ISA: Consensus Statement

Recommendations for the Early Management of Acute Ischemic Stroke: A Consensus Statement for Healthcare Professionals from the Indian Stroke Association

1.0 INTRODUCTION

Stroke is one of the leading causes of disability and death in India. The estimated adjusted prevalence rates of stroke are between 84 and 262 strokes per 100,000 persons in rural areas and between 334 and 424 strokes per 100,000 persons in urban areas.[1] Based on few epidemiological studies conducted from 1971 to 1999 in India, the crude prevalence rate of stroke was reported to between 44 and 842 strokes per 100,000 persons, and the annual incidence rate was between 13 and 124 strokes per 100,000 persons.[2] Stroke-related mortality has increased by 7.8% from 1998 to 2004. During the last one and a half decade, there is an increase of 17.5% in the number of stroke cases in India.[3]

Stroke incidence and mortality are higher in Asian countries than in western countries.[4] In the early 1980s, the prevalence rates of stroke were around 500-700 strokes per 100,000 persons in the western countries[5] and 900 strokes per 100,000 persons in Asian countries.[6] The disparity between the incidence rates of stroke and coronary heart disease (CHD) in Asian and western populations is usually attributed to higher prevalence of hypertension and a lower level of serum total cholesterol in the Asian population.[4,7]

As per the National Vital Statistics Report, cerebrovascular disease (stroke) in the US has now dropped down to the fifth leading cause of death after chronic lower respiratory diseases and accidents while in India it is 2nd leading cause of death. More than 795,000 people suffer from stroke and almost 130,000 patients die because of stroke each year in the United States while in India over 1.5 million stroke occur every year.[8] Loss of these patients from the work force and the extended hospitalization required for recovery has a considerable economic impact.[9]

Strategies and Efforts to Reduce Morbidity and Mortality Due to Stroke

Preventive measures and early interventions can reduce the morbidity and mortality along with the overall cost for management of stroke. This, in turn, would reduce the effect of stroke on all those involved from several perspectives, which are often overlapping: patients, their families and caregivers, primary care physicians, stroke hospitals, and healthcare professionals along with policy makers. Thus, it is essential that family physicians recognize which patients are at a risk for stroke and design systematic approaches for the patients that may include increasing awareness about the prevention and early treatment of stroke.[10]

The approach for early management of adults with acute ischemic stroke can be based on the stroke chain of survival (Table 1) that describes the approach in a stepwise strategy and specifies actions to be followed by patients and family members with recommended actions by out-of-hospital healthcare responders, emergency department (ED) personnel, and in-hospital specialty services.[11]

2.0 OBJECTIVES AND SCOPE

The objective of this consensus document is to provide and delineate a focused update on current recommendations for acute stroke management in India. These recommendations are based on the updated guidelines[12,13,14] for stroke management and care worldwide.

This document includes recommended practices for management of adult patients (over 18 years) with acute stroke (acute phase) from onset to chronic care and focuses on patients with a new clinical event (first stroke or recurrent stroke), and for secondary prevention of stroke.

Primary prevention of stroke and rehabilitation and management of subarachnoid hemorrhage are not within the scope of these guidelines. This consensus document stands as a revision and an update to the Indian Guidelines for Stroke Management 2011.[15] The intended audience includes all health professionals or healthcare planners involved in the management of patients with acute stroke. The applicability can also be extended to prospective family members, caregivers, and general population interested in being aware of stroke and its management.

3.0 RATIONALE OF THE UPDATE

Recently, substantial new, high-quality evidence on clinical efficacy of multiple treatment modalities (especially endovascular treatments) for acute ischemic stroke has emerged in various clinical studies, systematic reviews, and meta-analyses. The recommendations for the current update take cognizance of this are based on various international guidelines including but not limited to the 2013[12] American Heart Association/American Stroke Association (AHA/ASA) guidelines, 2015 AHA/ASA focused update of the 2013 guidelines,[13] Royal College of Physicians guidelines for stroke,[14] and other relevant published data. These recommendations serve to update the existing recommendations of stroke management described in the Indian Guideline for Stroke Management, 2011.[15] To minimize redundancy, the reader is referred to these publications where appropriate.

4.0 METHODOLOGY

Systematic literature reviews, clinical and epidemiology study publications, and clinical and public health guidelines were used to summarize the existing evidence and indicate gaps in the current knowledge and, when appropriate, formulate the recommendations.

5.0 STROKE DEFINITIONS

Based on the recently updated definition, stroke is characterized as a neurological deficit attributed to an acute focal injury of the central nervous system (CNS) by a vascular cause, including cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (Table 2).[16]

The arbitrary nature of the 24-hour time limit and lack of specific pathophysiologic meaning prompted reduction to the 1-hour time limit and later on led to a tissue-based definition driven by advances in neuroimaging. As per the AHA-endorsed revised definition, transient ischemic attack (TIA) is defined as "a transient episode of neurologic dysfunction caused by focal cerebral, spinal cord, or retinal ischemia, without acute infarction."[17,18]

Ischemic stroke (caused by focal cerebral, spinal, or retinal infarction) accounts for 87%[19] of all stroke cases, which is comparable to the Indian burden reported recently. Of the all stroke cases for which computed tomography (CT) imaging was performed, 80.2% of stroke cases in Mumbai[20] and 83.6% of stroke cases in Trivandrum[21] were ischemic. Around 70% of stroke cases in India were reported to be ischemic.[22]

The symptoms of a stroke caused by an embolism usually appear suddenly and are most intense right after the embolic episode while with thrombosis, symptoms (Table 3)may appear more slowly.However this distinction of the 2 mechanisms but may not always be seen. The types and degrees of disability post stroke depend upon the affected or damaged location in the brain. In general cardioembolic strokes tend to be larger and associated with greater degrees of disability.

6.0 ORGANIZATION OF HEALTHCARE SERVICES FOR STROKE

Organized Stroke Care

A stroke unit needs to be a dedicated, geographically clearly defined area or ward in a hospital, where stroke patients are admitted and cared for by a multiprofessional team (medical, nursing, and therapy staff having specialist knowledge, training, and skills in stroke care with well-defined individual tasks, regular interaction with other disciplines, and stroke leadership). The aim of a stroke unit is to provide 24X7 stroke management services.[15]

Stroke units may also include intensive monitoring capabilities and at least basic brain imaging services, including carotid artery imaging to permit close supervision for neurological worsening or other complications. Evidence suggests that stroke unit care significantly reduces mortality and disability after stroke compared with conventional care provided in a general ward.[23] Several non-randomized studies have revealed significantly improved outcomes when patients were admitted directly to a stroke unit rather than assessed at a non-stroke unit centre and transferred

subsequently.[23,24] In addition, functional outcome at three months was found to be better in patients who arrived at the stroke unit within 3 hours of symptom onset.[25]

A systematic review revealed that compared with patients admitted to a general medical ward, those admitted to a stroke unit had a 19% reduction in death, 20% reduction in death or institutionalization, and 21% reduction in institutionalization. There was a 13% reduction in death or dependency and a 12-day reduction in the length of hospital stay in patients admitted to stroke units.[26]

Facilities offering stroke care services can be broadly classified into primary stroke center and comprehensive stroke center. Criteria[27] established for these centers differentiating them from a basic hospital service are described in Table 4. Acute stroke-ready hospitals (ASRHs) are also capable to efficiently and effectively evaluate, diagnose, and treat stroke patients in an emergency department (ED) but do not have a fully organized inpatient system of stroke care.

Ambulance services

Availability of ambulance services is limited in most of the developing countries, especially in rural areas.[28] Dedicated ambulance service is one of the promising methods to help expedite presentation to stroke care service.[29] Ambulance services with pre-notification systems, training of paramedics, and triaging of patients to the most appropriate ED for stroke assessment and management improve the quality of overall management of stroke patients.

The Government of Odisha has initiated free of cost comprehensive pre-hospital emergency medical service, including a fleet of ambulances to cover the entire state of Odisha in a phased manner, that can be availed by dialing the toll-free number 108.[30] Similar services are available in some states across the country, e.g., Punjab.

Door-to-needle time (Door-to-groin puncture time)

Definitive management with thrombolysis is the only effective treatment for eligible acute ischemic stroke patients coming within 4.5 hours of symptoms onset with improved functional outcomes at 3 and 6 months.[16]

For every 15-minute reduction of the door-to-needle time (arrival to emergency room to thrombolysis), there is a 5% lower odds of in-hospital mortality. In patients with a door-to-needle time of ≤60 minutes, the unadjusted mortality rate was 8.6% versus 10.4% in patients with a door-to-needle time of >60 minutes ($P<0.0001$).[31]

Many Indian hospitals lack the necessary infrastructure and organization required to triage and treat stroke patients quickly and efficiently. The existing treatment gaps in stroke care include a dismal rate (0.5%) of thrombolysis for stroke, and non-availability of 24X7 stroke physicians, stroke interventionalists, stroke area maps, stroke care pathways, stroke units, stroke teams, sufficient community awareness programs, and efficient public emergency ambulance systems, which are all responsible factors for the delay in the door-to-needle time.[32] Lack of resources, ignorance, and overpopulation make it even more challenging.[33] Substantial proportion of patients (51%) contact their local or community doctor first rather than going directly to the ED. Contact with local doctor was found to be associated with significant delay.[34,35, 36,37,38,39,40,41,42]

The recommendations regarding the ideal time for each step have been presented in Table 5.[16] Recent guidelines for comprehensive stroke centers have proposed a target door-to-groin puncture time of <1 hour for intra-arterial therapy (IAT)[43]; however, even at stroke centers that are highly experienced with IAT, the 2-hour goal is achieved in only approximately half of the patients.[44] It is a time-critical intervention and can benefit from a systemically implemented protocol-driven approach split into key intervals such as the ED to CT time, CT to intervention laboratory time, and laboratory to puncture time, and puncture to recanalization time. While the methodology can be different in different places based on the available resources, its key elements include clear definition of roles and parallel processing of tasks along with constant monitoring and process improvements for consistent performance.[45,46]

Centres in the west have developed standardized processes for acute stroke management based on reliable, rapid team notification. It includes rapid evaluation and treatment of patients with acute stroke that has led to steep decline in door-to-treatment times and substantial increase in the number of patients (at least 3 times more) treated with tPA. Single-call notification of the acute stroke team can be carried out to improve this process. These systems may reduce the on-call neurologist response time by 90 percent, and also drastically reduce the door-to-CT completion time.[47]

Hospitals treating strokes should have “code strokes,” which can rapidly notify and mobilize the stroke team and effectively reduce the times to treatments (door-to-needle or door-to-puncture times).[48]

Telestroke

Telestroke is an integrated audio and visual remote assessment that can provide acute stroke expertise to hospitals without full-time neurological service. Teleradiology is an important aspect of telestroke wherein radiographic images from one location can be transmitted to another for

diagnostic and consultative purposes. Both government and private sectors should come together to develop stroke systems of care in India (for both urban and rural sectors).

The telemedicine network implemented by the Indian Space Research Organization in 2001 presently extends to around 100 hospitals all over the country and is currently used in India for diagnosing stroke patients, subtyping stroke as ischemic or hemorrhagic, and treating accordingly. However, a dedicated telestroke system for providing acute stroke care is needed. Simpler alternatives like smartphones, online data transfer, and new mobile applications, like WhatsApp, can be used in the current scenario.[49] By using a low-cost smart phone technology and WhatsApp, the state of Himachal Pradesh has successfully implemented telestroke services in the entire state with 12 district hospitals and 4 neurologists. These services have successfully established acute stroke care pathways and thrombolysed patients with acute ischemic stroke at the district level with trained emergency doctors, free of cost to the patients.[32]

Challenges in India

Stroke unit implementation is a big challenge in India. A major hurdle in stroke care provision is the lack of service integration between the authorities, healthcare professionals, and stakeholders involved in the process. Inadequate number of skilled and trained staff is one of the main challenges. There is an urgent need to provide supplementary trainings to healthcare professionals, including nursing staff, as well as training of family members and support workers. Furthermore, the required constant medical supervision for early detection of post stroke complications demands involvement of a relatively larger group of trained healthcare personnel. Dedicated stroke units need monitoring equipments, medications, and adequate bedding and seating arrangements. Lack of awareness and proper infrastructure, limited access to tertiary stroke care, scarce use of tissue plasminogen activator, and poor affordability continues to contribute to inadequate management of stroke.

Several nontraditional risk factors including water-pipe (hookah) use, desi ghee (saturated fatty acids), chewable tobacco, and infectious causes of stroke, including infections causing vasculitis, have been understudied in India. Russell viper snakebite has been reported as a cause of stroke and the squatting position during use of toilets has been proposed as an etiology of stroke.[22]

Recommendations

1. Written emergency protocols for stroke management should be available at all stroke centers.
2. Evolving triage rules, systems and processes, and training new and existing emergency personnel are recommended.

3. A plan for transport (dedicated ambulance service), prenotification, and triage of patients from peripheral medical centers to stroke care centers should be identified.
4. Telestroke and teleradiology systems should be available for sites without in-house imaging interpretation expertise to allow rapid diagnosis and reduce the time for definitive management.
5. Implementation of telestroke consultation along with stroke education and training for healthcare providers can be useful in developing skilled professionals at stroke centers.
6. Stroke care centers should be capable of performing a cranial CT scan or magnetic resonance imaging (MRI) scan within 30 minutes of patient presenting at the center. The center should have a capability of performing at least a non-contrast CT scan 24X7.
7. Door-to-needle time should be reduced to <1 hour as per global recommendations.
8. Stroke care quality measures of the stroke centers should be monitored and analyzed for continuous improvement.

7.0 EMERGENCY EVALUATION AND DIAGNOSIS OF ACUTE PHASE

Early intervention including strategies for the rapid identification, accurate triage, and expedient transportation of stroke patients to appropriate facilities are vital in the acute phase of stroke.[50] Currently, India lacks an organized emergency medical service (EMS) that can provide a fast and responsive service in urban and rural areas. A coordinated participation of EMS with public and private hospitals and increased levels of stroke awareness among the masses will help optimize stroke management in India. In addition, it is insufficient to strengthen only the stroke infrastructure if patients cannot be transported within the treatment window.[51]

Pre-hospital Evaluation and Triaging

There is a need to roll out a mass stroke awareness program to help identify symptoms of stroke. The facial drooping, arm weakness, speech difficulties, and onset time (FAST) test can help detect and enhance responsiveness to stroke patient needs, thereby reducing the door-to-needle time.[52] Data indicate that public knowledge of stroke warning signs is often inadequate.[53] Stroke campaigns and awareness programs relevant to local requirements should be developed.

The Cincinnati Pre-hospital Stroke Scale is a simplification of the 15-item National Institutes of Health Stroke Scale (NIHSS) and evaluates the presence or absence of facial palsy, asymmetric arm weakness, and speech abnormalities in potential stroke patients.[54]

The Los Angeles Pre hospital Stroke Screen (LAPSS) is a longer instrument consisting of 4 history items, blood glucose measurement, and 3 examination items designed to detect unilateral motor weakness (facial droop, hand grip, and arm strength).[55] Based on the results of a few

studies, LAPSS demonstrated identification of acute cerebral ischemia and ICH with a high degree of sensitivity or specificity.[54,56]

The Recognition of Stroke in the Emergency Room (ROSIER) tool incorporates all FAST items and additionally examines visual field deficit, leg weakness, loss of consciousness or syncope, and seizure activity. A ROSIER score, the total of all 7 items, of ≥1 suggests a stroke or TIA, whereas a ROSIER score of ≤0 indicates no stroke.[57] The criteria for these scales have been mentioned in Table 6. It may be considered as one of the appropriate scales used by Indian physicians with a sensitivity of 80%–89% and a specificity of 79%–83%.[58,59]

A revised version of the FAST incorporating seizure assessment may enhance prehospital stroke recognition and decision making, thus improving patient outcomes.[56] Nor et al. showed that initial assessment for stroke screening conducted by a paramedic or a physician using FAST is irrelevant.[60]

Triaging of stroke patients at the ED is essential to allocate adequate resources to rapidly treat stroke patients. The American College of Emergency Physicians recommends a 5-level triaging system like the emergency severity index (ESI) for a busy ED.[61] Stroke patients would ideally come under level 2 in the ESI, indicating a high risk patient who needs immediate attention.

EMS personnel can correctly identify 80% of all strokes if the observer/caller/patient's bystander mentions specific words such as stroke, facial droop, weakness/fall, or communication problem.[62]

The ED patients with a suspected acute stroke should be triaged with the same priority as patients with acute myocardial infarction or serious trauma, regardless of the severity of neurological deficits. The EMS personnel must perform immediate stabilization of the airways, breathing, and circulation (ABC). The recommendations regarding pre-hospital evaluation and management are presented in the Table 7.[16]16

Patient History and Underlying Cause

Patient history should be comprehensive and should be taken within 5 minutes. The time of symptom onset is the most important historical information along with the last seen normal time. For patients with "wake-up" strokes, the time of onset is defined as when the patient was last awake and symptom-free or known to be "normal." The family members and/or other witnesses can be of great help and should be asked the information about the onset time and historical issues of the event.[12, 63]

The overall aim of collecting patient history is not only to identify a possible stroke but also to exclude stroke mimics (conditions with stroke-like symptoms, e.g., primary tumor of brain, metastatic neoplasm of brain, meningoencephalitis, thyrotoxicosis, hypoglycemia [Table 8]), and identify the need for immediate interventions and determine potential causes of stroke for secondary prevention measures.[12]

Physical Examination

A thorough general physical examination needs to be performed to identify other potential causes of patients' symptoms and an ischemic stroke, coexisting comorbidities, or issues that may affect the management of an ischemic stroke.[12] Physical examination should have special attention to the symptoms mentioned in Table 9.[62]

Diagnostic Tests

Various investigations as mentioned in Table 10 should be performed to exclude important alternative diagnoses (especially ICH), assess for serious comorbid diseases, aid in treatment selection, and search for acute medical or neurological complications of stroke.[12]

Laboratory tests to be considered in all patients include measurement of blood glucose, electrolytes with renal function studies, complete blood count with platelet count, cardiac markers, prothrombin time (PT), international normalized ratio (INR), and activated partial thromboplastin time (aPTT). Blood glucose and INR can be measured with point-of-care machines for expedited results. Hypoglycemia may cause focal signs and symptoms that mimic stroke, and hyperglycemia is associated with unfavorable outcomes. Determination of the platelet count and, in patients taking warfarin or with liver dysfunction, the PT/INR is important.[64] Cardiac markers are frequently elevated in acute ischemic stroke, with elevations occurring in 5% to 34% of patients: these elevations have prognostic significance. Elevation of cardiac troponin T is associated with increased stroke severity and mortality risk and worse clinical outcomes.[65,66,67,68]

There must be no delay in fibrinolytic treatment while awaiting the results of diagnostic tests unless a bleeding abnormality or thrombocytopenia is suspected or the patient is on warfarin and heparin or the use of an anticoagulant is uncertain.

Neurological Stroke Scales

Performing standardized neurological examination ensures that the major components of a neurological assessment are evaluated in a timely and uniform fashion. Use of a standardized assessment and stroke scale helps to quantify the degree of neurological deficits, facilitate communication, identify the probable location of vessel occlusion, provide early prognosis, help select patients for various interventions, and identify the potential for developing complications.[12]

The NIHSS and the Canadian Neurological Scale are among the most reliable stroke severity assessment scales. The NIHSS was first developed as a part of National Institute of Neurological Disorder and Stroke (NINDS) study and is one the most commonly used stroke severity tool in clinical trials.[69] It can be performed rapidly and may be administered by a broad spectrum of healthcare providers.[70] The NIHSS has been detailed in Table 6. The CNS includes the following components: comprehension, consciousness level, speech, and motor function (face, arm, and leg).[71]

Neuroimaging

An important step in the evaluation of patients with symptoms of acute stroke is to differentiate between hemorrhagic and ischemic stroke.

Non-contrast head computed tomography (NCHCT) has been widely accepted as the standard method for detecting acute ICH. It needs to be performed and interpreted within 30 minutes of arrival to the ED. Early ischemic changes in NCHCT include loss of gray-white distinction, indistinct insular cortex and obscured basal ganglia, and hyper-attenuated clot in the proximal vessels. NCHCT allows rapid diagnosis and correlation with presenting symptoms, if obvious signs are present.[72,73] However, acute ischemic changes are often subtle and carry variability with intra-observers and inter-observers. The Alberta Stroke Program Early CT Score (ASPECTS), a 10-point scoring system based on imaging features, offers grading of the extent of ischemic changes on NCHCT.[74] Studies have shown that baseline ASPECTS correlates inversely with severity as assessed by the NIHSS within the first 3 hours of middle cerebral artery (MCA) stroke onset. An ASPECTS score of ≤7 has been shown to predict poor functional outcome (78% sensitivity and 96% specificity) and symptomatic hemorrhage (90% sensitivity and 62% specificity).[75]

Standard MRI sequences (T1-weighted, T2-weighted, fluid-attenuated inversion recovery) are relatively insensitive to the changes of acute ischemia. Diffusion-weighted imaging (DWI) is approximately 4 to 5 times more sensitive in detecting acute stroke than NCHCT. Of note,

restricted diffusion is not exclusively observed in acute ischemic stroke but can also be seen in some nonischemic entities. Occasionally, clinical differentiation of seizures from acute stroke may be difficult. Discerning DWI lesions confined to a major vascular territory, a distinctive feature of acute stroke lesions, may also be helpful.[71,72]

Other useful imaging techniques are intracranial vascular imaging (including CT angiography, MR angiography, Doppler ultrasound, and conventional angiography) and extracranial vascular imaging (including carotid Doppler ultrasound, CT angiography, MR angiography, and conventional angiography), and perfusion CT and MRI techniques.

Table 11[76] mentions about the advantages and disadvantages of various imaging techniques.
The potential to detect ischemia and salvageable tissue is almost equal in both CT and MRI. The major drawback of CT is the high radiation dose while in MRI it is the more complicated and time-consuming aspect of the examination. Hence, as per the general practical recommendation, acute stroke patients should be evaluated by native CT followed by CT angiography, with MRI reserved for more chronic cases of brain ischemia or control examinations in stroke patients. However, when state-of-the-art CT and high-quality MR scanners are used, both techniques are practically equivalent in the hands of experienced personnel, and local clinical configurations may often dictate which technique should be used.[77] CT angiography is commonly used in India while there are few studies advocating the use of MR perfusion.

Complications of Late Diagnosis and Treatment

In an acute ischemic stroke, vast numbers of neurons, synapses, and nerve fibers are irretrievably lost every moment when untreated. Quantitative estimates of the pace of neural circuitry loss in human ischemic stroke emphasize the time urgency of acute stroke care. A typical patient with untreated stroke looses 1.9 million neurons each minute. Compared with the normal rate of neuron loss in brain aging, the ischemic brain ages at the rate of 3.6 years each hour without definitive treatment.[78] For every 15-minute reduction of the door-to-needle time (arrival to emergency room to thrombolysis), there is a 5% lower odds of in-hospital mortality.[31] Each 15-minute decrease in treatment delay can provide an average equivalent of 1 month of additional disability-free life.[79]

Of the five stent retriever studies, two studies specified a 6-hour window after stroke onset while the third study specified 6 hours to start treatment.[13] Time-dependent data available from the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke (MR CLEAN) study demonstrated no benefit of treatment beginning after 6 hours.[80]

Time-to-reperfusion including onset-to-reperfusion time and puncture-to-reperfusion time in patients with poor collaterals proved to be an important limiting factor for favorable outcome in a time-dependent fashion.[81] For every hour of reperfusion delay, the initially large benefit of IAT decreases and the absolute risk difference for a good outcome is reduced by 6% per hour of delay.[79]

Recommendations

- The EMS personnel should screen the patient using a validated tool such as FAST to identify stroke or TIA.
- Prehospital care providers should use pre-hospital stroke assessment tools such as the LAPSS or Cincinnati Pre-hospital Stroke Scale.
- Initial management of stroke in the field should be performed as per Table 1.
- The use of stroke rating scale, preferably the NIHSS, is recommended.
- There must be no delay in fibrinolytic treatment while awaiting the results of diagnostic tests, such as the prothrombin time (PT), activated partial thromboplastin time (aPTT), or platelet count, unless a bleeding abnormality or thrombocytopenia is suspected or the patient is on warfarin and heparin or the use of anticoagulant is uncertain. The INR can be rapidly assessed using a point-of-care machine
- Brain imaging should be performed immediately for patients with suspected stroke. A non-contrast CT scan is recommended as the initial imaging should be sufficient in most cases. In centers with multislice CT scanners, CT angiography along with a CT scan should be performed.
- Emergency brain imaging is recommended before initiation of any specific therapy
- Noninvasive imaging of the cervical vessels should be performed routinely as part of the evaluation of patients with suspected TIAs.

8.0 ACUTE TRANSIENT EVENT (TRANSIENT ISCHEMIC ATTACK, TIA) MANAGEMENT

This section covers the management of a TIA (defined in Section 5) from the onset of first symptoms suggesting a possible occurrence of acute cerebrovascular event. In people who have a history of TIA, the incidence of subsequent stroke is as high as 11% over the next 7 days and 24-29% over the following 5 years.[82] Several studies have demonstrated the relation between TIA and an elevated long-term stroke risk.[83,84] The short term risk of stroke has also been demonstrated to be particularly high, exceeding 10% in span of 90 days.[85,86] One quarter to one half of the recurrent strokes occurring within 3 months after the first episode, have been reported to occur within the first 2 days.[87, 88] The age, blood pressure, clinical features, duration of TIA,

and presence of diabetes ($ABCD^2$) scale[89] based on clinical data available before neuroimaging can be used to estimate the risk of stroke after TIA.

Recommendations

- Patients with a suspected TIA, should be assessed as soon as possible for their risk of subsequent stroke by using a validated scoring system such as $ABCD^2$ (Table 12).This score can be assessed even by a nurse or a primary physician.
- Patients with suspected TIA who are at a high risk of stroke (eg an ABCD2 score of 4 or above) should receive:
    - ➢ aspirin or clopidogrel (each as a 300 mg loading dose and 75 mg thereafter) and a statin immediately
    - ➢ Admission to a hospital for observation and investigations
    - ➢ Specialist assessment and investigation (Carotid doppler, Echocardiography) within 24 hours of onset of symptoms
    - ➢ Adequate measures for secondary prevention introduced as soon as a specific risk factor is identified.
- Patients with crescendo TIA (two or more TIAs in a week), atrial fibrillation or those on anticoagulants should be treated as being at high risk of stroke even though they may have an ABCD2 score of 3 or below.
- Patients with suspected TIA who are at low risk of stroke (eg an ABCD2 score of 3 or below) should receive:
    - ➢ aspirin or clopidogrel (each as a 300 mg loading dose and 75 mg thereafter) and a statin, eg. simvastatin / Atorvastatin / Rosuvastatin 40 mg started immediately
    - ➢ specialist assessment and investigations as soon as possible, but definitely within 1 week of onset of symptoms
    - ➢ measures for secondary prevention introduced as soon as the diagnosis is confirmed, including discussion of the individual risk factors.
- In patients who have a suspected TIA who need brain imaging (that is, those in whom vascular territory or pathology is uncertain) should undergo diffusion-weighted MRI or CT scan.

9.0 GENERAL MANAGEMENT AND SUPPORTIVE CARE

Oxygenation

Maintaining adequate tissue oxygen saturation of >94% is important during periods of acute cerebral ischemia to prevent hypoxia and potential worsening of the neurologic injury. Supplemental oxygen should be administered if there is evidence of hypoxia. Hyperbaric oxygen therapy (HBOT) may be used to treat patients with ischemic neurological symptoms secondary to air embolism or decompression sickness. However, a few randomized control trials have shown either beneficial results or no improvement in the outcomes; the possibility of clinical benefit needs to explored further before recommending HBOT as a practice.[90,91, 92]

Antihypertensives

In patients with acute stroke, blood pressure may be elevated for the first 24–48 hours. Antihypertensive agents should be withheld unless the diastolic blood pressure is above 120 mmHg or the systolic blood pressure is above 220 mmHg. When antihypertensives are indicated, lowering of blood pressure should be done cautiously (Table 13) to minimize the risk of relative hypotension. Parenteral agents, such as labetalol, or an intravenous (IV) infusion of nicardipine or labetalol may be necessary for adequate blood pressure control among patients who are candidates for treatment with thrombolytic agents.[93] Careful management of blood pressure is critical before, during, and 24 hours after alteplase administration. Thrombolytic therapy should not be given to patients who have a systolic blood pressure above 185 mmHg or a diastolic blood pressure above 110 mmHg despite repeated attempts to lower blood pressure to the desired level.[12]

Enhanced Control of Hypertension and Thrombolysis Stroke Study (ENCHANTED) compared low dose versus normal dose of r-tPA and intensive blood pressure reduction versus standard reduction in thrombolysed patients.[94] The BP lowering arm of ENCHANTED is ongoing and it might answer this question of optimal Blood pressure for Acute stroke patients.

Insulin

Hypoglycemia can cause focal neurologic signs that mimic stroke and can itself lead to brain injury. Moreover, hyperglycemia is associated with poor outcomes.[95] Therefore, prompt measurement and normalization of serum glucose concentration is important. Subcutaneous insulin can be administered to keep glucose levels lower than 180 mg/dL.[96]

Antipyretics

Increased body temperature in patients with acute ischemic stroke has been associated with poor neurologic outcome, possibly due to increased metabolic demands, enhanced neurotransmitter

release, and increased free radical production. Maintaining normothermia improves the prognosis of patients. This was proved in two meta-analyses showing that significantly higher morbidity and mortality rates are associated with high body temperature after stroke in hyperthermic patients compared with normothermic patients.[97],[98]

Source of infection should be identified in all febrile patients or those at risk for infection. Pneumonia, urinary tract infections, and secondary sepsis are common causes of mortality after stroke during hospitalization. An indwelling bladder catheter should be avoided.

Cardiac monitoring

Cardiac monitoring should begin in the prehospital setting and continue throughout the initial assessment and management of the acute phase. Continuous cardiac monitoring is indicated for at least the first 24 hours after stroke.[99,100]

Prevention of venous thrombosis

Patients with acute ischemic stroke in advanced age, immobility, severe paralysis, and atrial fibrillation have an increased risk of deep vein thrombosis(DVT). Pulmonary embolism accounts for a significantly higher in-hospital mortality rate (31.5%)[101]. Anticoagulants should be given to prevent deep vein thrombosis and pulmonary embolism. Low molecular weight heparin / unfractionated heparin can be used for prevention of DVT.

Nasogastric feeding

All patients irrespective of the stroke severity should be assessed optimally for ability to swallow before they are allowed to eat or drink. A validated swallow screen tool should be applied for assessment. An abnormal gag reflex, impaired voluntary cough, dysphonia, and cranial nerve palsies are important pointer for the risk. If necessary, a nasogastric tube can be inserted to provide feedings and to expedite administration of medications.

Recommendations

- Supplemental oxygen should be administered to maintain oxygen saturation >94%.
- Patients who have elevated blood pressure and are otherwise eligible for treatment with IV rtPA should have their blood pressure carefully lowered so that their systolic blood pressure is <185 mmHg and their diastolic blood pressure is <110 mmHg before fibrinolytic therapy is initiated.
- Blood pressure should be maintained below 180/105 mmHg for at least the first 24 hours after IV rtPA treatment.

- Sources of hyperthermia (temperature >38°C) should be identified and treated, and antipyretic medications should be administered to lower temperature in hyperthermic patients with stroke.
- Hypoglycemia (blood glucose <60 mg/dL) should be treated in patients with acute ischemic stroke.
- Subcutaneous insulin should be administered to hyperglycemic patients.
- Cardiac monitoring is recommended to screen for atrial fibrillation and other potentially serious cardiac arrhythmias that would necessitate emergency cardiac interventions. Cardiac monitoring should be performed for at least the first 24 hours.
- DVT prophylaxis should be initiated in the early phase except in patients who are thrombolysed in which case it should be started 24 hours after IV tPA administration

10.0 DEFINITIVE TREATMENT

10.1 Intravenous thrombolysis

Recombinant Tissue-Type Plasminogen Activator

Intravenous recombinant tissue-type plasminogen activator remains the only approved treatment worldwide for patients within the first 4.5 hours of the onset of acute stroke. Recombinant t-PA was first approved in 1996 based on the results of a 2-part National Institute of Neurological Disorder and Stroke (NINDS) rtPA Study for use within the first 3 hours after the onset of stroke.[68] Four subsequent trials, the European Cooperative Acute Stroke Study (ECASS I and ECASS II)[102,103] and the Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke (ATLANTIS A and B)[104,105] showed results similar to the NINDS study. In a pooled individual patient level analysis of these four trials, a benefit of therapy in the 3- to 4.5-hour window was observed. The results of ECASS III trials showed improved outcomes for carefully selected patients treated 3 to 4.5 hours after a stroke. The Third International Stroke Trial (IST-3) demonstrated some benefit of IV rtPA administered within 6 hours of symptom onset. A meta-analysis of 12 IV rtPA trials with 7012 enrolled patients confirmed the benefits of IV rtPA administered within 6 hours from symptom onset (odds ratio [OR], 1.17; 95% confidence interval [CI], 1.06–1.29; P=0.001) compared with placebo, and reinforced the importance of timely treatment by showing highest benefit in patients treated within 3 hours from symptom onset (OR, 1.53; 95% CI, 1.26–1.86; P<0.0001).[106]

Treatment with IV rtPA initiated within 1.5 hours of symptom onset was associated with an OR of 2.81 (95% CI, 1.75–4.50) for favorable outcome at 3 months compared with placebo. The OR for good outcome at 3 months for treatment with IV rtPA initiated within 1.5 to 3 hours was 1.55 (95% CI, 1.12–2.15) compared with 1.40 (95% CI, 1.05–1.85) within 3 to 4.5 hours and 1.15 (95% CI, 0.90–1.47) within 4.5 to 6 hours. The clinical trial evidence indicates the fundamental

importance of minimizing the total ischemic time and restoring blood flow to threatened but not yet infarcted tissue as soon as feasible. Table 13 summarizes the findings of major clinical trials for IV rtPA.[107]

Eligibility criteria for IV-rtPA therapy

Over the past few decades, an plethora of clinical data has proven the safety and efficacy of IV tPA in eligible patients. The eligibility criteria have evolved over time based on expert opinion and recent clinical trial data. Initiating early treatment is an important factor in successful thrombolytic therapy, followed by selection of appropriate candidates for thrombolysis. Intracranial hemorrhage is an absolute contraindication for reperfusion therapies. Evidence from clinical studies supports the timely use of imaging to exclude hemorrhage in stroke patients before initiating IV thrombolytic therapy.[108] The ECASS I predicted an increased risk of brain hemorrhage and poor clinical outcomes in patients with early signs or infarction in more than one-thirds of the MCA territory and undergoing IV thrombolysis within 6 hours of stroke onset. [101] Ischemia involving more than one-thirds of the MCA territory on images obtained within the 0- to 6-hour window constitutes a relative contraindication to IV thrombolysis.

All three randomized stroke trials [NINDS, Echoplanar imaging thrombolytic evaluation trial (EPITHET), and Third International Stroke Trial (IST-3)] that included patients ≥80 years of age provided evidence of the benefits of alteplase for older patients with acute ischemic strokes. Evidence from these clinical trials suggested that there should be no upper limit of the NIHSS score for patients otherwise eligible for alteplase presenting to medical attention within 3 hours of onset of symptoms. The ECASS III trial included thrombolytic therapy in the extended window period from 3 to 4.5 hours with the addition 4 exclusion criteria: age >80 years, NIHSS score >25, history of diabetes and prior stroke, and taking oral anticoagulants. Prevalance of symptomatic intracranial hemorhage (sICH) is variable (0%-36%) and is higher in patients taking anticoagulants even with subtherapeutic INR at the time of thrombolysis.[109] Table 14 summarizes the standard inclusion exclusion criteria for selection of patients for IV rtPA. Currently the exclusions have further evolved and some from the original NINDS trial have been removed.

Recommendations[13]

- Intravenous alteplase should not be administered to patients whose CT reveals any type of acute intracranial hemorrhage.
- IV alteplase (0.9 mg/kg; maximum dose 90 mg) is recommended for selected patients who may be treated within 3 hours of onset of ischemic stroke.

- IV alteplase is recommended for administration to patients in the time period of 3 to 4.5 hours after stroke onset taking into consideration additional exclusion criteria: age >80 years, NIHSS score >25, history of diabetes and prior stroke, and those taking oral anticoagulants.
- For patients with severe stroke and those with mild but disabling stroke symptoms, IV alteplase is indicated within 3 hours of symptom onset of ischemic stroke.
- In patients eligible for IV alteplase, benefit of therapy is time dependent, and treatment should be initiated soonest. The door-to-needle time should be <60 minutes from hospital arrival (emergency room).
- IV alteplase may be used in patients who have a history of warfarin use and an INR of ≤1.7 but not in those with an INR of >1.7
- In patients who have received a dose of LMWH within the previous 24 hours, IV alteplase is not recommended.
- The use of IV alteplase in patients taking direct thrombin inhibitors and direct factor Xa inhibitors has not been firmly established and relevant laboratory investigation must be consulted to determine the residual anticoagulant effect.
- IV rtPA may be considered reasonable in some cases if patients have a normal thrombin time (TT), activated partial thromboplastin time (aPTT), and prothrombin time (PT), but this should be a subject of future research.[110]

Tenecteplase

Tenecteplase is a modified tissue plasminogen activator that is more fibrin-specific, more resistant to plasminogen activator inhibitor and has a half life longer than alteplase.[111] However potential advantage of delayed clearance or prolonged half life in acute ischemic stroke is yet to be determined. Molecules with longer half-life may augment the ICH risk in the setting of ischemic stroke; though this remains to be proven clinically.[112] Three phase II trials have evaluated the efficacy and safety of tenecteplase in doses of 0.1, 0.25 and 0.4 mg/kg against alteplase in acute ischemic stroke.[113,114,115] A meta-analysis of these trials (n=291) showed no significant difference between any dose of tenecteplase and alteplase for either efficacy or safety end points.[116] Most studies had early neurological improvement (at 24 hrs) and penumbra salvaged based on the CT perfusion as the primary end point. Phase III clinical trials (TASTE [ACTRN12613000243718] and ATTEST-2 [NCT02814409]) are ongoing and will provide more conclusive evidence on its efficacy and safety in large numbers of AIS patients. The Study of Tenecteplase Versus Alteplase for Thrombolysis (Clot Dissolving) in Acute Ischemic Stroke "NOR-TEST" has recently been completed and the results presented.* 1107 ischemic stroke patients were randomly assigned to tenecteplase, **0.4 mg/kg bolus**, or alteplase, 0.9 mg/kg infusion within 4.5 hours of symptom onset. The drugs were comparable on outcomes using

modified Rankin score 0-1 sugesting no major difference between two drugs. The rates of intracerebral hemorrhage were similar in two groups. Formal publication is awaited to assess the results in detail.

Biosimilar Tenecteplase has been evaluated in Indian patients for the treatment of acute ischemic stroke at doses of 0.1 and 0.2 mg/kg in an open-label, single-arm, non-randomized studies.[117,118] The clot lysis activity of the biosimilar tenecteplase was 72%-78% in standardized clot lysis assays as against 97%-100% for the innovator tenecteplase.[119] The drug although has been recently approved in India, at a dose of 0.2 mg/kg within 3 hours of stroke onset, the efficacy of this dose has not been completely established. Other thrombolytic agents (e.g. streptokinase, reteplase, desmoteplase) are not currently approved for use in AIS.

10.2 Endovascular Revascularization (Guidelines being published separately)

Early reperfusion is crucial for the good outcome of reperfusion therapy. The recanalization efficacy of IV rtPA is not as high as that of endovascular treatment especially when there is occlusion of larger intracranial arteries such as the internal carotid artery (ICA) or proximal MCA.[120] A recanalization rate of 6% and 30% was observed with IV rtPA in the terminal ICA and M1, respectively.[121] In addition, a large proportion of patients still present > 4.5 hours after the onset of stroke symptoms and are compelled to be excluded from rtPA therapy. These limitations of rtPA therapy have prompted widespread use of endovascular therapy to treat patients having contraindications for rtPA therapy to improve recanalization rates. Especially in the Indian context, endovascular therapy is one of the viable options because of poor availability of resources and delayed presentation (outside door-to-needle window period).[122]

Endovascular revascularization includes intra-arterial fibrinolysis, mechanical clot retrieval with the Mechanical Embolus Removal in Cerebral Ischemia (MERCI) Retrieval System (Concentric Medical, Inc, Mountain View, CA, USA), mechanical clot aspiration with the Penumbra System (Penumbra, Inc, Alameda, CA, USA), and acute angioplasty and stenting. Different intra-arterial agents have been used for thrombolytic treatment of acute ischemic stroke. These include tissue plasminogen activator (tPA), urokinase (UK), and prourokinase (pro-UK). Mechanical thrombectomy devices are divided into two major groups based on their mechanism of action: those that use an approach distal (retrievers) or proximal to thrombi (aspiration devices). The MERCI was the first stroke mechanical thrombectomy device approved by the FDA in 2004. The aspiration devices include the Penumbra System (Penumbra Inc.), the QuickCat (DSM Inc., PA, USA), and PRONTO (Vascular Solutions Inc., MN, USA) extraction devices.[123] A summary of trials involving endovascular therapies is available in Table 15.

Recent times have seen completion of major trials of endovascular therapy and establish it as an accepted treatment for proximal large vessel occlusive stroke. A meta-analysis of eight trials included 1313 patients who underwent endovascular thrombectomy and 1110 patients who received standard medical care with tPA. Endovascular therapy was associated with a significant proportional treatment benefit across modified Rankin scale (mRS) scores (OR, 1.56; 95% CI, 1.14–2.13; P=0.005). Functional independence at 90 days (mRS score, 0-2) occurred among 557 of 1293 patients (44.6%; 95% CI, 36.6%-52.8%) in the endovascular therapy group versus 351 of 1094 patients (31.8%; 95% CI, 24.6%-40.0%) in the standard medical care group (risk difference, 12%; 95% CI, 3.8%-20.3%; OR, 1.71; 95% CI, 1.18-2.49; P=0.005). Compared with standard medical care, endovascular thrombectomy was associated with significantly higher rates of angiographic revascularization at 24 hours (75.8% vs. 34.1%; OR, 6.49; 95% CI, 4.79-8.79; P<0.001) but no significant difference in rates of symptomatic intracranial hemorrhage within 90 days (70 events [5.7%] vs. 53 events [5.1%]; OR, 1.12; 95% CI, 0.77-1.63; P=0.56) or all-cause mortality at 90 days (218 deaths [15.8%] vs. 201 deaths [17.8%]; OR, 0.87; 95% CI, 0.68-1.12; P=0.27).[124]

Recommendations[13]

- All patients eligible for IV rtPA should receive IV rtPA even if endovascular treatments are being considered.
- Reduced time from symptom onset to reperfusion with endovascular therapies is associated with better clinical outcomes. To ensure benefit, reperfusion to thrombolysis in cerebral infarction (TICI) grade 2b/3[125] should be achieved as early as possible and within 6 hours of stroke onset.
- Patients should receive endovascular therapy with a stent retriever if they meet all the following criteria:
    - ➢ prestroke mRS score 0 to 1,
    - ➢ acute ischemic stroke receiving IV rtPA within 4.5 hours of onset according to guidelines from professional medical societies,
    - ➢ causative occlusion of the ICA or proximal MCA (M1),
    - ➢ age ≥18 years,
    - ➢ NIHSS score ≥6,
    - ➢ ASPECTS score ≥6, and
    - ➢ treatment can be initiated (groin puncture) within 6 hours of symptom onset.
- When treatment is initiated beyond 6 hours from symptom onset, the effectiveness of endovascular therapy is uncertain for patients with acute ischemic stroke who have causative occlusion of the ICA or proximal MCA (M1).

- In carefully selected patients with anterior circulation occlusion who have contraindications to IV rtPA, endovascular therapy with stent retrievers completed within 6 hours of stroke onset is reasonable.
- The technical goal of the thrombectomy procedure should be a TICI 2b/3 angiographic result to maximize the probability of a good functional clinical outcome.
- If endovascular therapy is contemplated, a noninvasive intracranial vascular study is strongly recommended during the initial imaging evaluation but should not delay IV rtPA (if indicated in eligible patients).
- Noninvasive intracranial vascular imaging should then be obtained as quickly as possible.
- When mechanical thrombectomy is pursued, stent retrievers such as Solitaire and Trevo are generally preferred to coil retrievers such as MERCI. The relative effectiveness of the Penumbra system versus stent retrievers has not been characterized.

10.3 Combined Intravenous and Intra-arterial Fibrinolysis

The combined IV and IA fibrinolysis approach can address the concern that delays to IA therapy may negate the potential benefits of more efficacious recanalization. This allows immediate initiation of IV fibrinolysis in an emergency setup, followed by transportation of the patient to the angiographic suite for further titrated IA fibrinolytic therapy, if necessary. This approach has been evaluated in a series of pilot trials showing mixed findings.[126,127,128] As demonstrated in a post-hoc pooled analysis of the Interventional Management of Stroke I and II pilot trials, reducing the time to reperfusion with endovascular therapies (like IV fibrinolysis) is likely to be pivotal in achieving the best clinical outcomes. Table 16 summarizes the findings of studies with the combined approach.[129]

10.4 Role of Anticoagulants

Anticoagulants are prescribed in an effort to prevent first or recurrent stroke, especially in patients with cardioembolism due to atrial fibrillation and large artery atherosclerotic disease. Several clinical trials have demonstrated increased risk of bleeding complications with early administration of unfractionated heparin[130] or LMWH and danaparaoid[131]. Early administration of anticoagulants does not show reduction in risk of early neurological worsening or early recurrent stroke.[132,133] Early anticoagulation should be avoided when potential contraindications to anticoagulation are present, such as a large infarction (based on clinical syndrome or brain imaging findings), uncontrolled hypertension, or other bleeding conditions.

Nonvitamin K antagonists (dabigatran, rivaroxaban, apixaban, and edoxaban) have been shown to prevent stroke or systemic embolization in patients with atrial fibrillation[134] and have been

approved by the US FDA for preventing stroke and systemic embolism in patients with atrial fibrillation.

Recommendations:

- Urgent anticoagulation, with the goal of preventing early recurrent stroke, halting neurological worsening, or improving outcomes after acute ischemic stroke, is not recommended for the treatment of patients with acute ischemic stroke.
- Initiation of anticoagulant therapy within 24 hours of treatment with IV rtPA is not recommended.

10.5 Antiplatelets

Various oral antiplatelet agents including aspirin, clopidogrel, and dipyridamole are being used routinely for treatment of acute ischemic stroke. Some clinical trials have shown mixed results[135,136] but these data do not provide solid evidence for the benefit of using antiplatelet agents in the management of acute ischemic stroke. Early treatment with aspirin plus extended-release dipyridamole for TIA or ischemic stroke within 24 hours of symptom onset (EARLY) trial[137] and Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial[138] suggested that in patients who received fibrinolytic therapy, both early and late initiation of antithrombotic therapy for the secondary prevention of recurrent stroke appeared to be safe.

Administration of aspirin within 48 hours after stroke has demonstrated a small but statistically significant decline in mortality and unfavorable outcomes. However, data regarding utility of other antiplatelet agents, including clopidogrel alone or in combination with aspirin, for treatment of acute ischemic stroke are limited and those on the safety of antiplatelet agents when given within 24 hours of IV fibrinolysis are lacking. The relative indications for the long-term administration of antiplatelet agents to prevent recurrent stroke are included in other guidelines and advisory statements.[139,140]

Inhibitors of the platelet glycoprotein IIb/IIIa receptor[141,142] like abciximab[143, 144] and parenterally administered glycoprotein IIb/IIIa receptor blockers[145,146,147,148,149,150] are also being studied in patients with acute ischemic stroke. However, more research is needed to determine the role of these agents in acute ischemic stroke management.

Recommendations

- Oral administration of aspirin (initial dose of 325 mg) within 24 to 48 hours after acute ischemic stroke onset is recommended as part of overall management.

- Administration of aspirin (or other antiplatelet agents) as an adjunctive therapy is recommended after 24 hours after IV tPA.

1. Surgical Interventions

Carotid Endarterectomy

Carotid endarterectomy (CEA) involves removal of the source of thromboembolic debris leading to reduction in stroke recurrence and restoration of normal perfusion pressure to the ischemic penumbra in the brain. A delay in intervention may reduce the potential benefit of revascularization.[151] However, early intervention may also lead to transformation of ischemic infarction to hemorrhagic infarction and increased edema or hyperperfusion syndrome from sudden restoration of normal perfusion pressure to the brain. Table 17 highlights few studies demonstrating the effects of this intervention.[152,153,154,155,156,157]

Recommendations

- Usefulness of emergent or urgent CEA when clinical indicators or brain imaging suggests a small infarct core with large territory at risk (e.g., penumbra), compromised by inadequate flow from a critical carotid stenosis or occlusion, or in the case of acute neurological deficit after CEA, in which acute thrombosis of the surgical site is suspected, is not well-established and needs further evidence.

11 TREATMENT OF ACUTE NEUROLOGICAL COMPLICATIONS

Clinical deterioration can occur in 25% of patients after initial stroke assessment,[158,159] possibly because of stroke progression, brain edema, hemorrhage, and recurrent ischemia. Multidisciplinary care is required for management of the potential complications due to complexity of stroke.

Ischemic Brain Edema

Delayed deterioration caused by edema of the infarcted tissue often occurs after acute cerebral infarction.[160] Cerebral edema occurs in all infarcts especially in large volume infarcts. Edema may produce a range of clinical findings from being clinically silent and not associated with new neurological symptoms to precipitous fatal deterioration, depending on stroke location, infarct volume, patient age, and degree of pre-existing atrophy.[161] Cytotoxic edema normally peaks 3 to 4 days after injury,[162] but early reperfusion of a large volume of necrotic tissue can accelerate and worsen the edema towards malignancy course with decreased cerebral perfusion pressure within the first 24 hours.[163] Careful observation is required in patients with severe stroke or posterior fossa infarctions enabling early intervention to address potentially life-threatening edema.

- Medical management

Management of cerebral edema aims to reduce or minimize edema formation before clinically significant increases in intracranial pressure (ICP) happens and the interventions may include the following:

- restriction of free water to avoid hypo-osmolar fluid
- osmotherapy includes IV mannitol (0.25 to 0.5 g/kg) and/or glycerol or 3% normal saline
- acute IV bolus of 40 mg of furosemide
- avoidance of excess glucose administration
- minimization of hypoxemia and hypercarbia
- treatment of hyperthermia
- avoidance of antihypertensives, particularly those that induce cerebral vasodilatation
- elevation of the head end of the bed to 20° to 30° to assist in venous drainage
- initiation of ICP management when edema produces increased ICP including hyperventilation, hypertonic saline, osmotic diuretics, intraventricular drainage of cerebrospinal fluid, and decompressive surgery.

The death rate in patients with increased ICP remains as high as 50% to 70% despite intensive medical management.[164] Hence, the above interventions need to be considered temporizing, extending the window for definitive treatments.

- Decompressive Surgery

The secondary involvement of the frontal and occipital lobes during a primary brain stem compression, presumably attributable to anterior cerebral and posterior cerebral artery compression against dural structures, can greatly limit the potential for a meaningful clinical recovery or even survival. Surgical decompression with decompressive hemicraniectomy performed within 48 hours of stroke onset in patients of 18 to 60 years of age with malignant infarctions significantly reduced mortality from 78% to 29% and significantly increased favorable outcomes.[165] Similar benefit was observed in patients with dominant and nondominant hemisphere infarctions, but the outcome was affected in older patients who had worse outcomes.[166] Surgical decompression can reduce mortality from 80% to ≈20%[167] but the decision to perform decompressive surgery may be individualized due to the risk of survival with moderate to severe disability.[168]

Hemorrhagic Transformation

Ischemic infarction may be accompanied by petechial hemorrhage occurring in patients not treated with recanalization strategies[169] or symptomatic hemorrhage in patients after IV rtPA and IA recanalization strategies and anticoagulant use.[170] It can also occur in patients not undergoing reperfusion therapies who may require similar vigilance, especially in patients with larger

strokes, older age, or with a cardioembolic pathogenesis. Most hemorrhages occur within the first 24 hours after IV rtPA; majority of hemorrhages occurring within the first 12 hours are fatal. The symptoms include worsening neurological symptoms, decreasing mental status, headache, increased blood pressure and pulse, and vomiting.[171]

If a patient demonstrates signs of symptomatic hemorrhage, any remaining IV rtPA should be withheld immediately. An emergent noncontrast CT scan and a complete blood count, coagulation parameters (PT, aPTT, INR), type and screen, and fibrinogen levels should be tested. Antithrombotics can be used safely after hemorrhagic infarction.[172]

As mentioned in a case report, no further hematoma expansion was reported after use of tranexamic acid in the treatment of an IV rtPA–associated hemorrhage in a Jehovah's Witness stroke patient.[173] Evacuation may be considered for large hemorrhages but smaller hematomas may be tolerated without clinical relevance[174] since cerebellar hemorrhagic conversion is more likely to become symptomatic.[175]

Seizures

Some of the studies reported the following incidences of seizures after ischemic infarction:

- Varied incidences with most reports indicating an incidence of <10%[176]
- Increased incidence in patients with hemorrhagic transformation[177]
- Varied incidences of recurrent and late-onset seizures.[178]

Little to no information is available regarding the effects of prophylactic anticonvulsants after ischemic stroke or its long-term use after seizure.

Recommendations[12]

- Patients with major infarctions are at high risk for brain edema and increased ICP. Measures to lessen the risk of edema and close monitoring of the patient for signs of neurological worsening during the first few days after stroke are recommended.
- Decompressive surgical evacuation of a space-occupying cerebellar infarction is effective in preventing and treating herniation and brain stem compression.

12.0 STROKE REHABILITATION

Evidence describes rehabilitation as a major contributor to positive outcomes for stroke survivors. The effects of stroke cannot be reversed but rehabilitation should be aimed to improve function and/or prevent deterioration of function, and to achieve the highest possible level of independence: physically, psychologically, socially, and financially. The outcome depends largely upon the time when rehabilitation is commenced and the facilities provided. Early commencement of rehabilitation provides better outcomes for stroke survivors.[27] In addition, rehabilitation provided in a dedicated Stroke Rehabilitation Unit has shown better outcomes than in a general ward.

The rehabilitation depends on the patient's needs and may work on improving one or more of the following skills:

- Self-care skills such as feeding, grooming, bathing, toileting, and dressing
- Mobility skills such as transferring, walking, or self-propelling a wheelchair
- Communication skills in speech and language
- Cognitive skills such as memory or problem solving
- Social skills for interacting with other people

The rehabilitation techniques or services may include one or more of the following:

- Rehabilitation nursing
- Physical therapy
- Occupational therapy
- Speech-language pathology
- Audiology
- Recreational therapy
- Nutritional care
- Rehabilitation counseling
- Social work
- Psychiatry/Psychology
- Patient/Family education
- Support groups

There is strong evidence for physical therapy interventions favoring intensive highly repetitive task-oriented and task-specific training in all phases after stroke.[179] In high quality randomized clinical trials, the effect of task-oriented exercise training to restore balance and gait and for strengthening the lower paretic limb was strongly evident.[180]

The National Stroke Foundation Clinical Guidelines 2010 recommends that all patients including those with severe stroke, who are not receiving palliative care, be assessed by a specialist rehabilitation team before discharge from hospital regarding their suitability for ongoing rehabilitation. A future follow-up assessment and/or revaluation for patients discharged into long-term care, to identify opportunities to access public rehabilitation services is also needed, where appropriate.

Rehabilitation is part of the continuum of care that has to be offered in outpatient or inpatient settings. Home-based rehabilitation is being commonly practiced and can be encouraged; however, evidence in the Indian setting is needed.

13.0 PREVENTION

Risk Factors

The Framingham Heart Study and other international prospective epidemiological studies identified the major atherogenic risk factors for stroke as hypertension, diabetes mellitus, hyperlipidemia, and smoking. Based on the results of a case-control study in the West Central India, diabetes mellitus, hypertension, tobacco use and low hemoglobin were the main risk factors for ischemic stroke. [181]Cross-sectional community based case-control study for risk factor analysis in Kolkata demonstrated that hypertension was the most important risk factor for stroke. [182] Another community based cross-sectional case-control study demonstrated heart disease, hypertension, and smoking to be significantly associated with stroke.[183]

The risk factors of stroke can be hereditary, function of natural process, or result from a person's lifestyle as presented in Table 18.[184,185]

Primary Prevention

A number of risk factors are amenable to prevention and early intervention and can be targeted across the different stages of disease. Table 19 summarizes the effectiveness of drug therapies for the primary prevention of first-ever stroke.[186]

Secondary Prevention

Secondary prevention includes measures to reduce the risk of recurrence of stroke in patients who have had TIA or stroke. The following risk factors should be evaluated within one week of the onset of acute phase:

- Hypertension
- Diabetes mellitus
- Smoking
- Carotid artery stenosis (for those with nondisabling stroke)

- Artial fibrillation or other arrhythmias
- Structural cardiac disease
- Investigation of rare causes in the absence of above mentioned risk factors

The secondary prevention measures include, but are not limited to[49]

- Antiplatelet therapy for all patients with established noncardiac causes of ischemic stroke unless there is an indication of anticoagulation, including aspirin, or combination of aspirin and dipyridamole or clopidogrel etc
- Oral anticoagulation for patients with ischemic stroke associated with mitral wall disease, prosthetic heart valves, or within 3 months of myocardial infarction
- NOACs should be preferred over VKAs in cases of nonvalvular atrial fibrillation.
- Lowering of blood pressure for all patients using diuretics or combination of diuretics and an angiotensin converting enzyme inhibitor
- Carotid intervention along with other secondary measures
- Lipid lowering therapy including use of statins

Not all stroke patients may be good candidates for all of the secondary prevention measures due to contradicting conditions and hence one or more of these measures need to be implemented on case-to-case basis. Long-term management of lifestyle risk factors and adherence to recommended medications (particularly in relation to the management of hypertension, cholesterol, and diabetes), carotid artery surgery and antiplatelet therapies are essential for effective secondary stroke prevention. Table 20 describes the effectiveness of secondary prevention initiatives.[49]

Lifestyle Measures

The following lifestyle measures can aid in timely recovery as well as secondary prevention of stroke[15]:

- Regular exercise
- Smoking cessation and avoiding environmental smoke
- No alcohol or remaining within safe drinking limits
- Effective weight loss
- Use of low fat dairy products and products based on vegetable and plant oils, and reduction of red meat intake
- Reduction of salt intake

14.0 STROKE CARE QUALITY DETERMINANT AND BENCHMARKING

The provision of performance measure (PM) benchmarks in cardiac care has been shown to improve adherence leading to effective stroke management.[187] In the Stroke Practice Improvement Network (SPIN) study, the baseline data were used to derive the below-mentioned achievable benchmarks for nine in-hospital PMs. These PMs were not meant to quantify the quality of care of the hospital but to include different aspects of acute stroke care: hyper-acute care, in-hospital care, and discharge care.[188]

- door-to-needle time of ≤ 1 hour for tPA
- screening for dysphagia
- prophylaxis for deep vein thrombosis (DVT)
- warfarin for atrial fibrillation
- discharge on antithrombotics
- tPA considered
- etiology documented
- smoking assessed and counsel given
- stroke education and resources given

Action plans like the Global Stroke Guidelines and Quality Action Plan include similar measures and can be used to inform stroke policy and setting strategic directions to elevate standards of care for people with stroke. The key quality indicators in these action plans provide a mechanism and opportunity for benchmarking of stroke care delivery, with a common goal of achieving high quality comprehensive stroke care. Successful implementation with similar action plans may have a significant positive effect on decreasing mortality and morbidity from stroke.[189]

A formative research study aimed to systematically develop educational intervention for management of post stroke disability for stroke survivors in India, and evaluate the feasibility and acceptability of delivering the intervention by using smart phones and with caregiver support. [190]

“Care for Stroke” is a smart phone-enabled, educational intervention for management of physical disabilities following stroke. It is delivered through a web-based, smart phone-enabled application and includes inputs from stroke rehabilitation experts in a digitized format. Evaluation indicated that the Care for Stroke intervention was feasible and acceptable in an Indian context. An assessment of effectiveness is now warranted.[191] Data suggest that opportunities exist for establishing programs like Get With The Guidelines®-Stroke (GWTG-Stroke) in India.[192]

15.0 FUTURE SCOPE

The gaps between the new evidence-based knowledge and the current guidelines can act as triggers for conducting future extensive research in form of clinical trials, case series, etc. Data of patients with stroke regarding the utility of endotracheal intubation in management of critically ill patients, induced hypothermia as a treatment, prophylactic administration of medications to prevent cardiac arrhythmias, efficacy of mechanical flow augmentation techniques, benefit of long-term prophylactic anticonvulsant use after ischemic stroke, safety or efficacy of adjunctive anticoagulation, safety of antiplatelet agents when given within 24 hours of IV fibrinolysis, and routine use of hyperbaric oxygen in treatment of patients with acute ischemic stroke are limited.

The usefulness of other antithrombin medications, other antiplatelet agents (clopidogrel alone or in combination with aspirin), and precise timing of initiation for long-term secondary prevention, except dabigatran, efficacy of near-infrared laser therapy in acute phase, effectiveness of urgent anticoagulation for treatment of patients with arterial dissection or vertebrobasilar disease, and role of anticoagulants as an adjunct in addition to mechanical or pharmacological fibrinolysis has not been established. Limited data are available regarding the utility of early statin administration, use of external compression of the veins in the lower extremities, role of angioplasty and stenting of the extracranial carotid arteries in the early management of acute stroke, safety and efficacy of CEA in various subsets of patients with acute stroke, optimal timing for revascularization and its role in emergency management of stroke. Although several devices have resulted in recanalization with acceptable safety, direct comparative data between the devices are not available.

In India, thrombolysis is not possible in majority of patients due to delay in reaching hospital, no early access to scanning facility, lack of infrastructure, and high cost required for thrombolytic and/or endovascular therapy. Thus, for patients who reach after 6 hours of acute ischemic stroke, only supportive treatment is offered. This creates the scope for research on adjuvant therapy, which may help to improve stroke outcome. In addition, a continued research is required to identify the best means for triaging patients and integrating non-stroke centers with PSCs and CSCs due to the challenges in building effective stroke systems.

16.0 KEY RECOMMENDATIONS

The key recommendations include the following:

- Certified stroke units/centers and better emergency transport systems
- Emergency brain imaging should be performed before initiation of any specific therapy
- Door-to-needle time of ≤60 minutes from hospital arrival
- IV rtPA to be initiated as quickly as possible (within 1 hour, if possible) in patients eligible for IV rtPA
- Endovascular therapy preferably with stent retrievers should be performed for all eligible patients with proximal large vessel occlusion.
- Cardiac monitoring within at least 24 hours to screen for atrial fibrillation and other potentially serious cardiac arrhythmias
- Continuation of previously described antihypertensive drugs, unless otherwise indicated
- Patient monitoring for stroke-related complications, bleeding complications after IV rtPA, infections, and glucose levels
- Primary prevention strategies to promote general awareness
- Better palliative care

Conclusion

The burden of acute ischemic stroke and its risk factors in India calls for a sound public health initiative to stem the epidemic. Modern medicine has now entered in an era of proactive approach. Management of patients with acute ischemic stroke is multifaceted, and indications for definitive therapies vary among patients. Early intervention is crucial and requires shortening of prehospital period. This is possible through education of patients and healthcare professionals and optimization of transport strategies. Availability and access to stroke centers/units with Telestroke expertise will help to treat a larger number of acute stroke patients. There is an urgent need for efforts to be put in place for an intervention program that is complemented with a robust surveillance mechanism to monitor, evaluate, and guide policies and programs regarding acute stroke management in India.

It has been demonstrated in a pilot mode that it is feasible to establish surveillance for cardiovascular disease risk factors at the community levels. It has been scaled up to the national level, and is now included in the National Programme for Prevention and Control of Diabetes, Cardiovascular Diseases and Stroke. The future of surveillance systems lies in its timeliness, systems approach, and enduring partnerships for an effective stroke management guideline with quality standards.

REFERENCES

[1] Banerjee TK, Das SK. Epidemiology of stroke in India. Neurology Asia 2006; 11: 1 – 4

[2] Pandian JD, Sudhan P. Stroke Epidemiology and Stroke Care Services in India. Journal of Stroke 2013;15(3):128-134 http://dx.doi.org/10.5853/jos.2013.15.3.128

[3] Burden of disease in India. New Delhi: Ministry of Health and Family Welfare, Government of India; 2005. Background papers for the National Commission on Macroeconomics.

[4] Ueshima H, Sekikawa A, Miura K, Turin TC, Takashima N, Kita Y. Cardiovascular Disease and Risk Factors in Asia: A Selected Review. Circulation. 2008 Dec 16; 118(25): 2702–2709. doi: 10.1161/CIRCULATIONAHA.108.790048.

[5] Kurtzke JF. Epidemiology of cerebrovascular disease. In Siekert RG, ed: Cerebrovascular Survey. Report of the Joint Council of the Subcommittee on cerebrovascular Disease, National Institute of neurological and communicable Disorders and Stroke and the National Heart and Lung Institute. Rochester, Minnesota: Whiting Press, 1980: 135-76.

[6] Wallin MT, Kurtzke JF. Neuroepidemiology. In:Bradley WG, Daroff RB, Fenichel GM, et al. eds:Neurology in Clinical Practice. Philadelphia:Butterworth Heinemann, 2004: 763-79.

[7] Valappil AV, Chaudhary NV, Praveenkumar R, Gopalakrishnan B, and Girija AS. Low cholesterol as a risk factor for primary intracerebral hemorrhage: A case–control study. Ann Indian Acad Neurol. 2012 Jan-Mar; 15(1): 19–22. doi: 10.4103/0972-2327.93270

[8] CDC, NCHS. Underlying Cause of Death 1999-2013 on CDC WONDER Online Database, released 2015. Data are from the Multiple Cause of Death Files, 1999-2013, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Accessed Feb. 3, 2015.

[9] Roger VL, Go AS, Lloyd-Jones DM, Adams RJ, Berry JD, Brown TM, *et al.* Heart disease and stroke statistics-2011 update: A report from the American Heart Association. Circulation 2011;123:e18-209.

[10] Solberg LI. The KISS principle in family practice: keep it simple and systematic. Fam Pract Manag. 2003;10:63–6.

[11] Jauch EC, Cucchiara B, Adeoye O, Meurer W, Brice J, Chan YY, Gentile N, Hazinski MF. Part 11: adult stroke: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care [published correction appears in Circulation. 2011;124:e404]. Circulation. 2010;122(suppl 3):S818–S828.

[12] Jauch EC, Saver JL, Adams HP Jr, Bruno A, Connors JJ, Demaerschalk BM et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013 Mar;44(3):870-947. doi: 10.1161/STR.0b013e318284056a. Epub 2013 Jan 31.

[13] Powers WJ, Derdeyn CP, Biller J, Coffey CS, Hoh BL, Jauch EC et al. Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke 2015 Oct;46(10):3020-35. doi: 10.1161/STR.0000000000000074. Epub 2015 Jun 29.

[14] National clinical guideline for stroke. Prepared by the Intercollegiate Stroke Working Party. Royal College of Physicians. Fourth edition 2012.

[15] Prasad K, Kaul S, Padma MV, Gorthi SP, Khurana D, Bakshi A. Stroke management. Ann Indian Acad Neurol. 2011 Jul; 14(Suppl1): S82–S96. doi: 10.4103/09722327.83084 [PMCID: PMC3152174]

[16] Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A et al. An Updated Definition of Stroke for the 21st Century: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2013;44:2064-2089; doi: 10.1161/STR.0b013e318296aeca

[17] Easton JD, Saver JL, Albers GW, Alberts MJ, Chaturvedi S, Feldmann E, et al. Definition and evaluation of transient ischemic attack: a scientific statement for healthcare professionals from the American Heart Association/American Stroke Association Stroke Council; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Radiology and Intervention; Council on Cardiovascular Nursing; and the Interdisciplinary Council on Peripheral Vascular Disease. Stroke 2009; 40:2276. doi: 10.1161/STROKEAHA.108.192218

[18] Albers GW, Caplan LR, Easton JD, Fayad PB, Mohr JP, Saver JL, et al. Transient ischemic attack--proposal for a new definition. N Engl J Med. 2002 Nov 21. 347(21):1713-6.

[19] Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics—2015 update: a report from the American Heart Association. *Circulation*. 2015 ;e29-322.

[20] Dalal PM, Malik S, Bhattacharjee M, Trivedi ND, Vairale J, Bhat P, et al. Population-based stroke survey in Mumbai, India: Incidence and 28-day case fatality. Neuroepidemiology. 2008;31:254–261.

[21] Sridharan SE, Unnikrishnan JP, Sukumaran S, Sylaja PN, Nayak SD, Sarma PS, et al. Incidence, types, risk factors, and outcome of stroke in a developing country: The Trivandrum Stroke Registry. Stroke. 2009;40:1212–1218.

[22] Wasay M, Khatri IA, Kaul S. Stroke in South Asian Countries. Nature Reviews Neurology; 2014; 10:135-143. doi:10.1038/nrneurol.2014.13

[23] Muller R, Pfefferkorn T, Vatankhah B, Mayer TE, Schenkel J, Dichgans M, et al. Admission facility is associated with outcome of basilar artery occlusion. Stroke;2007;38(4):1380-3.

[24] Perez de La Ossa N, Sanchez-Ojanguren J, Palomeras E, Millan M, Arenillas J, Dorado L, et al. Influence of the stroke code activation source on the outcome of acute ischemic stroke patients. Neurology 2008;70(15):1238-43.

[25] Silvestrelli G, Parnetti L, Paciaroni M, Caso V, Corea F, Vitali R, et al. Early admission to stroke unit influences clinical outcome. European Journal of Neurology 2006;13(3):250-5.

[26] Health Quality Ontario. Effectiveness of stroke unit care: a special report [Internet]. Toronto: Queen's Printer for Ontario; 2014 October. 42 p.

[27] National Stroke Foundation. Acute Stroke Services Framework 2008: A Framework to Enable the Delivering and Monitoring of Optimal Acute Stroke Care Across Australia. Melbourne: National Stroke Foundation; 2008

[28] Durai Pandian J, Padma V, Vijaya P, Sylaja PN, Murthy JM. Stroke and thrombolysis in developing countries. Int J Stroke 2007;2:17-26.

[29] Ashraf V V, Maneesh M, Praveenkumar R, Saifudheen K, Girija A S. Factors delaying hospital arrival of patients with acute stroke. Ann Indian Acad Neurol [serial online] 2015 [cited 2016 Mar 11];18:162-6.

[30] 108 Services, National Ambulence Service. A joint initiative of MoHFW, Gol and Govt. of Odisha

[31] Fonarow GC1, Smith EE, Saver JL, Reeves MJ, Bhatt DL, Grau-Sepulveda MV, Olson DM, Hernandez AF, Peterson ED, Schwamm LH. Timeliness of tissue-type plasminogen activator therapy in acute ischemic stroke: patient characteristics, hospital factors, and outcomes associated with door-to-needle times within 60 minutes. Circulation. 2011 Feb 22;123(7):750-8. doi: 10.1161/CIRCULATIONAHA.110.974675. Epub 2011 Feb 10.

[32] Padma Srivastava M V. Management of stroke: The triumphs and the travails. Neurol India 2016;64, Suppl S1:6-7

[33] Pandey S. Challenges in neurological practice in developing countries. Indian J Public Health 2012;56:227-30

[34] Derex L, Adeline P, Nighoghossian N, Honnorat J, Trouillas P. Factors influencing early admission in a French stroke unit. Stroke. 2002;33:153–9.

[35] Ferro JM, Melo TP, Oliveira V, Crespo M, Canhao P, Pinto AN. An analysis of admission delay of acute strokes. Cerebrovasc Dis. 1994;4:72–5.

[36] Harraf F, Sharma AK, Brown MM, Lees KR, Vass RI, Kalra L. A multicentre observational study of presentation and early assessment of acute stroke. BMJ. 2002;325:17.

[37] Morris DL, Rosamond W, Madden K, Schultz C, Hamilton S. Prehospital and emergency department delays after acute stroke: The Genentech stroke presentation survey. Stroke. 2000;31:2585–90.

[38] Evenson KR, Foraker RE, Morris DL, Rosamond WD. A comprehensive review of prehospital and in-hospital delay times in acute stroke care. Int J Stroke. 2009;4:187–99.

[39] Jin H, Zhu S, Wei WJ, Wang J, Liu M, Wu Y, et al. for China QUEST (Quality Evaluation of Stroke Care and Treatment) Investigators. Factors associated with prehospital delays in the presentation of acute stroke in urban China. Stroke. 2012;43:362–70.

[40] Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Factors delaying hospital admission in acute stroke: The Copenhagen stroke study. Neurology. 1996;47:383–7.

[41] Kothari R, Jauch E, Broderick J, Brott T, Sauerbeck L, Khoury J, et al. Acute stroke: Delays to presentation and emergency department evaluation. Ann Emerg Med. 1999;33:3–8.

[42] Carroll C, Hobart J, Fox C, Teare L, Gibson J. Stroke in Devon: Knowledge was good, but action was poor. J Neurol Neurosurg Psychiatry. 2004;75:567–71.

[43] Leifer D, Bravata DM, Connors JJ III., Hinchey JA, Jauch EC, Johnston SC et al. Metrics for measuring quality of care in comprehensive stroke centers: detailed follow-up to Brain Attack Coalition comprehensive stroke center recommendations: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2011; 42:849-877.

[44] Sun CH, Ribo M, Goyal M, Yoo AJ, Jovin TG, Cronin CA et al. Door-to-puncture: a practical metric for capturing and enhancing system processes associated with endovascular stroke care, preliminary results from the rapid reperfusion registry. J Am Heart Assoc. 2014; 3:e000859

[45] Ansaar T Rai, Matthew S Smith, SoHyun Boo, Abdul R Tarabishy, Gerald R Hobbs, Jeffrey S Carpenter. The ‘pit-crew’ model for improving door-to-needle times in endovascular stroke therapy: a Six-Sigma project. J NeuroIntervent Surg doi:10.1136/neurintsurg-2015-012219

[46] Mehta BP, Leslie-mazwi TM, Chandra RV et al. Reducing Door-to-Puncture Times for Intra-Arterial Stroke Therapy: A Pilot Quality Improvement Project. J Am Heart Assoc. 2014; 3: e000963 originally published November 11, 2014 doi: 10.1161/JAHA.114.000963

[47] Rapid team notification accelerates acute stroke treatment at St. John Hospital and Medical Center. PerfectServe, Inc.2015

[48] Rapid team notification accelerates acute stroke treatment at St. John Hospital and Medical Center. PerfectServe, Inc.2015

[49] Srivastava PV, Sudhan P, Khurana D, Bhatia R, Kaul S, Sylaja PN, Moonis M, Pandian JD. Telestroke a viable option to improve stroke care in India. Int J Stroke. 2014 Oct;9 Suppl A100:133-4. doi: 10.1111/ijs.12326. Epub 2014 Jul 18.

[50] Model of stroke care 2012. Neurosciences health network. Department of Health, State of Western Australia (2012).

[51] Sharma M, Sethi NK. Meeting the challenges of stroke in India. Neurology January 7, 2014 vol. 82 no. 1 95-96. doi: http://dx.doi.org/10.1212/01.wnl.0000442494.46850.f1

[52] Wall HK, Beagan BM, O'Neill J, Foell KM, Boddie-Willis CL. Addressing stroke signs and symptoms through public education: the Stroke Heroes Act FAST campaign. *Prev Chronic Dis*. 2008;5:A49.

[53] Jurkowski JM, Maniccia DM, Dennison BA, Samuels SJ, Spicer DA. Awareness of necessity to call 9-1-1 for stroke symptoms, upstate New York. Prev Chronic Dis. 2008;5:A41.

[54] Harbison J, Hossain O, Jenkinson D, Davis J, Louw SJ, Ford GA. Diagnostic Accuracy of Stroke Referrals From Primary Care, Emergency Room Physicians, and Ambulance Staff Using the Face Arm Speech Test. Stroke. 2003; 34: 71-76. doi: 10.1161/01.STR.0000044170.46643.5E

[55] Chen S, Sun H, Lei Y, Gao D, Wang Y, Wang Y, Zhou Y, Wang A, Wang W, Zhao X. Validation of the Los Angeles pre-hospital stroke screen (LAPSS) in a Chinese urban emergency medical service population. PLoS One. 2013 Aug 7;8(8):e70742. doi: 10.1371/journal.pone.0070742. eCollection 2013.

[56] Kidwell CS, Starkman S, Eckstein M, Weems K, Saver JL. Identifying stroke in the field: prospective validation of the Los Angeles prehospital stroke screen (LAPSS). Stroke. 2000;31:71–76. doi: 10.1161/01.STR.31.1.71

[57] Fothergill RT, Williams J, Edwards MJ, Russell IT, Gompertz P. Does Use of the Recognition Of Stroke In the Emergency Room Stroke Assessment Tool Enhance Stroke Recognition by Ambulance Clinicians? Stroke. 2013;44:00-00. DOI: 10.1161/STROKEAHA.13.000851

[58] Purrucker JC, Hametner C, Engelbrecht A, et al. Comparison of stroke recognition and stroke severity scores for stroke detection in a single cohort. J Neurol Neurosurg Psychiatry. 2015;86(9):1021-8.

[59] Mingfeng H, Zhixin W, Qihong G, et al. Validation of the use of the ROSIER scale in prehospital assessment of stroke. Ann Indian Acad Neurol. 2012;15:191-5.

[60] Nor AM, McAllister C, Louw SJ, Dyker AG, Davis M, Jenkinson D, Ford GA. Agreement Between Ambulance Paramedic- and Physician-Recorded Neurological Signs With Face Arm Speech Test (FAST) in Acute Stroke Patients. *Stroke* 2004;35:1355-1359.

[61] M McHugh, Tanabe P, McClelland M, Khare RK. More Patients Are Triaged Using the Emergency Severity Index Than Any Other Triage Acuity System in the United States. Acad Emerg Med 2012 Jan; 19(1):106-09. doi: 10.1111/j.1553-2712.2011.01240.x.

[62] Ramanujam P, Castillo E, Patel E, Vilke G, Wilson MP, Dunford JV. Prehospital transport time intervals for acute stroke patients. J Emerg Med. 2009;37:40–45.

[63] Prasad K, Kaul S, Padma MV, Gorthi SP, Khurana D, Bakshi A. Stroke management. Ann Indian Acad Neurol. 2011 Jul; 14(Suppl1): S82–S96. doi: 10.4103/09722327.83084

[64] Kerr G, Ray G, Wu O, Stott DJ, Langhorne P. Elevated troponin after stroke: a systematic review. Cerebrovasc Dis. 2009;28:220–226.

[65] James P, Ellis CJ, Whitlock RM, McNeil AR, Henley J, Anderson NE. Relation between troponin T concentration and mortality in patients presenting with an acute stroke: observational study. *BMJ*. 2000;320:1502–1504.

[66] Di Angelantonio E, Fiorelli M, Toni D, Sacchetti ML, Lorenzano S, Falcou A, Ciarla MV, Suppa M, Bonanni L, Bertazzoni G, Aguglia F, Argentino C. Prognostic significance of admission levels of troponin I in patients with acute ischaemic stroke. *J Neurol Neurosurg Psychiatr*. 2005;76:76–81.

[67] Jensen JK, Kristensen SR, Bak S, Atar D, Høilund-Carlsen PF, Mickley H. Frequency and significance of troponin T elevation in acute ischemic stroke. *Am J Cardiol*. 2007;99:108–112.

[68] Ay H, Koroshetz WJ, Benner T, Vangel MG, Melinosky C, Arsava EM, Ayata C, Zhu M, Schwamm LH, Sorensen AG. Neuroanatomic correlates of stroke-related myocardial injury. *Neurology*. 2006;66:1325–1329.

[69] 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

[70] Lyden P, Raman R, Liu L, Emr M, Warren M, Marler J. National Institutes of Health Stroke Scale certification is reliable across multiple venues. *Stroke*. 2009;40:2507–2511

[71] Retrospective Assessment of Initial Stroke Severity: Comparison of the NIH Stroke Scale and the Canadian Neurological Scale. Cheryl D. Bushnell, Dean C.C. Johnston and Larry B. Goldstein. Stroke. 2001;32:656-660 doi: 10.1161/01.STR.32.3.656.

[72] Tong E, Hou Q, Fiebach JB, Wintermark M. The Role of Imaging in Acute Ischemic Stroke. Neurosurg Focus. 2014;36(1):e3.

[73] Na DG, Sohn C-H, Kim EY. Imaging-Based Management of Acute Ischemic Stroke Patients: Current Neuroradiological Perspectives. *Korean Journal of Radiology*. 2015;16(2):372-390. doi: 10.3348/kjr.2015.16.2.372.

[74] Barber PA, Demchuk AM, Zhang J, Buchan AM: Validity and reliability of a quantitative computed tomography score in predicting outcome of hyperacute stroke before thrombolytic therapy. ASPECTS Study Group. Alberta Stroke Programme Early CT Score. Lancet 355:1670–1674, 2000. (Erratum in Lancet 355: 2170, 2000)

[75] Wahlgren N, Ahmed N, Eriksson N, Aichner F, Bluhmki E, Dávalos A, et al. Multivariable analysis of outcome predictors and adjustment of main outcome results to baseline data profile in randomized controlled trials: Safe Implementation of Thrombolysis in Stroke-MOnitoring STudy (SITSMOST). Stroke 39:3316–3322, 2008

[76] Balami JS, Hadley G, Sutherland BA, Karbalai H, Buchan AM. The exact science of stroke thrombolysis and the quiet art of patient selection. Brain. 2013; 136(12): 3528-3553. doi: http://dx.doi.org/10.1093/brain/awt201

[77] Vymazal J, Rulesh AM, Keller J, Janouskova L. Comparison of CT and MR imaging in ischemic stroke. Insights Imaging. 2012 Dec; 3(6): 619–627. doi: 10.1007/s13244-012-0185-9

[78] Saver JL. Time Is Brain—Quantified. *Stroke.* 2006;37:263-266; doi: 10.1161/01.STR.0000196957.55928.ab

[79] Meretoja A, Keshtkaran M, Saver JL, Tatlisumak T, Parsons MW, Kaste M, et al. Stroke thrombolysis: save a minute, save a day. Stroke 2014; 45: 1053-1058. doi: 10.1161/STROKEAHA.113.002910

[80] Fransen PSS, Berkhemer OA, Lingsma HF etal. Time to Reperfusion and Treatment Effect for Acute Ischemic Stroke: A Randomized Clinical Trial. JAMA Neurol. 2016;73(2):190-196. doi: 10.1001/jamaneurol.2015.3886

[81] Y.-H. Hwang, D.-H. Kang, Y.-W. Kim, Y.-S. Kim, S.-P. Park, and D.S. Liebeskind. Impact of Time-to-Reperfusion on Outcome in Patients with Poor Collaterals. AJNR Am J Neuroradiol 36:495–500 Mar 2015.

[82] Giles MF, Rothwell PM. Risk of stroke early after transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2007 Dec. 6(12):1063-72

[83] Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke: EAFT (European Atrial Fibrillation Trial) Study Group. Lancet. 1993;342:1255–1262.

[84] Kernan WN, Horwitz RI, Brass LM, Viscoli CM, Taylor KJ. A prognostic system for transient ischemia or minor stroke. Ann Intern Med.1991;114:552–557.

[85] Coull AJ, Lovett JK, Rothwell PM, for the Oxford Vascular Study.Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. BMJ. 2004;328:326 –328.

[86] Hill MD, Yiannakoulias N, Jeerakathil T, Tu JV, Svenson LW, Schopflocher DP. The high risk of stroke immediately after transient ischemic attack: a population-based study. Neurology. 2004;62:2015–2020.

[87] Eliasziw M, Kennedy J, Hill MD, Buchan AM, Barnett HJ, for the North American Symptomatic Carotid Endarterectomy Trial Group. Early risk of stroke after a transient ischemic attack in patients with internal carotid artery disease. CMAJ. 2004;170:1105–1109.

[88] Gladstone DJ, Kapral MK, Fang J, Laupacis A, Tu JV. Management and outcomes of transient ischemic attacks in Ontario. CMAJ. 2004;170:1099–1104

[89] Johnston SC, Rothwell PM, Nguyen-Huynh MN, et al. Validation and refinement of scores to predict very early stroke risk after transient ischemic attack. Lancet. 2007;369(9558):283–292.

[90] Anderson DC, Bottini AG, Jagiella WM, Westphal B, Ford S, Rockswold GL, Loewenson RB. A pilot study of hyperbaric oxygen in the treatment of human stroke. Stroke. 1991;22:1137–1142.

[91] Nighoghossian N, Trouillas P, Adeleine P, Salord F. Hyperbaric oxygen in the treatment of acute ischemic stroke: a double-blind pilot study. Stroke. 1995;26:1369–1372.

[92] Bennett MH, Weibel S, Wasiak J, Schnabel A, French C, Kranke P. Hyperbaric oxygen therapy for acute ischaemic stroke. Cochrane Database Syst Rev. 2014 Nov 12;11:CD004954. doi: 10.1002/14651858.CD004954.pub3.

[93] De A, Bala NN. Drug treatment for hypertensive emergencies. International Journal of Research in Pharmaceutical and Biomedical Sciences. 2011. 2(2). ISSN: 2229-3701

[94] Huang Y, Sharma VK, Robinson T, Lindley RI, Chen X, Kim JS, et al. Rationale, design, and progress of the ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy (ENCHANTED) trial: An international multicenter 2 × 2 quasi-factorial randomized controlled trial of low- vs. standard-dose rt-PA and early intensive vs. guideline-recommended blood pressure lowering in patients with acute ischaemic stroke eligible for thrombolysis treatment. Int J Stroke. 2015 Jul;10(5):778-88. doi: 10.1111/ijs.12486. Epub 2015 Apr 2.

[95] Bruno A, Biller J, Adams HP, Jr., et al. Acute blood glucose level and outcome from ischemic stroke: Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators Neurology. 1999;52:280–284.

[96] McDonnell ME, Umpierrez GE. Insulin Therapy for the Management of Hyperglycemia in Hospitalized Patients. Endocrinol Metab Clin North Am. 2012 Mar; 41(1): 175–201. doi: 10.1016/j.ecl.2012.01.001

[97] Hajat C, Hajat S, Sharma P. Effects of poststroke pyrexia on stroke outcome : a meta-analysis of studies in patients. Stroke 2000 Feb;31(2):410-4.

[98] Greer DM, Funk SE, Reaven NL, Ouzounelli M, Uman GC. Impact of fever on outcome in patients with stroke and neurologic injury: a comprehensive meta-analysis. Stroke. 2008 Nov; 39(11):3029-35. doi: 10.1161/STROKEAHA.108.521583. Epub 2008 Aug 21.

[99] Christensen H, Fogh Christensen A, Boysen G. Abnormalities on ECG and telemetry predict stroke outcome at 3 months. J Neurol Sci. 2005;234:99–103.

[100] Cavallini A, Micieli G, Marcheselli S, Quaglini S. Role of monitoring in management of acute ischemic stroke patients. Stroke. 2003;34:2599–2603.

[101] Pongmoragot J, Rabinstein AA, Nilanont Y, Swartz RH, Zhou L, Saposnik G. Pulmonary Embolism in Ischemic Stroke: Clinical Presentation, Risk Factors, and Outcome. J Am Heart Assoc. 2013;2:e000372 doi: 10.1161/JAHA.113.000372

[102] Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, et al. The European Cooperative Acute Stroke Study (ECASS) Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. JAMA.1995;274:1017–1025.

[103] Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Second European-Australasian Acute Stroke Study Investigators. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II) Lancet. 1998;352:1245–1251.

[104] Clark WM, Albers GW, Madden KP, Hamilton S. Thromblytic therapy in acute ischemic stroke study investigators. The rtPA (alteplase) 0- to 6-hour acute stroke trial, part A (A0276g): results of a double-blind, placebo-controlled, multicenter study. Stroke.2000;31:811–816.

[105] Clark WM, Wissman S, Albers GW, Jhamandas JH, Madden KP, Hamilton S. Recombinant tissue-type plasminogen activator (Alteplase) for ischemic stroke 3 to 5 hours after symptom onset. The ATLANTIS Study: a randomized controlled trial. Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke. JAMA.1999;282:2019–2202.

[106] Sandercock P, Wardlaw JM, Lindley RI, Dennis M, Cohen G, Murray G et al. The benefits and harms of intravenous thrombolysis with recombinant tissue plasminogen activator within 6 h of acute ischaemic stroke (the Third International Stroke Trial [IST-3]): a randomised controlled trial [published correction appears in Lancet. 2012;380:730]. Lancet. 2012;379:2352–2363.

[107] Cheng NT, Kim AS. Intravenous Thrombolysis for Acute Ischemic Stroke Within 3 Hours Versus Between 3 and 4.5 Hours of Symptom Onset. Demaerschalk BM, ed. The Neurohospitalist. 2015;5(3):101-109. doi:10.1177/1941874415583116.

[108] IST-3 collaborative group. Effect of thrombolysis with alteplase within 6 h of acute ischaemic stroke on long-term outcomes (the third International Stroke Trial [IST-3]): 18-month follow-up of a randomised controlled trial. Lancet Neurol. 2013;12:768–776.

[109] Demaerschalk BM, Kleindorfer DO, Adeoye OM, Demchuk AM, Fugate JE, Grotta JC et al. Scientific Rationale for the Inclusion and Exclusion Criteria for Intravenous Alteplase in Acute Ischemic Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2016 Feb;47(2):581-641. doi: 10.1161/STR.0000000000000086. Epub 2015 Dec 22.

[110] Winkler AM, Tormey CA. Pathology consultation on monitoring direct thrombin, inhibitors, and overcoming their effects in bleeding patients. AJCP 2013. 140(5). 610-622. DOI: http://dx.doi.org/10.1309/AJCP9VJS6KUKNCHW 610-622

[111] Behrouz R etal. Intravenous tenecteplase in acute ischemic stroke: an updated review. J Neurol. 2014 Jun;261(6):1069-72. doi: 10.1007/s00415-013-7102-0. Epub 2013 Sep 15.

[112] Stroke pathophysiology, diagnosis, and management. Mohr JP, Wolf PA, Grotta JC, Moskowitz MA, Mayberg MR, von Kummer R, editors. 5th Edition. Philadelphia, PA: Elsevier/Saunders; 2011. pp. 946-948.

[113] Parsons M et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012 Mar 22;366(12):1099-107. doi: 10.1056/NEJMoa1109842.

[114] Huang X et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol. 2015 Apr; 14(4):368-76. doi: 10.1016/S1474-4422(15)70017-7. Epub 2015 Feb 26.

[115] Haley EC Jr et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. Stroke. 2010 Apr;41(4):707-11. doi: 10.1161/ STROKEAHA.109.572040. Epub 2010 Feb 25.

[116] Huang X, MacIsaac R, Thompson JL, Levin B, Buchsbaum R, Haley EC Jr, Levi C, Campbell B , Bladin C, Parsons M, Muir KW. Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta- analysis of randomized controlled trials. Int J Stroke. 2016 Jul; 11(5):534-43. doi: 10.1177/1747493016641112. Epub 2016 Apr 5.

[117] CTRI/2015/02/005556 [Registered on: 19/02/2015]

[118] CTRI/2009/091/000251 [Registered on: 24/06/2009]

[119] Kliche W, Krech I, Michel MC, Sangole NV, Sathaye S. Comparison of clot lysis activity and biochemical properties of originator tenecteplase (Metalyse®) with those of an alleged biosimilar. *Frontiers in Pharmacology*. 2014;5:7. doi:10.3389/fphar.2014.00007.

[120] Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: a meta analysis. Stroke. 2007;38:967–973

[121] Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. 2010;41:2254–2258.

[122] Huded V, Nair RN, de Souza R, DVyas D. Endovascular treatment of acute ischemic stroke: An Indian experience from a tertiary care center. Neurology India. 2014:62(3): 276-279.doi: 10.4103/0028-3886.136919

[123] Balasubramanian A, Mitchell P, Dowling R, Yan B. Evolution of Endovascular Therapy in Acute Stroke: Implications of Device Development. J Stroke. 2015 May;17(2):127-37. doi: 10.5853/jos.2015.17.2.127. Epub 2015 May 29.

[124] Badhiwala JH, Nassiri F, Alhazzani W, Selim MH, Farrokhyar F, Spears J et al. Endovascular Thrombectomy for Acute Ischemic Stroke: A Meta-analysis. JAMA. 2015 Nov 3;314(17): 1832-43. doi: 10.1001/jama.2015.13767.

[125] Fugate JE, Klunder AM, Kallmes DF. What is meant by "TICI"? AJNR Am J Neuroradiol 2013. 10.3174/ajnr.A3496

[126] IMS Study Investigators. Combined intravenous and intra-arterial recanalization for acute ischemic stroke: the Interventional Management of Stroke Study. Stroke. 2004;35:904–9-1-1

[127] IMS II Trial Investigators. The Interventional Management of Stroke (IMS) II Study. Stroke. 2007;38:2127–2135.

[128] Ernst R, Pancioli A, Tomsick T, Kissela B, Woo D, Kanter D et al. Combined intravenous and intraarterial recombinant tissue plasminogen activator in acute ischemic stroke. Stroke. 2000;31:2552–2557.

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

[130] Chamorro A. Heparin in acute ischemic stroke: the case for a new clinical trial. *Cerebrovasc Dis*. 1999;9(suppl 3):16–23.

[131] The Publications Committee for the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) Investigators. Low molecular weight heparinoid, ORG 10172 (danaparoid), and outcome after acute ischemic stroke: a randomized controlled trial. *JAMA*. 1998;279:1265–1272

[132] Saxena R, Lewis S, Berge E, Sandercock PA, Koudstaal PJ. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the International Stroke Trial. *Stroke*. 2001;32:2333–2337.

[133] Chamorro A, Busse O, Obach V, Toni D, Sandercock P, Reverter JC, Cervera A, Torres F, Dávalos A; RAPID Investigators. The rapid Anticoagulation Prevents Ischemic Damage Study in Acute Stroke: final results from the writing committee. *Cerebrovasc Dis*. 2005;19:402–404.

[134] Kakkos SK, Kirkilesis GI, Tsolakis IA. Editor's Choice - efficacy and safety of the new oral anticoagulants dabigatran, rivaroxaban, apixaban, and edoxaban in the treatment and secondary prevention of venous thromboembolism: a systematic review and meta-analysis of phase III trials. Eur J Vasc Endovasc Surg. 2014 Nov;48(5):565-75. doi: 10.1016/j.ejvs.2014.05.001. Epub 2014 Jun 18.

.

[135] Suri MF, Hussein HM, Abdelmoula MM, Divani AA, Qureshi AI. Safety and tolerability of 600 mg clopidogrel bolus in patients with acute ischemic stroke: preliminary experience. Med Sci Monit. 2008;14:PI39–PI44.

[136] Meyer DM, Albright KC, Allison TA, Grotta JC. LOAD: a pilot study of the safety of loading of aspirin and clopidogrel in acute ischemic stroke and transient ischemic attack. J Stroke Cerebrovasc Dis. 2008;17: 26–29.

[137] Dengler R, Diener HC, Schwartz A, Grond M, Schumacher H, Machnig T et al. Early treatment with aspirin plus extendedrelease dipyridamole for transient ischaemic attack or ischaemic stroke within 24 h of symptom onset (EARLY trial): a randomised, open-label, blinded-endpoint trial. Lancet Neurol. 2010;9:159–166.

[138] Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM; FASTER Investigators. Fast assessment of stroke and transient ischaemic attack to prevent early recurrence (FASTER): a randomized controlled pilot trial. *Lancet Neurol*. 2007;6:961–969.

[139] Adams RJ, Albers G, Alberts MJ, Benavente O, Furie K, Goldstein LB et al. Update to the AHA/ASA recommendations for the prevention of stroke in patients with stroke and transient ischemic attack [published correction appears in *Stroke*. 2010;41:e455]. *Stroke*. 2008;39:1647–1652.

[140] Sacco RL, Adams R, Albers G, Alberts MJ, Benavente O, Furie K et al. Guidelines for prevention of stroke in patients with ischemic stroke or transient ischemic attack: a statement for healthcare professionals from the American Heart Association/American Stroke Association Council on Stroke: co-sponsored by the Council on Cardiovascular Radiology and Intervention: the American Academy of Neurology affirms the value of this guideline. *Stroke*. 2006;37:577–617.

[141] Lapchak PA, Araujo DM. Therapeutic potential of platelet glycoprotein IIb/IIIa receptor antagonists in the management of ischemic stroke. Am J Cardiovasc Drugs. 2003;3:87–94.

[142] Seitz RJ, Siebler M. Platelet GPIIb/IIIa receptor antagonists in human ischemic brain disease. Curr Vasc Pharmacol. 2008;6:29–36.

[143] The Abciximab in Ischemic Stroke Investigators. Abciximab in acute ischemic stroke: a randomized, double-blind, placebo-controlled, doseescalation study. Stroke. 2000;31:601–609.

[144] Adams HP Jr, Effron MB, Torner J, Dávalos A, Frayne J, Teal P et al. Emergency administration of abciximab for treatment of patients with acute ischemic stroke: results of an international phase III trial: Abciximab in Emergency Treatment of Stroke Trial (AbESTT-II). Stroke. 2008;39:87–99.

[145] Bukow SC, Daffertshofer M, Hennerici MG. Tirofiban for the treatment of ischaemic stroke. Expert Opin Pharmacother. 2006;7:73–79.

[146] Del Pace S, Scheggi V. Acute ischaemic stroke treated with combined intra-arterial thrombolysis and intravenous tirofiban despite oral anticoagulant therapy at an international normalised ratio > or = 2.0. InternEmerg Med. 2006;1:250–252.

[147] Mangiafico S, Cellerini M, Nencini P, Gensini G, Inzitari D. Intravenous glycoprotein IIb/IIIa inhibitor (tirofiban) followed by intra-arterial urokinase and mechanical thrombolysis in stroke. AJNR Am J Neuroradiol.2005;26:2595–2601.

[148] Mangiafico S, Cellerini M, Nencini P, Gensini G, Inzitari D. Intravenous tirofiban with intra-arterial urokinase and mechanical thrombolysis in stroke: preliminary experience in 11 cases. Stroke. 2005;36:2154–2158.

[149] Seitz RJ, Meisel S, Moll M, Wittsack HJ, Junghans U, Siebler M. The effect of combined thrombolysis with rtPA and tirofiban on ischemic brain lesions. Neurology. 2004;62:2110–2112.

[150] Song TJ, Lee KO, Kim DJ, Lee KY. Rescue treatment with intra-arterial tirofiban infusion and emergent carotid stenting. Yonsei Med J. 2008;49:857–859.

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

[152] Sbarigia E, Toni D, Speziale F, Acconcia MC, Fiorani P. Early carotid endarterectomy after ischemic stroke: the results of a prospective multicenter Italian study. *Eur J Vasc Endovasc Surg*. 2006;32:229–235.

[153] Ballotta E, Meneghetti G, Da Giau G, Manara R, Saladini M, Baracchini C. Carotid endarterectomy within 2 weeks of minor ischemic stroke: a prospective study. *J Vasc Surg*. 2008;48:595–600.

[154] Huber R, Müller BT, Seitz RJ, Siebler M, Mödder U, Sandmann W. Carotid surgery in acute symptomatic patients. *Eur J Vasc Endovasc Surg*. 2003;25:60–67.

[155] Welsh S, Mead G, Chant H, Picton A, O'Neill PA, McCollum CN. Early carotid surgery in acute stroke: a multicentre randomised pilot study. *Cerebrovasc Dis*. 2004;18:200–205.

[156] Paty PS, Darling RC 3rd, Feustel PJ, Bernardini GL, Mehta M, Ozsvath KJ, Choi D, Roddy SP, Chang BB, Kreienberg PB, Shah DM. Early carotid endarterectomy after acute stroke. *J Vasc Surg*. 2004;39:148–154.

[157] Rerkasem K, Rothwell PM. Systematic review of the operative risks of carotid endarterectomy for recently symptomatic stenosis in relation to the timing of surgery. *Stroke*. 2009;40:e564–e572.

[158] Castillo J. Deteriorating stroke: diagnostic criteria, predictors, mechanisms and treatment. *Cerebrovasc Dis*. 1999;9(suppl 3):1–8.

[159] Yamamoto H, Bogousslavsky J, van Melle G. Different predictors of neurological worsening in different causes of stroke. *Arch Neurol*. 1998;55:481–486.

[160] Manno EM, Nichols DA, Fulgham JR, Wijdicks EF. Computed tomographic determinants of neurologic deterioration in patients with large middle cerebral artery infarctions. *Mayo Clin Proc*. 2003;78:156–160.

[161] Ropper AH, Shafran B. Brain edema after stroke: clinical syndrome and intracranial pressure. *Arch Neurol*. 1984;41:26–29.

[162] Heo JH, Han SW, Lee SK. Free radicals as triggers of brain edema formation after stroke. *Free Radic Biol Med*. 2005;39:51–70.

[163] Berrouschot J, Barthel H, von Kummer R, Knapp WH, Hesse S, Schneider D. 99mTechnetium-ethyl-cysteinate-dimer single-photon emission CT can predict fatal ischemic brain edema. *Stroke*. 1998;29:2556–2562.

[164] Koenig MA, Bryan M, Lewin JL 3rd, Mirski MA, Geocadin RG, Stevens RD. Reversal of transtentorial herniation with hypertonic saline. Neurology. 2008;70:1023–1029.

[165] Vahedi K, Hofmeijer J, Juettler E, Vicaut E, George B, Algra A, Amelink GJ, Schmiedeck P, Schwab S, Rothwell PM, Bousser MG, van der Worp HB, Hacke W; DECIMAL, DESTINY, and HAMLET investigators. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6:215–222.

[166] Foerch C, Lang JM, Krause J, Raabe A, Sitzer M, Seifert V, Steinmetz H, Kessler KR. Functional impairment, disability, and quality of life outcome after decompressive hemicraniectomy in malignant middle cerebral artery infarction. J Neurosurg. 2004;101:248–254.

[167] Curry WT Jr, Sethi MK, Ogilvy CS, Carter BS. Factors associated with outcome after hemicraniectomy for large middle cerebral artery territory infarction. Neurosurgery. 2005;56:681–692.

[168] Carter BS, Ogilvy CS, Candia GJ, Rosas HD, Buonanno F. One-yearoutcome after decompressive surgery for massive nondominant hemispheric infarction. Neurosurgery. 1997;40:1168–1175

[169] Motto C, Ciccone A, Aritzu E, Boccardi E, De Grandi C, Piana A,Candelise L. Hemorrhage after an acute ischemic stroke. MAST-I Collaborative Group. Stroke. 1999;30:761–764.

[170] Derex L, Hermier M, Adeleine P, Pialat JB, Wiart M, Berthezène Y,Philippeau F, Honnorat J, Froment JC, Trouillas P, Nighoghossian N. Clinical and imaging predictors of intracerebral haemorrhage in stroke patients treated with intravenous tissue plasminogen activator. J Neurol Neurosurg Psychiatr. 2005;76:70–75.

[171] The NINDS t-PA Stroke Study Group. Intracerebral hemorrhage after intravenous t-PA therapy for ischemic stroke. Stroke. 1997;28:2109–2118.

[172] Kim J-T, Heo S-H, Park M-S, Chang J, Choi K-H, Cho K-H (2014) Use of Antithrombotics after Hemorrhagic Transformation in Acute Ischemic Stroke. PLoS ONE 9(2): e89798. doi: 10.1371/journal.pone.0089798

[173] French KF, White J, Hoesch RE. Treatment of intracerebral hemorrhage with tranexamic acid after thrombolysis with tissue plasminogen activator.Neurocrit Care. 2012;17:107–111.

[174] Bayramoglu M, Karatas M, Leblebici B, Cetin N, Sözay S, Turhan N.Hemorrhagic transformation in stroke patients. Am J Phys Med Rehabil.2003;82:48–52.

[175] Koh MG, Phan TG, Atkinson JL, Wijdicks EF. Neuroimaging in deterioratingpatients with cerebellar infarcts and mass effect. Stroke.2000;31:2062–2067.

[176] Kilincer C, Asil T, Utku U, Hamamcioglu MK, Turgut N, Hicdonmez T, Simsek O, Ekuklu G, Cobanoglu S. Factors affecting the outcome of decompressive craniectomy for large hemispheric infarctions: a prospective cohort study. Acta Neurochir (Wien). 2005;147:587–594.

[177] Alberti A, Paciaroni M, Caso V, Venti M, Palmerini F, Agnelli G. Early seizures in patients with acute stroke: frequency, predictive factors, and effect on clinical outcome. Vasc Health Risk Manag. 2008;4:715–720.

[178] Awada A, Omojola MF, Obeid T. Late epileptic seizures after cerebral infarction. Acta Neurol Scand. 1999;99:265–268.

[179] Veerbeek JM, van Wegen E, van Peppen R, van der Wees PJ, Hendriks E, Rietberg M, Kwakkel G. What is the evidence for physical therapy poststroke? A systematic review and meta-analysis. PLoS One. 2014 Feb 4;9(2):e87987. doi: 10.1371/journal.pone.0087987. eCollection 2014.

[180] Van Peppen RP1, Kwakkel G, Wood-Dauphinee S, Hendriks HJ, Van der Wees PJ, Dekker J. The impact of physical therapy on functional outcomes after stroke: what's the evidence? Clin Rehabil. 2004 Dec;18(8):833-62.

[181] Dalal PM. Studies in young and elderly: risk factors and strategies for stroke prevention. J Assoc Physicians India 1997; 45: 125-31.

[182] Banerjee TK, Mukherjee CS, Sarkhel A. Stroke in the urban population of Calcutta- an epidemiological study. Neuroepidemiology 2001; 20: 201-7.

[183] Bhattacharya S, Saha SP, Basu A, Das SK. A 5-year prospective study of incidence, morbidity and mortality profile of stroke in a rural community of Eastern India. J Indian Med Assoc 2005; 103: 655-9.

[184] Understanding stroke risk. American Heart Association. 2016

[185] National Stroke Foundation. Make Yourself Strokesafe: Understand and Prevent Stroke (brochure). Melbourne: National Stroke Foundation; 2009.

[186] Hankey G. Ischaemic stroke--prevention is better than cure. Journal of the Royal College of Physicians of Edinburgh 2010;40(1):56-63.

[187] Kiefe CI, Allison JJ, Williams OD, Person SD, Weaver MT, Weissman NW. Improving quality improvement using achievable benchmarks for physician feedback: a randomized controlled trial. JAMA. 2001;285:2871–2879.

[188] Hinchey JA, Shephard T, Tonn ST, Ruthazer R, Selker HP, Kent DM. Benchmarks and determinants of adherence to stroke performance measures. Stroke. 2008 May;39(5):1619-20. doi: 10.1161/STROKEAHA.107.496570. Epub 2008 Mar 6.

[189] Lindsay P1, Furie KL, Davis SM, Donnan GA, Norrving B. World Stroke Organization global stroke services guidelines and action plan. Int J Stroke. 2014 Oct;9 Suppl A100:4-13. doi: 10.1111/ijs.12371. Epub 2014 Sep 23.

[190] K SureshKumar, GVS Murthy, Kinra S, Goenka S, Kuper H. Development and evaluation of a Smartphone-enabled, caregiver-supported educational intervention for management of physical disabilities following stroke in India: protocol for a formative research study. BMJ Innov 2015;1:117-126 doi:10.1136/bmjinnov-2015-000042

[191] K SureshKumar, GVS Murthy, Kinra S, Goenka S, Kuper H. Evaluation of the feasibility and acceptability of the ‘Care for Stroke’ intervention in India, a smartphone-enabled, carer-supported, educational intervention for management of disability following stroke. BMJ Open 2016;6:e009243 doi:10.1136/bmjopen-2015-009243

[192] Singhal AB, PN Sylaja, Khurana D, Kaul S, Padma MV, Arora D, et al. Quality of Stroke Care in India: the Indo-US Stroke Project. Stroke. 2015; 46: ATMP84

* Logallo N, Novotny V, Thomassen L. The Norwegian Tenecteplase Stroke Trial (NOR-TEST): randomised controlled trial of Tenecteplase vs. Alteplase in acute ischaemic stroke (abstract). European Stroke Journal 2017, Vol. 2(IS) 3–97)