



# Stroke

TEACHING THE TEACHERS AND  
EXCELLENCE  
PROGRAM

Programs Summary  
Including Extension  
Conclusions Under  
Cluster Meets



## ATTENDEES OF TEACHING THE TEACHERS AND EXCELLENCE PROGRAM ON STROKE

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A stroke program was conducted in Hyderabad by Dr Jose Rafael Romero, Department of Neurology, Boston University Medical Center. The following report summarizes the salient features of the program.

## EPIDEMIOLOGY AND RISK FACTORS OF STROKE

Stroke ranks high among the most devastating neurological diseases, often causing gross physical impairment or death. The global burden of stroke is high, inclusive of rising prevalence, mortality and disability-adjusted life years. Epidemiological researchers have demonstrated the worldwide prevalence of stroke in 2010 to be 33 million, with 16.9 million having a first stroke. In contrast to this, the age-adjusted stroke incidence appears to have declined over the past few decades. This trend is believed to be either a consequence of decrease in the prevalence of risk factors of stroke or their impact. The most effective means available for reducing the burden of stroke involve modification and treatment of risk factors. These risk determinants can be classified into modifiable and non-modifiable. The former category includes various medical and behavioral conditions which can be potentially modified to provide a great window of opportunity for stroke prevention, while the latter includes age, sex, ethnicity and family history.

## MEDICAL RISK FACTORS

### Hypertension

Among the modifiable medical risk factors, hypertension is believed to be the single most robust factor that predisposes to stroke at all ages. It is also the most prevalent, accounting for 30% cases of stroke in the U.S. alone. It is accepted by a broad consensus that a blood pressure (BP) in an adult  $\geq 140$  mm Hg systolic (SBP) and  $\geq 90$  mm Hg diastolic (DBP) is detrimental to the vascular system and may contribute to increased frequency of ischemic and hemorrhagic stroke. Moreover, for every 20mmHg SBP or 10mmHg DBP increase, the risk of cardiovascular mortality is doubled. A great deal of evidence suggests that adequate control of hypertension mitigates the risk of initial stroke. Further, it has been demonstrated that appropriate treatment of isolated systolic hypertension in the elderly can potentially alleviate the possibility of stroke occurrence. Studies have suggested that reduction in SBP by 10mmHg or DBP by 5mmHg results in 40% lower risk of stroke death and 30% lower risk of death from

### HIGHLIGHT POINTS

- The global burden of stroke is high, inclusive of rising prevalence and mortality.
- The most effective means for reducing the burden of stroke involve modification and treatment of risk factors.

ischemic heart disease or other vascular disorders. The United Kingdom transient ischemic attack (TIA) trial showed that lowering DBP by 5mmHg was associated with 1/3 fewer strokes.

Due to the evident contribution of hypertension to stroke development, the Joint National Committee (JNC) issued an updated report, which provided guidelines for the diagnosis and management of the disease. The stage of hypertension along with the initial drug therapy recommended by the guidelines is summarized in table 1.

Classification	BP	Initial drug therapy
Pre HTN	120-139/80-89 mmHg	None if no compelling indication
Stage I HTN	140-159/90-99 mmHg	Usually thiazide monotherapy unless there are compelling indications ( ACE inhibitor, ARB, $\beta$ -blocker, Ca channel blocker, or combinations)
Stage II HTN	$\geq 160/100$ mmHg	Two-drug combination for most cases adding a second agent to a thiazide diuretic (ACE inhibitor, ARB, $\beta$ -blocker, Ca channel blocker, or combinations)

The American Stroke Association guidelines 2014 suggest that goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized, but it is reasonable to achieve an SBP < 140 and a DBP < 90 mmHg. Thiazides  $\pm$  ACEI/ARB, or CCB are the preferred options for achieving target BP levels. The guidelines also recommend lifestyle interventions including salt restriction, weight management, dietary modifications, regular physical activity, smoking cessation and limited alcohol consumption, as an adjunct to pharmacotherapy.

### HIGHLIGHT POINTS

- Reduction in SBP by 10mmHg or DBP by 5mmHg  $\rightarrow$  40% lower risk of stroke death and 30% lower risk of death from ischemic heart disease or other vascular disorders
- Thiazides + ACEI/ARB, or CCB are the preferred options for achieving target BP levels and lifestyle interventions serve as an important adjunct to pharmacotherapy

### Hyperlipidemia

Although epidemiological studies show no consistent relation between cholesterol levels and stroke incidence, randomized clinical trials demonstrate a substantial reduction in stroke occurrence following lipid lowering treatments. The SPARCL trial showed statin therapy to reduce the overall incidence of stroke and cardiovascular events in patients with recent stroke or TIA.

For those with any atherosclerotic cardiovascular disease (ASCVD) including stroke or TIA of presumed atherosclerotic origin, the ACC/AHA Blood Cholesterol Guidelines recommend evaluation of fasting lipid profile and ALT, prior to statin initiation. While patients with clinical ASCVD  $\leq 75$  yrs of age should be initiated on a high-intensity statin therapy, those  $\geq 75$  yrs

should be administered moderate-intensity statin therapy under regular monitoring. This can serve as an important strategy in preventing stroke occurrence among the ASCVD population.

## Atrial fibrillation

Atrial fibrillation (AF), which is frequently associated with hypertension, coronary heart disease, and cardiac failure, has been demonstrated to be a robust indicator of stroke occurrence. AF is the underlying mechanism in ~15-30% of all strokes and is associated with strokes that carry higher mortality and disability. The use of anticoagulants such as warfarin has been shown to be beneficial for stroke prevention in AF. Current guidelines also recommend anticoagulation with adjusted-dose warfarin in patients with persistent or paroxysmal AF at high risk for stroke. The recommendation is based on the results of several prospective randomized trials that have shown relative risk reduction of stroke to be 68% and absolute annual risk reduction from 4.5% to 1.4% in those treated with adjusted-dose warfarin. However, since warfarin carries an approximately 1% per year risk of serious and fatal hemorrhage, some novel oral anticoagulants (NOACs), such as dabigatran, rivaroxaban, and apixaban, have been introduced to reduce the risk of stroke in AF patients. Warfarin use also warrants frequent INR monitoring and has a narrow therapeutic index. NOACs, in contrast, have predictable pharmacokinetics, which obviates the need for routine anticoagulant monitoring.

Despite its proven benefit, anticoagulant use for stroke prevention is highly underutilized in patients with AF. Investigators posit that only 20 to 58% of patients eligible for anticoagulation actually receive it.

## Smoking and alcohol

Smoking is known to amplify stroke risk by up to 50%. The risk increases proportionally with the number of cigarettes smoked per day. When combined with oral contraceptive pills, the risk increases by 7-fold. Besides, passive smoking also significantly enhances the risk of ischemic stroke.

To curb the exponential rise in stroke prevalence due to smoking, treatment goals have been directed toward smoking cessation. For this purpose, appropriate counseling via formal programs for smoking cessation, nicotine replacement and use of other drug therapies such as bupropion, TCAs and SSRIs have been suggested. These strategies have been demonstrated to increase likelihood of smoking cessation by nearly 70%.

Alcohol abuse also elevates the risk of stroke by causing hypertension, increased coagulability,

## HIGHLIGHT POINTS

- ➔ Randomized clinical trials demonstrate a substantial reduction in stroke occurrence following lipid lowering treatments
- ➔ Initiation of moderate to high statin therapy can serve as an important strategy in preventing stroke occurrence among the ASCVD population

cardiacarrhythmias and cerebral blood flow reduction. Mild to moderate alcohol intake, on the contrary can increase HDL cholesterol and endogenous t-PA levels, and alleviate the risk of CAD. Hypertensive patients, in particular, should be warned about the risks of alcohol and urged to avoid binge drinking to prevent stroke occurrence.

### Diet, weight and physical activity

Abdominal obesity is associated with several chronic health conditions such as insulin resistance, hypertension, dyslipidemia, CAD, and stroke. Thereby, structured weight loss programs based on moderate exercises along with lifestyle modification targets in overweight and obese persons are highly recommended. Patients are advised to follow a Mediterranean-type diet which emphasizes on consumption of vegetables, fruits, and whole grains and includes low-fat dairy products.

### Diabetes

The relative risk of stroke in a person with diabetes ranges from 1.8 to 6.0 and diabetic patients tend to have strokes at a younger age. Furthermore, in patients with a history of TIA or stroke, impaired glucose tolerance doubles the risk of stroke. The Action to Control Cardiovascular Risk in Diabetes Mellitus (ACCORD) trial concluded that aggressive management of glycemia, lipidemia, and BP in high-risk diabetic individuals is desirable. ACEI and ARBs are the preferred antihypertensive agents in this subset of patients.

### TIA

A history of TIA also signals an increased risk of subsequent stroke. TIA heralds 15% of all strokes with a prevalence of nearly 2.3% (5 million) in the U.S. alone. Research reveals that people with TIA carry a 10-year stroke risk of 18.8% and a 10-year combined risk of stroke, MI, or vascular death of 42.8%.

### HIGHLIGHT POINTS

- AF is the underlying mechanism in ~15-30% of all strokes and is associated with strokes that carry higher mortality and disability
- While warfarin use warrants frequent INR monitoring, NOACs have predictable pharmacokinetics, which obviates the need for routine anticoagulant evaluation in stroke patients with AF

### HIGHLIGHT POINTS

- Smoking and alcohol significantly increase the risk of stroke occurrence, due to which stroke prevention strategies have been directed toward limiting their use
- Abdominal obesity is also associated with high stroke incidence. Physical exercises along with lifestyle modification targets in overweight and obese persons are thereby recommended

## INTRACEREBRAL HEMORRHAGE

Intracerebral hemorrhage (ICH) accounts for a high mortality rate, and hematoma growth is associated with a nearly 5-fold increase in clinical deterioration, poor outcome, and death. Investigators believe that ICH is an independent predictor of poor neurologic outcomes, nearly doubling the odds of long-term disability.

### Diagnosis

MRI is equivalent to CT for the diagnosis of acute hemorrhage in patients presenting with acute focal stroke symptoms, and is more accurate than CT for the detection of chronic hemorrhage. However, MRI is not always available and is also associated with higher costs, making CT the more preferred modality.

### Treatment

ICH is a neurological emergency and initial management should be focused on assessing the patient's ABC, blood pressure and signs of increased intracranial pressure. The patient must be kept under intensive monitoring and promptly treated for hypertension and coagulopathy. The role of surgery remains controversial, particularly for spontaneous supratentorial ICH, which has the highest morbidity and mortality among all strokes. Although improved neurological outcomes with IV thrombolytic drugs have been reported, mechanical embolectomy is employed for patients ineligible for receiving these drugs. The MERCI (Mechanical Embolus Removal in Cerebral Ischemia) trial showed that recanalization was achieved in 46% of patients on intention-to-treat analysis, and in 48% of patients in whom the embolectomy device was deployed. Good neurological

### HIGHLIGHT POINTS

- In patients with a history of TIA or stroke, impaired glucose tolerance doubles the risk of stroke
- The ACCORD trial concluded that aggressive management of glycemia, lipidemia, and BP in high-risk diabetic individuals is desirable

### HIGHLIGHT POINTS

- ICH is an independent predictor of poor neurologic outcomes, nearly doubling the odds of long-term disability
- MRI is equivalent to CT for the diagnosis of acute hemorrhage but is more accurate than CT for the detection of chronic hemorrhage
- Mechanical embolectomy is employed for stroke patients ineligible for receiving thrombolytic drugs, and has shown high rates of successful recanalization

outcomes were more frequent in patients with successful recanalization compared to those with unsuccessful recanalization (46% versus 10%). In contrast to this, the STICH trial showed that patients with spontaneous supratentorial ICH experienced no overall benefit from early surgery compared to initial conservative treatment. However, hematomas < 1 cm from cortical surface showed favorable outcomes with surgery within 96 hours. Based on the accumulating evidences, the AHA/ASA guidelines recommend that patients with ICH who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage at the earliest.

## HIGHLIGHT POINTS

- Citicoline exhibits the potential to enhance endogenous brain plasticity and protect neuronal tissues following an acute ischemic event
- The ICTUS trial showed the absence of any untoward effects on citicoline administration in patients with ischemic stroke
- Intravenous alteplase administered between 3 to 4.5 hours after the symptom onset significantly improves clinical outcomes in stroke patients

## NEUROPROTECTION

Neuroprotective agents exhibit the potential to enhance endogenous brain plasticity and repair, thereby protecting neuronal tissues following an acute ischemic event. The most promising therapies enhancing neurorecovery in the subacute phase of stroke include granulocyte colony stimulating factor, G-CSF, citicoline, and cell-based therapies. Among these, citicoline appears to provide both neuroprotection and enhanced neurorepair by improving synthesis of phosphatidylcholine and nucleic acids, stabilizing membranes, suppressing free radical formation, inhibiting apoptosis and promoting synaptic outgrowth. In addition, citicoline has a benign safety profile. The ICTUS trial was a randomized, multicenter trial that showed the absence of any untoward effects on citicoline administration in patients with ischemic stroke.

Thrombolytic therapy, another management option for acute ischemic stroke, has been approached cautiously due to high rates of ICH in early clinical trials. Few authors suggest that t-PA is beneficial when treatment is begun within three hours of stroke onset. The NINDS Stroke Trial showed that when compared with placebo, patients treated with t-PA are at least 30 percent more likely to have minimal or no disability at three months, without any increase in mortality.

Intravenous alteplase is also an approved treatment modality for acute ischemic stroke and can be administered within 4.5 hrs. The ECASS III trial demonstrated that intravenous alteplase administered between 3 to 4.5 hours after the symptom onset significantly improved clinical outcomes in patients with acute ischemic stroke compared to placebo. However, alteplase was more frequently associated with symptomatic ICH.

## GENERAL PRINCIPLES OF STROKE CARE

Since stroke occurs due to primary failure of focal tissue oxygenation and energy supply, clearing airway and providing supplemental oxygen or ventilatory support are absolutely essential. Arterial blood pressure, is commonly elevated during ischemic stroke, and should therefore be monitored frequently and treated according to the clinical scenario. Arterial hypotension, although rare in stroke patients, has been associated with poor outcomes in multiple studies. A physician may prescribe vasopressors to improve cerebral blood flow in such cases, but under regular cardiac and neurological monitoring. IV fluid administration with hypotonic solutions may exacerbate ischemic brain edema and must therefore be avoided. It is also important to sustain nutrition and restore swallowing while taking aspiration precautions. Besides, hyperthermia must be treated aggressively with acetaminophen and cooling blankets.

### HIGHLIGHT POINTS

- Arterial hypertension should be frequently monitored and treated according to the clinical scenario
- Arterial hypotension can be treated with vasopressors in exceptional cases
- IV fluid administration with hypotonic solutions should be avoided. Sustain nutrition and restore swallowing while taking aspiration precautions



## PROGRAM ATTENDEES

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Dr. Avinash Singh  
Dr. Priyanshu Singh  
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Dr. Mohd Javed  
Dr. Mohd Roushon Ali  
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Dr. Lokesh B  
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# Closing comments

Medical literature is inundated with reports of rising prevalence of stroke. Remarkable research in the past few decades reveals that modification of risk factors for stroke can serve as an important strategy to reduce this burden. Since hypertension is the most robust risk determinant for all ages, its prompt management is prudent to prevent stroke occurrence. Investigators posit that adequate control of hypertension can mitigate the risk of mortality due to stroke, ischemic heart disease or other vascular disorders. Further, antihypertensive drugs, if combined with lifestyle modifications, can subserve control of blood pressure in at-risk individuals. The spectrum of lifestyle interventions most importantly encompasses smoking cessation and limited alcohol intake, as they both significantly predispose individuals to ischemic stroke. The relative risk of stroke in people with diabetes or impaired glucose tolerance and hyperlipidemia is also high. Thereby aggressive management of glycemia, lipidemia, and BP in this subset of patients is desirable.

Investigators believe that ICH is an independent predictor of poor neurologic outcomes and clinical deterioration, nearly doubling the odds of long-term disability due to hemorrhagic stroke. The AHA/ASA guidelines thereby recommend that patients with ICH who are deteriorating neurologically or who have brainstem compression and/or hydrocephalus from ventricular obstruction should undergo surgical removal of the hemorrhage at the earliest. Management with neuroprotective agents such as citicoline has also shown promising results in this setting as it provides both neuroprotection and neurorepair without significant safety concerns.



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