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## General Guidelines for the Management of Stroke

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### Review Article

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#### ABSTRACT

Stroke is one of the leading causes of death worldwide and should be considered as a medical emergency. It is caused by obstruction of blood flow to the brain and neurons. It is of two types namely ischemic and hemorrhagic. The major risk factors of stroke are hypertension, cardiac diseases, diabetes mellitus, hyperlipidemia, cigarette smoking and alcohol consumption. ABCD2 score is used to predict the risk of incidence of stroke after a transient ischemic attack. Computed tomography and magnetic resonance imaging are generally used to detect areas of ischemia and bleeding in brain. Tissue plasminogen activator and aspirin are the preferred first line treatment options for treating ischemic stroke while hemorrhagic stroke has no standard therapy. Regular physician visits and clinical check-ups reduce the chance of occurrence of secondary stroke.

### INTRODUCTION

Stroke is one of the most common causes of death across the world. It is third most fatal disease after cardiac diseases and cancers. Stroke is the common end result of almost all the cardiovascular disorders like hypertension, hyperlipidemia, ischemic heart disease. etc. <sup>[1,2]</sup>.

Stroke is the word used to explain a sudden onset of neurological deficit caused by an injury to the nervous system due to a vascular reason and lasts for a minimum of 24 h. It is generally caused by a decreased blood flow to the brain when a blood vessel is damaged or blocked by clot or atheroma. This reduces the transfer of oxygen and required nutrients to brain tissue and causes cell damage. The word Stroke was first used by in late 17th century by William Cole. Neurological deficits that last for less than 24 h are generally called as Transient Ischemic Attacks (TIA). They usually last for 30 min to 1 h. TIA is sometimes called as mini-stroke <sup>[1,3]</sup>.

According to World Health Organization, more than 20 million people across the world suffer from stroke each year, out of which more than 50% of the cases are reported for the first time <sup>[4,5]</sup>. It is most frequently observed in African-Americans and Asians at a younger age compared to Caucasians. Modern lifestyle, high fat diet and decreased physical activity are considered to be the major factors that led to a worldwide increase in the number of newer stroke cases <sup>[1,6-9]</sup>.

### PATHOPHYSIOLOGY

Stroke is generally classified into two types namely and ischemic (85%) or hemorrhagic (15%). Ischemic strokes occurring due to the formation of thrombus or emboli causing the obstruction of cerebral arteries account for about 85% of all the stroke cases. Atherosclerosis of cerebral blood vessels is the cause in majority of ischemic stroke cases. In atherosclerosis, accumulation of lipids and inflammatory cells in the cerebral arteries results in plaque formation. Eventually plaque may rupture due to stress causing platelet aggregation, and clot formation. The clot may stay in the blood vessel or travel as an embolus to a cerebral vessel

and block the artery. Normal cerebral blood flow is about 50 ml/100 g per min and this is maintained over a wide range of blood pressures of 50 to 150 mm Hg by cerebral autoregulation. This autoregulation is impaired by atherosclerosis and acute injury. Ischemia starts when cerebral blood flow decreases below 20 ml/100 g per minute and when it reduces below 12 ml/100 g per min, irreversible damage to the brain called infarction occurs. Ischemic tissue with intact membrane integrity is termed as the ischemic penumbra which can be treated with suitable therapy [1,10-12].

Reduction in blood flow reduces the availability of nutrients to the ischemic cell causing depletion of the energy sources like ATP necessary for the maintenance of membrane integrity. Eventually, accumulation of electrolytes and water causes swelling and cell lysis which leads to cell depolarization and calcium influx causes activation of cellular enzymes and release of free fatty acids from cell membrane. Cell depolarization also leads to the release of excitatory amino acids like glutamate and aspartate causing neuron damage. Free fatty acid accumulation leads to formation of prostaglandins, leukotrienes and free radicals. All these happen in a time span of 2 to 3 h of the onset of ischemia and lead to ultimate cell death [13,14].

Hemorrhagic strokes include less than 15% of all stroke cases and most lethal. The 30 day mortality rate is very high in hemorrhagic stroke compared to ischemic stroke. They are caused by subarachnoid hemorrhage, intracerebral hemorrhage, and subdural hematomas. Subarachnoid hemorrhage occurs due to bleeding in subarachnoid space. Intracerebral hemorrhage occurs when a blood vessel ruptures within the brain itself leading to the formation of hematoma. They generally occur due to high blood pressure and antithrombotic therapy. Subdural hematomas refer to accumulation of blood below the dura and they are caused most often by accidents or injury. The exact pathophysiology of hemorrhagic stroke is not known [15,16].

## RISK FACTORS

Risk factors for stroke are broadly classified into non-modifiable and modifiable risk factors [17]. Non-modifiable risk factors include age (risk of stroke doubles for each decade after the age of 50 years), gender (men are at higher risk compared to women; the death rate due to stroke is higher among women), ethnicity (African-Americans, Asians and Hispanics are at greater risk and higher death rate compared to Caucasians) and heredity (cardiovascular disorders run among families) [18].

Modifiable risk factors include hypertension [19,20], cardiac diseases (atrial fibrillation, mitral stenosis, mitral annular calcification, myocardial disease, etc.) [21-24], diabetes mellitus [25-28], hyperlipidemia, cigarette smoking, alcohol consumption, lifestyle factors (obesity, physical inactivity, diet and stress) and glucose intolerance [29-33].

ABCD2 score (Age, Blood pressure, Clinical symptoms, Duration of symptoms and Diabetes) is used to predict the risk of incidence of stroke after TIA (**Table 1**). An ABCD2 score  $\geq 4$  is considered high risk and needs immediate assistance by a clinician [34,35].

**Table 1.** ABCD2 tool.

Parameter	Description	Points
A (Age)	$\geq 60$ years	1
B (Blood pressure)	Systolic BP $\geq 140$ mm Hg and/or diastolic BP $\geq 90$ mm Hg	1
C (Clinical features)	Unilateral weakness	2
	Speech impairment without weakness	1
D (Duration)	$>60$ min	2
	10-59 min	1
D (Diabetes)	Present	1

## SYMPTOMS

Symptoms of stroke include hemiplegia or hemiparesis (sudden weakness or numbness on one side of the body), confusion, speech difficulty, unsteady gait, loss of balance or coordination, dizziness, loss of consciousness. Hemorrhagic stroke patients report severe head ache while ischemic stroke is rather painless. Cognitive and language difficulties are very frequently observed [1,4].

Symptoms may vary depending on the area of the brain affected by infarct. Patients may present diplopia, aphasia, vertigo, dysarthria and visual impairment [23].

## DIAGNOSIS

Laboratory tests like protein C deficiency, antiphospholipid antibody, antithrombin estimations are done in steady state when the patients show no known risk factors for stroke [36-39].

The location of infarct or hemorrhage in brain is confirmed by neuroimaging. Computed tomography (CT) and magnetic resonance imaging (MRI) scans are generally used to detect areas of hemorrhages and infarction. MRI gives images of higher resolution earlier than CT ( $>24$  h to detect infarction). Carotid doppler (CD), electrocardiogram (ECG), transthoracic echocardiogram (TTE), transesophageal echocardiogram (TEE) and transcranial doppler (TCD) are employed to know the severity of various cardiovascular disorders in stroke patients [2,40,41].

## MANAGEMENT

Stroke and TIAs can be fatal if they are not treated at the earliest. The major approach to the therapy of a stroke patient must take following factors into consideration namely reduce the damage to the nervous system and decrease mortality and long-term disability; prevent long-term complications and prevent stroke recurrence [42-44].

The patient must be provided with adequate respiratory and cardiac support and a CT scan should be performed quickly to determine the type of brain lesion. Ischemic stroke patients presenting within hours of onset of symptoms should be evaluated for reperfusion therapy with thrombolytic drugs. The elevated blood pressure should not be treated unless it is more than 220/120 mm Hg or there is an indication of aortic dissection, acute myocardial infarction, pulmonary edema or encephalopathy. For the treatment of blood pressure in the acute phase within 7 days of onset, short-acting agents like labetalol, nicardipine, nitroprusside are preferred. Patients with hemorrhagic stroke should be assessed to determine whether surgery by an endovascular approach or craniotomy is possible [44-47].

### Non-pharmacologic therapy

Surgery options are less in case of acute ischemic stroke. Swelling caused by cerebral infarction can be reduced by surgical decompression [47]. Long-term disabilities can be prevented by early rehabilitation. Carotid endarterectomy and stenting are known to reduce the incidence and recurrence of stroke. Their usage is not well studied [48-54].

In subarachnoid hemorrhage, surgery to prevent the vascular abnormality substantially reduces mortality from bleeding again. Insertion of an extra ventricular drain (EVD) and subsequent monitoring of intracranial pressure are done commonly and are the least invasive of the procedures done in these patients [1,2,44].

### Pharmacological therapy

#### Ischemic stroke

The American Heart Association/American Stroke Association (AHA/ASA) Stroke Council guidelines suggest IV tissue plasminogen activator (t-PA) and aspirin as the first line drugs for ischemic stroke. Intravenous (IV) t-PA (e.g. alteplase) must be administered within 3 hours of stroke onset and aspirin within 48 hours [44,55-57].

Alteplase is known to reduce the secondary complications occurring due to stroke. A CT scan must be performed to rule out any hemorrhage before the therapy with alteplase. The dose is 0.9 mg/kg body weight (maximum 90 mg) IV over 1 h with 10% of the total dose given over 1 min initially [1,58,59]. The patient must be monitored closely for any hemorrhage while avoiding the use of anticoagulant drugs for 24 h. Aspirin dosing should be started at 50-325 mg/day within 24 to 48 h for the secondary prevention. The combinations of aspirin+clopidogrel and extended-release dipyridamole (ERDP)+aspirin are considered first-line antiplatelet agents for ischemic stroke. Warfarin is the choice drug in patients with atrial fibrillation (**Table 2**) [60-63].

**Table 2.** AHA/ASA recommendation for ischemic stroke.

	Primary agents	Alternate drugs
<b>Acute Treatment</b>	tPA or alteplase 0.9 mg/kg IV over 1 h within 3 h of onset. Aspirin 160–325 mg/day started within 48 h of onset	-
<b>Secondary Prevention</b>		
Noncardioembolic	Antiplatelet therapy with Aspirin 50–325 mg daily Clopidogrel 75 mg daily Asprin 25 mg+ERDP 200 mg twice daily	Ticlopidine 250 mg twice daily
Cardioembolic (Atrial fibrillation)	Warfarin	-
<b>Antihypertensive treatment</b> (Given for all patients)		
Previously hypertensive	ACE inhibitor+diuretic or ARB	
Previously normotensive	ACE inhibitor+diuretic or ARB	
<b>Antihyperlipidemic treatment</b> (Given for all patients)		
Dyslipidemic	Statin	
Normal lipids	Statin	

Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC7) and AHA/ASA guidelines angiotensin-converting enzyme (ACE) inhibitors and a diuretic for managing blood pressure in the acute phase of stroke. In patients with ACE inhibitor intolerance, angiotensin II receptor blockers (ARBs) are the preferred choice for hypertension management. Use of statins has shown to reduce the risk of the stroke by 30% in patients with coronary artery disease elevated plasma cholesterol. Low-molecular-weight heparin or subcutaneous low-dose unfractionated heparin (5,000 units twice/day) is advised for deep venous thrombosis in hospitalized patients [63]. They are advised in almost all stroke patients. Use of neuroprotective drugs like piracetam to treat cognitive decline in stroke is not well established [64]. Mesenchymal stem cell therapy for the regeneration of damaged neuron cells is in experimental stages [65,66].

#### Hemorrhagic stroke

There is no standard therapy for intracerebral bleeding. Nimodipine at a dose of 60 mg every 4 h for 21 days with regular monitoring is recommended to reduce the incidence and severity of delayed cerebral ischemia due to subarachnoid hemorrhage.

The patients must be closely monitored during the treatment for any complications like worsening of neurological symptoms, cerebral edema, infections, electrolyte imbalances and stroke recurrence. Suitable intervention must be done to prevent the fatal effects [1,67,68].

## **PREVENTION OF STROKE**

About 80% of the first time stroke cases can be prevented by making suitable lifestyle changes and management of potential risk factors [69-71]. Early detection is the prime criterion for the successful management of stroke. Moderate exercise of up to 30 min for 5 days/week reduces the risk of stroke. Patients must be advised to curb cigarette smoking and limit the consumption of alcohol as they directly increase the chances of developing stroke [72-79]. Blood pressure and blood sugar levels must always be kept in check. Consumption of healthy fruits and vegetables and reducing the amount of fats and red meat in diet greatly improves the chances of stroke survival. Yoga and physiotherapy are advised to strengthen the lower extremities in stroke patients [80-83].

Stroke is the largest contributor for physical disability in elderly patients. The early rehabilitation is very important in stroke patients. The patient's caregivers must take precautions in explaining the risk of the disease and suitable steps for managing the stroke to patients [84,85]. Regular physician visits and clinical check-ups reduce the chance of occurrence of secondary stroke and reduce the burden on patient's caretakers [86,87].

## **CONCLUSION**

Stroke is leading cause of death worldwide and should be considered as a medical emergency. Proper diagnosis and early medical intervention saves the life of the patient and reduces secondary complications of stroke. Alteplase and aspirin are the recommended first line drugs for the treatment of ischemic stroke. Lifestyle changes and rehabilitation reduce the risk of stroke recurrence.

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