admitted patients and 16% on a population-based estimate totaling over 300 IV thrombolysis annually at the Helsinki University Central Hospital.³ Challenges remain especially in patient awareness as many patients arrive late. Good results can be achieved only by combining multi-professional streamlined stroke care along with high-profile research and education.

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Yongjun Wang, MD, Ruijun Ji, MD, PhD, Tiantan Comprehensive Stroke Center, Tiantan Hospital, Capital Medical University, Beijing, China: Although considerable progress has been made in developing effective prevention and treatment strategies for acute ischemic stroke (AIS), substantial challenges remain to improve quality of care. Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) is currently the only evidence-based medical therapy for AIS and was approved by the State Food and Drug Administration of China in 2001. In this commentary, we sought to address the standard therapeutic strategies for AIS within the rtPA therapeutic window and the potential factors that would affect this approach in China.

**Standard therapeutic strategies for AIS within rtPA therapeutic window in China**

As in other national and international stroke guidelines, IV thrombolysis is recommended as first-line treatment for AIS within the therapeutic window by the Chinese stroke guideline. Although there is much variability for stroke thrombolysis throughout China, some general rules have been followed. Generally, it is highly recommended that patients with AIS should be treated with IV tPA within 4.5 hours or with urokinase within 6 hours of symptom onset in China. Intra-arterial thrombolysis (with tPA or urokinase) is an option for treatment of selected patients who have a major stroke of less than 6 hours’ duration due to occlusion of middle cerebral artery and who are not otherwise candidates for IV thrombolysis. In addition, intra-arterial thrombolysis could be an option for treatment of selected patients who have a major stroke of less than 24 hours’ duration due to large artery occlusion in posterior circulation (such as basilar or vertebral artery) and who are not otherwise candidates for IV thrombolysis. Although the menu available for clinicians and interventionists to reopen occluded
arteries has been greatly expanded in recent years, such as IV combination with intra-arterial thrombolysis (bridging fashion), mechanical clot retrieval, and angioplasty and/or stenting, currently these therapies can only be performed in a small number of qualified comprehensive stroke centers in China. Besides neuroimaging examination, some laboratory tests are usually carried out before stroke thrombolysis in China, such as complete blood count (including hematocrit, hemoglobin, platelet count, and white blood cell count), biochemistry tests (including liver function, kidney function, and serum glucose), and coagulation tests (including activated partial thromboplastin time, prothrombin time, international normalized ratio [INR], and fibrinogen). Routinely, head CT is required before tPA administration. If there are signs of neurologic deterioration after tPA administration, head CT will be performed to check for secondary intracranial hemorrhage. The general rules of pre- and post-thrombolysis management (e.g., blood pressure control) are similar to those recommended by American stroke guideline; however, traditional Chinese medicines for neuroprotection are often used post-thrombolysis in China.

Factors potentially affecting stroke thrombolysis in China

In China, the media, government, and authorities have called the attention of the public and of clinicians to stroke. However, based on data from the China National Stroke Registry (CNSR), only 2.4% of AIS patients were treated with either IV or intra-arterial thrombolysis. Potential reasons for this dismal record vary and can be classified into the following 4 categories: 1) prehospital delay; 2) in-hospital delay; 3) lack of basic infrastructure; and 4) lack of readiness of treating clinicians or patients/families for stroke thrombolysis treatment.

The results of China’s QUEST study (a prospective, multicenter, hospital-based registry of patients with acute stroke in urban China) showed that the median time from stroke onset to hospital presentation was 15.0 hours (interquartile range, 2.8–51.0 hours). Similarly, data from the CNSR indicated that the majority (82.9%) of patients with AIS arrived at hospital beyond 3 hours of symptom onset. Based on our experience, there are 2 major factors accountable for long prehospital delay in China: poor public knowledge about stroke (such as inability to recognize stroke signs and symptoms, a wait-and-see attitude, unwillingness to call emergency medical service) and ineffective emergency medical systems to deliver stroke patients to capable hospitals.

Data from the CNSR showed that the median door-to-needle time was 116 minutes. Meanwhile, 68.1% of eligible patients failed to receive thrombolysis due to in-hospital delay. Long process to obtain written consent, delay in completing laboratory tests, and waiting for patients’ families to purchase rtPA (before 2008, IV thrombolysis with rtPA for AIS was not covered by health care insurance) have been identified as major factors associated with in-hospital delay. More importantly, lack of standardized and effective clinical pathways for stroke thrombolysis are the fundamental reasons for long in-hospital delay in China.

Hospitals in China are classified into 3 levels according to location, bed number, staff expertise, and facilities. A Level I is a community-based hospital operating in a street or a village with only the basic facilities and very limited inpatient capability; a Level II hospital is a regional hospital operating in a predesigned administrative area with at least 100 inpatient beds providing acute medical care and preventive care services to populations of at least 100,000 people; a Level III hospital is a large hospital serving as a major tertiary reference center in the provincial capitals and major cities with more than 1,000 beds. Currently, stroke thrombolysis is mainly performed in Level III and some Level II hospitals. For many hospitals in China, there is lack of basic infrastructure (technique and personnel) to perform stroke thrombolysis, especially for community hospitals and hospitals in rural areas and underdeveloped regions.

Among a substantial proportion of Chinese physicians, there is excessive fear of adverse effects of stroke thrombolysis (e.g., symptomatic intracranial hemorrhage) and potential
relevant litigation, especially by emergency physicians who first see the patients with stroke. When obtaining consent, the treating physician might overemphasize the adverse effects, having a negative impact on patients’ or their families’ decision.

**Outlook of stroke thrombolysis in China**

A nationwide program focusing on improving quality of stroke thrombolysis is going on in China (Multidisciplinary and Organized Stroke Thrombolytic therapy Project [MOST]). In the future, health and medical care promotion strategies to improve community awareness of stroke, expanded availability and utilization of ambulance services, implementation of stroke center certification project, creation of effective clinical pathways for stroke thrombolysis, strengthening professional training on stroke thrombolysis, and establishment of telemedicine service are necessary and promising methods to expedite stroke thrombolysis in China.

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**BRAZIL**

**Ayrton Roberto Massaro, MD, Department of Neurology, Hospital Sirio-Libanes, São Paulo, Brazil:** On December 14, 1995, the *New England Journal of Medicine* published the results of the National Institute of Neurological Disorders and Stroke trial and suddenly neurologists from all over the world have started the war against stroke using IV recombinant tissue plasminogen activator (rtPA) within the first 3 hours of stroke onset as their first and strongest weapon against stroke.

Neurologists from the low- and middle-income countries like Brazil quickly realized the major challenges to implement this new treatment in their crowded emergency rooms that threaten delivery of timely care. One important suggestion for neurologists trained before the thrombolytic era is learning to work as a team during the acute care. First, neurologists need to evaluate the burden of stroke in their community and alert public health authorities to ensure that health, social care, and employment services are working together for the benefit of stroke victims, especially in countries with large socioeconomic inequalities.
Noncommunicable diseases including stroke are emergent conditions in low- and middle-income countries due to influence of socioeconomic determinants in the epidemiologic transition process. Countries like the BRICS group (Brazil, Russia, India, China, and South Africa) have among the highest stroke mortality rates and socioeconomic disparities in the world. Health authorities in these countries may identify their Stroke Belt regions measuring the magnitude of socioeconomic inequalities in a geographically defined population (state, city, or borough). This strategy will not only allow to locate resources in regions where the burden of stroke is disproportionately elevated, but also will ultimately help to break major barriers to universal health care access. The most striking example of this situation is seen in the figure, where a simple wall divides 2 contrasting communities living next to each other in São Paulo with different stroke risk profiles and unequal access to the health care system.

Epidemiologic studies demonstrating the burden of stroke in low- and middle-income countries are rare. Therefore, the stroke awareness campaigns should first be directed to the health authorities and hospital administrators to alert them to the economic burden of stroke in their community. At the same time, neurologists should report the burden of stroke in their emergency rooms, reviewing major stroke outcome indicators and treatment costs. Two publications demonstrated not only the substantial acute stroke treatment costs in Brazil, largely related to hospital complications, but also confirmed the cost-effectiveness of using IV rtPA in the acute setting of the Brazilian health care system.2,3

Brazilian neurologists started to improve training programs in acute stroke care before the approval of IV rtPA treatment in the United States. A few neurologists began to introduce the time window concept in their neurologic services. One of the earliest experiences came from a small acute stroke protocol developed at Albert Einstein Hospital in São Paulo and based on the ongoing similar trials running at that time in the United States. Only those patients with a documented intracranial arterial occlusion were included and the authors did not find major
safety concerns in the first 6 patients treated. However, the protocol was stopped due to uncertainties observed by the hospital neurologists regarding this timely oriented “hazard approach.”

After Food and Drug Administration approval in the United States, the use of IV rtPA for acute ischemic stroke became the cornerstone of the stroke centers movement in Brazil. Neurologists started to build a Brazilian Stroke Network with the help of the Brazilian Academy of Neurology to provide educational programs and guidelines for organizing stroke centers. However, this highly skilled group has not equalized the stroke treatment performed in their communities. Gains in knowledge have not reached clinical practice and physicians at the same time during those years. Not only was awareness of stroke symptoms low, but emergency services were not prepared for treating these patients, delaying access to acute stroke care.

Several years later, IV rtPA treatment was approved by the Brazilian Ministry of Health for acute ischemic stroke patients. This was an important step to support neurologists in their battle for the recognition of IV rtPA effectiveness in acute ischemic stroke. Soon after, the Brazilian Academy of Neurology published 2 guidelines, one for acute stroke management and the other for specific use of thrombolytic therapy. Although the proportion of ischemic stroke patients receiving IV rtPA has improved, reaching in some regions 13.7%, the overall IV rtPA stroke treatment in the country remained very low.

The socioeconomic disparities in stroke treatment are largely influenced by the level of education of the target population. Lower level of education prevents patients from identifying major stroke warning signs and calling the national emergency medical service number (192). The World Stroke Organization together with regional and national Stroke Societies has helped to improve stroke awareness in the Latin American region. The National Campaign for the World Stroke Day in Brazil has included many supporters throughout the country during recent years. Recently, the World Stroke Congress in Brasilia has definitively amalgamated Brazil and Latin America within the World Stroke Organization to strengthen its fight against stroke in the region.

Aging of the population is another concern, not only in the developed world, but also in low- and middle-income countries, where elderly are the fastest growing population. One of the major advances in the prior Brazilian Guidelines was the inclusion of elderly patients as a special category with warning considerations to receive IV rtPA. Stroke patients 80 years or older were allowed to receive the treatment under restricted conditions. This approach facilitated early access of the elderly population to thrombolytic treatment in Brazil. This was confirmed in a recent publication, where a significant proportion of elderly stroke patients received IV rtPA in a major Brazilian metropolitan area.

In recent years, Brazilian acute stroke patients have been evaluated in primary and comprehensive stroke centers and offered advanced treatment. The Joint Commission has certified primary stroke centers in Brazil and recently the acute stroke guidelines from the Brazilian Academy of Neurology has also extended the use of IV rtPA up to 4.5 hours from stroke onset. Neurointerventional procedures have increasingly been used in acute stroke patients in Brazil including mechanical thrombectomy with stent retrieval.

One may question whether the low- and middle-income countries are following the right pathway to the future of acute stroke treatment, chasing the boundaries of the therapeutic window using thrombolytic therapy with sophisticated imaging protocols and expensive recanalization tools affordable for few individuals. Instead, maybe they would rather innovate breaking the walls between emergency rooms and patients. One way of doing that is improving prehospital care with telemedicine systems connecting mobile stroke units to comprehensive stroke centers located in strategic areas that would permit rapid access to all stroke patients regardless of socioeconomic status. These strategies might reduce the symptom-to-needle time, allowing a higher efficacy of IV rtPA treatment in large metropolitan areas, where the majority of the Brazilian population lives. In addition, it could offer advanced treatment to selected stroke patients with higher chances of success than presently found.
Finally, several studies have demonstrated that stroke mortality rates in Brazil have progressively declined in recent years. However, the number of stroke survivors with functional incapacity increased. The majority of stroke patients in Latin America are discharged directly home from acute care. The next battle against stroke in these countries will need to facilitate early access to rehabilitation centers for keeping and improving the favorable outcome obtained by the acute stroke treatment.

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EGYPT

Nabil Kitchener, MD, PhD, General Organization for Teaching Hospitals and Institutes, Cairo, Egypt: Neurologists are trying to educate our fellow Egyptians that stroke is a preventable and treatable disease. Early recognition of stroke symptoms prior to arriving to hospitals, and the timing and methods by which patients are transferred to hospitals, are critical to ensure optimal outcome. A validated tool, such as FAST (Face Arm Speech Test), or in Arab countries, BMVSSC (impaired Balance, Movement abnormality, Vision [diplopia or visual loss], Speech, Sensory disturbance, and impaired or lost Consciousness), should be used to screen people with sudden onset of neurologic symptoms for a possible diagnosis of stroke or TIA.

Assessment protocol
There is a standard protocol established in most governmental and teaching hospitals. Prior to being admitted to hospital, the following items should be considered and assessed: positive FAST or BMVSSC; age 18 years or older; if symptoms were noted on waking, exclude thrombolysis; symptom onset within 3 hours (to allow time for assessment and imaging after reaching hospital); and no seizure at onset.
Once a patient has presented to the emergency department (ED), the approved clinical practice guidelines in Egypt give permission to ED staff to activate the stroke code and start the management procedures. Stroke is confirmed by clinical examination using approved checklist and time of onset is determined. The patient is then transported for urgent CT head. Blood pressure (BP) in both arms is manually measured, and repeat higher arm BP is measured after 15 minutes. IV access is put in both arms and blood is examined for random blood sugar, clotting, and international normalized ratio if on warfarin. ECG (and chest X-ray if needed) is performed. Inclusion and exclusion criteria are confirmed; high BP is managed as per protocol; NIH Stroke Scale is performed and repeated after 15 minutes to ensure the patient is not rapidly improving. Decision to thrombolysse must be undertaken by thrombolysing doctor (trained ED, stroke physicians, or neurologist). Treatment is started in the ED and the patient is monitored for complications.

**Thrombolysis with rtPA**

In Egypt, the Stroke Awareness Program started in 2009, when specialized stroke units were created in many teaching and general hospitals (32 units now working). IV thrombolysis is the only approved therapy for acute ischemic stroke.

As recombinant tissue plasminogen activator (rtPA) is recommended for the treatment of acute ischemic stroke when used by physicians trained and experienced in the management of acute stroke, our program aimed to train ED and intensive care unit staff for management of acute stroke patients. As the number of neurologists in relation to number of stroke patients is relatively low, neurology department staffs were responsible for following up the process even if they did not start it.

Thrombolysis with IV rtPA is an effective treatment for acute ischemic stroke. The number of treatable patients is limited because of the narrow time window, and because of contraindications for treatment. It is both surprising and disappointing that only a small proportion of Egyptian patients with acute ischemic stroke are currently treated with thrombolysis. There are many barriers: bystanders and patients need to be aware of the disease symptoms in order to seek medical help; crowded traffic conditions prevent timely arrival of patients at ED; patients must pay the whole cost of rtPA; there are inadequate numbers of stroke units in our country; and there is a paucity of resources.

**Other strategies used for management of acute ischemic stroke**

About 1 in 6 patients in Egypt makes it to the hospital during the 3-hour time window. Only 2%–3% of eligible stroke patients are treated with thrombolysis, due to causes mentioned previously.

Many stroke patients need other therapeutic interventions, so we still use antiplatelets loading in acute stroke, and heparinization for progressively thrombotic strokes, with good outcomes. At first we used heparin at the advice of our older neurologist colleagues, but we are currently conducting a multicenter study for assessing efficacy of heparinization within a defined time window in safe reperfusion in ischemic stroke.

**Patients with acute venous stroke**

People diagnosed with cerebral venous sinus thrombosis (including those with secondary parenchymal hemorrhage) should be managed by using anticoagulation treatment (initially heparin and then warfarin) unless there are comorbidities that preclude its use.

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AUSTRALIA

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The standard approach to the assessment and implementation of therapeutic strategies for acute stroke within 4.5 hours is to adhere to a local protocol developed jointly by staff from the prehospital emergency service, hospital emergency department (ED), neuroradiology service, and acute stroke team. The protocol includes systems to receive early notification by paramedical staff, high-priority transportation and triage, rapid referral from ED staff to the stroke team, and immediate access to brain imaging.1 Plain CT brain scan remains the standard initial imaging strategy, but some specialist centers adopt advanced brain imaging (e.g., CT perfusion, MRI diffusion and perfusion) in a quest to improve selection for thrombolytic therapy.

Thrombolysis with tPA is undertaken in hospitals with 1) a multidisciplinary acute care team trained in the assessment, delivery, and monitoring of patients undergoing thrombolysis, 2) immediate access to CT brain imaging and staff trained to interpret the images, and 3) pathways and protocols that guide medical, nursing, and allied health staff in acute phase management (particularly signs of complications, such as intracranial hemorrhage, and monitoring and managing blood pressure). IV tPA is administered as soon as possible and within 4.5 hours of onset of symptoms to consenting patients who satisfy standard inclusion and exclusion criteria.2-4 It is given under the authority of a physician trained and experienced in acute stroke management. The cost of tPA is Aus $1,725 per 50 mg/50 mL vial. As 2 vials are usually used, the cost is Aus $3,450 (US $3,600) per patient. The cost of tPA is not borne by the federal government (Medicare) but by state government health departments for public patients, and private health care funds (up to Aus $1,200 per year) and individuals for private patients. Antiplatelet therapy, usually aspirin, is delayed for 24 hours after thrombolysis, and usually after a follow-up brain scan has excluded significant bleeding.3 Australian guidelines recommend that all centers maintain a minimum set of deidentified data, which are recorded from all patients treated with thrombolysis and entered into a local or central register to allow monitoring, review, comparison, and benchmarking of key outcomes measured over time.1,3,5

The standard approach is otherwise to admit all people with a diagnosis of suspected stroke to a stroke unit, staffed by a multidisciplinary team, as soon as possible and preferably within 3 hours after stroke onset.6

Despite the standard approach outlined above, implementation is suboptimal.4 Only about 7% of all ischemic stroke patients in Australia undergo thrombolysis, despite thrombolysis rates of 20% in some centers.1,7 Further, only about 39% of patients with acute stroke receive stroke unit care. Despite recent increases in the number of stroke units, they remain too few (n = 74).1

One of the obvious challenges to optimal acute stroke care in Australia is its geography. Australia is a large continent with most of the 23 million population residing in capital cities around the coast yet a substantial minority spread widely throughout a vast rural and remote area. Delivering effective, appropriate, and affordable acute stroke services in all regions remains a goal. For most rural and remote areas, telemedicine is underdeveloped. Small hospitals are
encouraged to provide stroke services that adhere as closely as possible to organized multidisciplinary stroke unit care, but resources (i.e., trained and interested staff, and funding) are limited. Hospitals without stroke units are encouraged to facilitate urgent transfer of patients with suspected acute stroke to the nearest hospital that has a stroke unit. For larger centers with stroke units, one of the main barriers to higher rates of thrombolysis is delay getting to hospital; only 41% of all acute stroke patients arrive in hospital within 4.5 hours. The main culprit is time to seek medical help due to failure to recognize the symptoms of stroke and their significance. Another is that only 1 in 5 hospitals report arrangements with local ambulance services to preferentially transport suspected stroke patients to dedicated centers or to notify the hospital of a stroke admission in advance. Additional barriers are a shortage of stroke specialists and stroke units, lack of practitioner reimbursement for stroke thrombolysis in the private sector, and lack of support for thrombolysis by some members of an integrated thrombolysis service (e.g., the Australian College of Emergency Medicine). The latter has created uncertainty and confusion among some health care providers and purchasers outside the stroke community about the health economic benefits of thrombolysis for acute ischemic stroke. Such fragmentation, rather than unification, has retarded the more widespread implementation of thrombolysis for acute stroke in Australia. Clinical practice improvement programs that aim to augment the implementation of stroke thrombolysis are underway in Australia.

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