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PAKISTAN ISCHEMIC STROKE GUIDELINES

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ABSTRACT

Stroke is the second leading cause of death and disability. Mortality related to stroke is very high in low- and middle-income countries. Stroke imposes a great socioeconomical burden in Pakistan. It is important to take important steps for prevention and proper management of stroke in country. Purpose of developing stroke guidelines is to improve stroke care in Pakistan. Guidelines are designed to help neurologists and general practitioners for treating stroke. American stroke guidelines, NICE guidelines, Canadian guidelines and multiple important articles including those emphasizing stroke care in low- and middle-income countries were studied, and these current guidelines were designed in such a way that it could help a physician to treat stroke patients with minimal available health facilities even in the absence of neuroimaging.

Keywords:
Ischemic stroke, Guidelines, Management, Prevention

BACKGROUND

Stroke is the second leading cause of death globally and a significant cause of disability and despite significant progress in prevention and treatment strategies, the global burden still remains substantial.[1] Stroke related mortality and morbidity is particularly high in low- and middle-income countries (LMIC). In 2016, the case fatality rate from stroke was 56% in LMICs compared with 29% in high-income countries (HICs).[2] There are no large-scale epidemiological studies available to determine the true incidence of stroke in Pakistan.[3] Khyber Pakhtunkhwa integrated population and health survey determined the estimated stroke prevalence of 1.2% in KP province of Pakistan.[4] Risk factors of stroke in Pakistan are enormous. A cross-sectional survey at a community health center revealed that 39% of the people aged 18 years or above have either hypertension, dyslipidemia, or a history of active smoking. Same study reported family history of ischemic heart disease in 42%, obesity in 24%, hypertension in 19%, and diabetes mellitus in 15% of the subjects.[5] Majority of patients with stroke first consult general practitioner in Pakistan. Existing evidence-based guidelines for managing acute ischemic strokes are applicable in those areas where CT scan facility is available and cannot be applied in many areas of Pakistan with minimal level of resource availability and where District Hospitals lack the facility of neuroimaging. These guidelines will focus on acute ischemic stroke and its prevention in all settings.

AIMS

The primary objective of these guidelines is to establish a standardized framework for the prevention (both primary and secondary) and management of ischemic stroke, designed for use by physicians treating this condition. The guidelines are developed keeping in mind the expertise of healthcare professionals from varied backgrounds who take care of stroke patients in this country and the limitations in terms of availability of resources.

METHODS

The authors reviewed the major studies conducted in recent years that form the basis of ischemic stroke treatments as well as the guidelines from the American Heart Association/American Stroke Association 2019 and the European Stroke Association 2019. We also reviewed the systematic review and synthesis of global stroke guidelines that was published by World Stroke Organization recently.[6-8]

The following aspects of ischemic stroke management are covered in these guidelines.

1. Primary Stroke Prevention
2. Acute Management of Ischemic Stroke
    a. Pre-hospital care
    b. Thrombolysis
    c. Thrombectomy
    d. Post intervention care
3. Work-up of Ischemic Stroke
4. Secondary Stroke Prevention

PRIMARY STROKE PREVENTION

The INTERSTROKE study highlighted that ten potentially modifiable risk factors account for more than 90% of the population attributable risk of stroke in each major world region and by addressing these, the burden of stroke may be reduced substantially. Primary stroke prevention includes early diagnosis and management of hypertension, diabetes, dyslipidemia, obesity and coronary heart disease,[9] as well as life style modification like physical activity, cessation of tobacco and smoking and adopting good dietary habits.[10] The use of low dose Aspirin in primary prevention is still not considered safe, given the increase in risk of hemorrhage which does not outweigh its benefit in preventing ischemic stroke. Table 1 presents the recommendations for primary stroke prevention.

Table1: Recommendations for primary stroke prevention

Hypertension	Maintain healthy lifestyle with regular exercise, balanced diet, low in sodium, and early diagnosis and management of hypertension
Diabetes	Manage blood sugar levels through diet, medication and healthy lifestyle, with regular monitoring
High Cholesterol	Adopt a low cholesterol diet, exercise regularly, and take medications to lower cholesterol as indicated
Obesity	Aim for a healthy weight, through a combination of diet and exercise
Physical inactivity	Engage in regular physical activity, aiming for at least 150 minutes of moderate intensity exercise per week
Smoking and Tobacco use	All forms of tobacco use increases risk of stroke and should be avoided. smoking, This includes chewed tobacco, and second-hand smoke
Atrial Fibrillation/Coronary heart Disease	If heart disease has been identified, it must be appropriately treated. Rhythm disorders like Atrial fibrillation are risk factors for future stroke and risk must be calculated and treatment should be given accordingly.
Unhealthy Diet	Diet rich in saturated fats and red meat increases risk of stroke. Adopt a balanced diet rich in fruits, vegetables, whole grains and lean proteins.
Sleep Apnea	Sleep apnea should be screened for when suspected and once diagnosed must be treated to reduce risk of stroke
Aspirin use	Use of low dose Aspirin in healthy older people has shown an increase in risk of intracranial hemorrhage without a difference in incidence of ischemic stroke. Therefore, its use for primary prevention cannot be justified given the current level of evidence

ACUTE MANAGEMENT OF ISCHEMIC STROKE

Pre-hospital Stroke Care: Diagnosis and Referral

The concept of pre-hospital care is not well established in Pakistan. Currently, Pakistan lacks an organized and a unified emergency medical service (EMS) that can provide a fast and responsive service in urban and rural areas. A coordinated and organized participation of EMS with public and private hospitals and increased levels of stroke awareness in general public will help to optimize stroke management in Pakistan.[11] Available evidence suggests that any intervention related to public awareness about stroke recognition and referral to stroke facility can be very effective. Thus, stroke education campaigns should be designed in a targeted manner to optimize their effectiveness.[12] The EMS personnel should be trained to identify stroke or TIA patients and transfer to appropriate, nearby stroke centers. Table 2 summarizes pre-hospital care recommendations.

Table 2: Recommendations for pre-hospital care

Public Education	Public Awareness campaigns should be run on a regular basis to increase awareness about stroke signs and symptoms
	Both print and electronic media, as well as social media platforms should be utilized to create awareness. Pakistan Stroke Society and its local chapters should overlook these campaigns to ensure that accurate content is delivered to the public
Emergency Medical Services	It is recommended to have a unified number for emergency services, at least at the provincial level, to streamline services
	Patients suspected of stroke should be screened for hypoglycemia with capillary glucose testing and if found below 50 mg/dL it should be treated
	Educational programs should be organized to train EMS staff to recognize stroke early (using a standard stroke scale) and transfer patients in a timely manner to nearest stroke center.
	BEFAST stroke screening scale should be incorporated into the basic training for all EMS staff
	Efforts should be made at city and district levels to map the stroke centers for appropriate triaging of stroke patients. Where available, pre-hospital notification should be utilized by the EMS, to expedite care when taking patient to a stroke center.

In-Hospital Management

Stroke is a medical emergency and there should be no delay in its diagnosis and treatment. Any patient with acute onset of focal neurological deficit, should be managed in a priority setting, with focus on immediate resuscitation if unstable. Once on the ED bed, a rapid airway, breathing and circulation assessment should be performed and treatment of life-threatening conditions initiated. Supplemental oxygen should be given only if patient is hypoxemic.[13] Hypotension and hypovolemia should be corrected for adequate organ perfusion. Treating physician must identify the time of onset of stroke symptoms, which is the most crucial step in determining therapy. Once stabilized, an assessment of neurological deficits should be performed, which would require a quick history and physical examination. Every Emergency Department (ED) should have a protocol or pathway to prioritize stroke patients. Table 3 provides recommendations for management in ED.

Table 3: Recommendations for emergency department management	
Airway, breathing, circulation	Ensure stability of airway, breathing and circulation Supplemental oxygen if Saturation <95%
Blood Sugar	Check Blood Sugar: Dextrose 25%, if RBS <50 mg/dL
History with special focus on Time Last Seen Normal	SAMPLE questions
Neurological Examination:	Patient with suspected acute stroke should ideally be assessed by a specialist clinician (trained in acute stroke assessment)
Lab Tests	NIH Stroke Scale should be used to assess stroke severity
For all patients	• Blood glucose • Serum electrolytes • Renal function tests • ECG Markers of cardiac ischemia • Complete blood count, including platelet count • Coagulation profile including Prothrombin time/international normalized ratio (INR) Activated partial thromboplastin time.
For Selected patients	• Hepatic function tests • Toxicology screen • Blood alcohol level • Pregnancy test • Arterial blood gas tests (if hypoxia is suspected) • Chest radiography (if lung disease is suspected) • Lumbar puncture (if subarachnoid hemorrhage is suspected and CT scan is negative for blood) • Electroencephalogram (if seizures are suspected
Imaging	Patients with suspected acute stroke should receive brain imaging as soon as possible
CT brain	• CT/MR Perfusion • CT brain plain is the investigation of choice Interpretation of CT brain to take reperfusion decision should only be undertaken by healthcare personnel who have received appropriate training for this
CT Angiogram	• In centers capable of performing mechanical thrombectomy, patients with ischemic stroke who are potentially eligible for the procedure must undergo CT angiogram from arch of the aorta to skull vertex as soon as possible. This should not delay administration of thrombolysis. • CT angiogram should also be performed without delay in centers that can transfer patients to thrombectomy capable centers
MRI Brain	• For patients with unknown time of onset and those with wake-up stroke, MRI Brain with stroke specific sequences (DWI-FLAIR) can be done to select patients within window for thrombolysis (4.5 hours)
CT/MR Perfusion	• Patients with acute ischemic stroke and large vessel occlusion in the delayed window (6-24) can undergo CT/MR perfusion to determine their eligibility for endovascular therapy in the extended window up to 24 hours.

INTRAVENOUS THROMBOLYSIS

Thrombolysis with alteplase (TPA) 0.6-0.9mg/kg is recommended for acute ischemic stroke patients presenting within 4.5 hours of symptom onset. The treatment has shown efficacy regardless of age and stroke severity and should be offered as early as possible upon hospital arrival. However, there are strict indications and contraindications, and the medication must only be given in centers where staff are trained in administering it and taking care of complications related to it and to the stroke.

Tenecteplase (TNK) is another thrombolytic agent that in recent years has been tested in several trials and has shown equivalent, if not better efficacy and safety for stroke thrombolysis. It has been approved for use in the European Union for acute ischemic stroke and is being used in several centers in North America as well. The dose for acute ischemic stroke is 0.25mg/kg and is given as a single IV push. Table 4 provides recommendations for IV thrombolysis.

Table 4: Recommendations for intravenous thrombolysis (Adapted from AHA/ASA Guidelines 2019)

Indications	• Diagnosis of ischemic stroke causing measurable neurological deficit • Onset of symptoms 3-4.5 h before treatment • Age ≥18 y

Class of Recommendation I Benefit >>>>Risk	• Within 3 hours:
	  • Age: IV alteplase is equally beneficial in patients <80 years and >80 years of age
	  • Stroke Severity: IV alteplase is beneficial despite increased risk of hemorrhagic transformation
	  • Mild disabling stroke: IV alteplase is beneficial
	• 3-4.5 hours:
	  o IV alteplase for patients less than 80 years of age, without both DM and prior stroke, not taking OAC, NIHSS <25 and not without evidence of ischemic injury involving >1/3 of MCA

Class of Recommendation II Benefit >>Risk*	• IV alteplase may be as effective/reasonable for the following patients as a class II recommendation
	  • Age: >80 years in the 3-4.5 hours' window
	  • Patients with prior stroke and diabetes in the 3-4.5 hours' window
	  • Severe stroke: uncertain benefit in the 3-4.5-hour window
	  • Seizure at stroke onset
	  • Recent major trauma (within 14 days) not involving the head
	  • Recent major surgery (within 14 days)
	  • GI and GU bleeding in past
	  • Extracranial cervical artery dissection
	  • Unruptured and unsecured intracranial aneurysm <1cm
	  • Intracranial vascular malformations
	  • Concomitant MI
	  • Recent MI in the past 3 months: (details in legend)
	  • Acute pericarditis
	  • LA/LV thrombus
	  • Pregnancy

Class of Recommendation III	•0-4.5 hours: Mild non disabling stroke •CT reveals an acute intracranial hemorrhage

Contraindication
No Benefit
	• Patient has signs and symptoms suggestive of subarachnoid hemorrhage
	• Patients with history of any of the following in the previous 3 months
	  • Prior ischemic stroke
	  • Severe head trauma
	  • intracranial/spinal surgery
	• Post-traumatic infarction
	• Past history of intracranial hemorrhage
	• Patients with GI malignancy or history of GI bleeding in previous 21 days
	• Patients with Platelets <100,000/mm3, INR>1.7, PT>15s, APTT>40s. However, treatment can be initiated without checking for these and later stopped once results are available.
	• If a patient has received a full therapeutic dose of LMWH in the preceding 24 hours
	• Patients suspected of aortic arch dissection
	• Patients suspected of having infective endocarditis
	• Patients who harbor an intra-axial intracranial neoplasm.
	• Patients taking direct factor Xa inhibitors unless the last received dose was >48 hours ago

Dose
Alteplase
	0.6-0.9 mg/kg (maximum dose is 90 mg)
	  • 10% as bolus over one minute
	  • 90% as iv infusion over one hour
	  • Followed by 50-100 ml normal saline flush

Tenecteplase	0.25 mg/kg (maximum dose is 25 mg)
	  • Given as a single IV push over 5 seconds
	  • Not compatible with dextrose containing fluids

*IV alteplase may be as effective/reasonable for the following patients as a class II recommendation

- Age: >80 years in the 3-4.5 hours' window
- Patients with prior stroke and diabetes in the 3-4.5 hours' window
- Severe stroke: uncertain benefit in the 3-4.5-hour window
- For patients with seizure at onset, if the residual deficit is clinically judged to be due to stroke and not post ictal phenomenon
- Recent major trauma (within 14 days) not involving the head- iv alteplase may be carefully considered in such patients weighing risk of bleeding against disability risk
- Recent major surgery (within 14 days)- iv alteplase may be carefully considered in such patients weighing risk of surgical site hemorrhage against disability risk
- GI and GU bleeding in past (within 21 days is a contraindication)- iv alteplase administration may be reasonable in such patients
- Extracranial cervical artery dissection
- Intracranial cervical artery dissection- when this is suspected, usefulness of iv alteplase and hemorrhage risk is uncertain
- Unruptured and unsecured intracranial aneurysm <1cm, iv alteplase is reasonable and recommended. For larger aneurysms, benefit is not established
- For intracranial vascular malformations, the usefulness of iv alteplase is not well established. It may be considered if the disability from stroke is anticipated to be severe and outweighs the anticipated risk of hemorrhage.

- Acute stroke and acute MI: Patients with concurrent acute stroke and acute MI should receive iv alteplase in the dose appropriate for cerebral ischemia, followed by coronary angioplasty as indicated

- **Recent MI in the past 3 months:**
    - NSTEMI and STEMI involving right or inferior myocardium: reasonable to thrombolyse
    - STEMI involving left anterior myocardium: maybe reasonable to thrombolyse
- **Acute pericarditis**
    - If stroke is likely to produce severe disability: may be reasonable to thrombolyse- urgent consultation with cardiologist is recommended
    - If stroke is likely to produce mild disability, thrombolysis is of uncertain net benefit
- **LA/LV thrombus**
    - If stroke is likely to produce severe disability: may be reasonable to thrombolyse recommended
    - If stroke is likely to produce mild disability, thrombolysis is of uncertain net benefit
- **Pregnancy**
    - May be reasonable to thrombolyse moderate to severe stroke if benefit outweigh the anticipated increased risks of uterine bleeding
    - Risk of thrombolysis in early postpartum period (<14 days) is not established

Monitoring of Patient during and after Thrombolysis

Recommendations for monitoring patients during and after thrombolysis are given in Table 5.

Table 5: Recommendations for monitoring of patients during and after thrombolysis

Where to Admit	Patient should be admitted to a Stroke Unit or an intensive care unit for monitoring
Neurological Status Monitoring	GCS, NIHSS monitoring Watch for severe headache, nausea, vomiting, acute hypertension Obtain emergent CT brain if any of the above develop
BP Monitoring	Measure BP and perform neurological assessments every 15 min during and after IV alteplase infusion for 2 h, then every 30 min for 6 h, then hourly until 24 h after IV alteplase treatment.
Hypotension and Hypovolemia Oxygen	Hypotension and hypovolemia should be corrected to maintain systemic perfusion levels necessary to support organ function Keep oxygen saturation above 94%, supplemental oxygen is needed only if falls below this
Temperature	Avoid elevation in Body temperature. Temperature above 38 degrees should be treated with antipyretics and source of infection should be identified and treated.
Blood Glucose	Capillary blood glucose should be monitored. • Hypoglycemia (glucose below 60mg/dL) should be treated with IV dextrose. • Hyperglycemia should also be treated to achieve blood glucose levels between 140-180 mg/dL
Monitoring for Angioedema	Patients who have received IV thrombolysis should be closely monitored for orolingual angioedema.

Table 6: Blood Pressure >185/110 and patient is candidate for IV thrombolysis
• IV labetalol 10-20 mg over 1-2 minutes, may repeat 1 time; or • IV hydralazine 5-10 mg as slow iv infusion **If BP is not maintained below 185/110, do not administer thrombolytic**
Management of BP during and after thrombolysis to maintain BP <180/105 mmHg • IV Labetalol 10 mg followed by continuous infusion 2–8 mg/min • IV hydralazine 0.05 to 0.15mg/minute

Table 7: Management of orolingual angioedema	
Maintain Airway	• Edema limited to anterior tongue and lips- no need for endotracheal intubation
	• Edema involving larynx, palate, floor of mouth or oropharynx with rapid progression poses high risk for intubation
	• Nasotracheal intubation may be required. Cricothyroidotomy is rarely needed
Discontinue	• iv alteplase
Administer	• i.v. methylprednisolone 125 mg
	• i.v. diphenhydramine 50 mg
	• i.v. ranitidine 50 mg
	• epinephrine (0.1%) s/c 0.3ml or neb 0.5ml

Table 8: Management of symptomatic intracranial hemorrhage within 24 hours of thrombolysis
Stop TPA infusion
Send blood tests- CBC, PT (INR), APTT, fibrinogen level, type and cross match
Emergent Non contrast CT head
Cryoprecipitate (includes factor VIII): 10 U infused over 10–30 min (onset in 1 h, peaks in 12 h); administer additional dose for fibrinogen level of <150 mg/dL
Tranexamic acid 1000 mg IV infused over 10 min
Refer to Neurosurgery
Supportive therapy, including BP management, ICP, CPP, MAP, temperature, and glucose control

MECHANICAL THROMBECTOMY

3-22% of patients with acute ischemic stroke are potential candidates for mechanical thrombectomy. Important determinant for mechanical thrombectomy in acute ischemic stroke are time of symptoms onset, clinical severity of stroke, pre stroke functional level, magnitude of early ischemic changes on initial image and anatomic location of vessel occlusion[14].

Thrombectomy should be accessible at major public hospitals in large cities and performed exclusively by personnel trained in stroke thrombectomy procedures. A trained neurologist must conduct pre-thrombectomy evaluations and determine patient eligibility at all thrombectomy centers. Individual centers may develop protocols tailored to their thrombectomy services and expertise, which could differ from national guidelines. Centers offering thrombolysis services only, but with connections to comprehensive thrombectomy centers, should establish protocols to expedite patient transfers after initiating thrombolytic therapy, ensuring timely transport of all LVO patients to comprehensive units.

Table 9: Mechanical Thrombectomy for Anterior Circulation LVO (ICA or MCA M1) within 6 hours of Last Known Normal
Recommended investigations: CT brain and CT Angiogram
1. National Institute of health stroke scale of more than 6
2. Alberta Stroke Program Early Computed Tomography Score of ≥6
3. Pre stroke modified Rankin Scale (mRs) score of 0 to 1
4. IVTPA to be used as a bridge therapy when eligible
5. No role of waiting for clinical improvement with TPA

Table 10: Mechanical Thrombectomy for Anterior Circulation LVO (ICA or MCA M1) from 6 hours up to 24 hours of Last Known Normal is indicated for the following patients		
Recommended investigations: CT brain, CT Angiogram, CT Perfusion/MR Perfusion		
Study	**Dawn**	**Defuse 3**
Occlusion Site	Internal Carotid, MCA or both	Internal Carotid, MCA or both
Mismatch	Clinical-core Mismatch One of the following Group A: >80 y NIHSS>=10, infarct<21 cc Group B: <80 y NIHSS >=10, infarct <31cc Group C: NIHSS >=20, infarct 31-50cc	Core-penumbra Mismatch Initial infarct volume <70 cc NIHSS >=6 Ratio of ischemic tissue to initial infarct volume of >=1.8 Penumbra volume (Tmax >6s) >=15 cc
Age and Functional Status	>=18 years, mRS 0-1	18-90 years, mRS 0-2
Time since last known well	6-24 hours	6-16 hours
Other imaging	No evidence of ICH on MRI or CT No evidence of stroke involving >1/3 of MCA	No evidence of ICH ASPECT >=6
There is emerging evidence of Mechanical thrombectomy for larger core infarcts (ASPECT score below 6) but this can be judged on a case-by-case basis by the treating stroke team (stroke neurologist and interventionist).		

Table 11: Mechanical Thrombectomy for Basilar Occlusion up to 12 hours	
Recommended investigations: CT brain and CT Angiogram +/- MRI brain (at the discretion of treating physician)	
1.	National Institute of health stroke scale of more than 10
2.	Posterior Circulation Alberta Stroke Program Early Computed Tomography Score of ≥8
3.	Pre stroke modified Rankin Scale (mRs) score of 0 to 2
4.	IVTPA to be used as a bridge therapy when eligible
5.	No role of waiting for clinical improvement with TPA

GENERAL MANAGEMENT OF PATIENTS WITH ACUTE ISCHEMIC STROKE

The following measures apply care of all ischemic stroke patients, irrespective of whether they have received thrombolysis or thrombectomy. The care of stroke patients should be carried out in an organized unit, called a stroke unit.

1) Oxygen during acute phase of stroke

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 only if there is evidence of hypoxia[15].

2) Blood pressure management

Blood pressure may be elevated for the first 24–48 hours in patients with acute stroke. This is due to acute hypertensive response which takes 7-10 days to recover. Antihypertensive agents should be withheld unless the diastolic blood pressure is above 120 mmHg, or the systolic blood pressure is above 220 mmHg in those patients who are not candidate for IV thrombolytic therapy. Short acting intravenous anti-hypertensive like Labetalol is the drug of choice with the dose of 10 mg intravenous stat followed by 1-2 mg /min infusion if needed. BP should be lowered by 15% within the first 24 hours but the benefit of treating hypertension within the first 48 to 72 hours is unclear.[16] A period of autoregulation (up to 180/105 as above) lasting 48 to 72 hours may be considered before beginning to pursue long-term control of blood pressure in the normotensive range. The target blood pressure for patients with stroke or TIA is <130/80 mmHg.

3) Hyperglycemia and hypoglycemia

It is reasonable to treat hyperglycemia to achieve blood glucose levels in a range of 140 to 180 mg/dL and to closely monitor to prevent hypoglycemia in patients with AIS. Hypoglycemia of < 60 mg should be treated in acute stroke patients. Insulin sliding scale is recommended to manage hyperglycemia before, during and after thrombolytic therapy. Intravenous insulin infusion can be used cautiously in patients with very high glucose levels.

4) Antithrombotic Agents

After IV thrombolysis with Alteplase antiplatelet will be started after 24 hours. If patient is not a candidate for thrombolysis, antiplatelet should be initiated as early as possible, ideally within 12-24 hours of symptom onset, after an intracranial hemorrhage has been ruled out. Details of which agents are recommended are discussed in secondary prevention section.

If the patient is a candidate for anticoagulation, the timing of anticoagulation will depend on the size of ischemic infarct and risk of hemorrhagic transformation.

5) Lipid Lowering Agents

Patients with ischemic stroke and TIA without a proven cardioembolic mechanism, and an LDL cholesterol above 100mg/dL should be started on Atorvastatin 80mg daily. Target LDL in patients with atherosclerotic etiology of stroke, is <70 mg/dL and Ezetimibe 10 mg daily may be added to achieve this target.

6) Nutrition and Hydration

Patients should receive isotonic hydration and free fluids should be avoided. Nutritional supplementation is not necessary. However, an evaluation for aspiration is needed prior to initiation of diet and the diet should be modified accordingly. Consultation with nutritionist is recommended to advise regarding dietary restrictions keeping in view the risk factor profile of the patient.

7) Dysphagia and aspiration

Incidence of dysphagia varies among stroke patients. Dysphagia can lead to complications, such as aspiration pneumonia; dehydration; and malnutrition which in turn can lead to prolonged hospital stay; psychological disorders such as stress, anxiety, and depression; decreased quality of life; increased health costs; increased mortality and decreased patient outcomes after stroke.[17] Management of dysphagia is carried out by a multidisciplinary team approach, consisting of doctors, nurses, speech therapists, occupational therapists, and nutritionists. Multiple national and international guidelines recommend that stroke patients should have their dysphagia screened by a trained health care professional. The recommended time from admission to dysphagia screening ranges from 4 hours to 24 hours.[18] A wet gurgling voice after stroke, a marked facial weakness, marked cognitive slowing or inattention, a cough or choking after eating, taking longer time than usual to eat are clinical features of dysphagia and need immediate attention. The oldest and most frequently used method is the Water Swallowing Test by giving water ranging from 3 ml, 5 ml, 10 ml, 20 ml, 50 ml to 60 ml and modifications in the diet should be made accordingly.[19] Nasogastric tube feeding should be given to patients with dysphagia.

8) Prevention of bed sores

The stroke patients who are unable to mobilize are at the risk of developing bed sores. Ideally, they should be provided with a pressure-relieving mattress as an alternative to a standard hospital mattress. There should be standing instructions for re-positioning these patients every two hours to avoid pressure sores.

9) Deep vein thrombosis

Avoidance of deep vein thrombosis in immobilized patients via frequent movements and the use of low dose s/c heparin is suggested in the acute phase.[20]

10) Corticosteroids

Contrary to the popular practice, steroids do not appear to have any beneficial role in management of patients with presumed acute stroke. Usage of steroids in these cases may elicit unwanted adverse effects such as hyperglycemia and infections.[21] Steroid should be avoided in patients with acute stroke or intracranial hemorrhage.

ESTABLISHMENT OF MINIMALLY EQUIPPED STROKE UNITS IN PAKISTAN

Neuroimaging and stroke treatment centers are more of an exception than the norm in Pakistan due to accessibility and cost parameters. Main factors leading to stroke mortality in first few hours and days are aspiration pneumonia, cardiac events and thromboembolism. This is an area where acute stroke care makes a difference. Minimally equipped stroke unit (MESU) are option in many cities of Pakistan. Minimally equipped stroke unit consist of at least three acute stroke beds separated from the main ward with monitoring of heart rate and rhythm, oxygen saturations, blood pressure, NIHSS, prevention of complications such as aspiration pneumonia and pressure ulcers, screening for dysphagia, engaging patients and their families in the rehabilitation and discharge planning process by a dedicated team. In a study conducted in Guinea in Africa, mortality and medical complications including frequency of UTIs, bedsores, and pneumonia were significantly lower in the patient's receiving treatment in a MESU compared to those receiving treatment in the normal ward. Patients treated in MESU also had better post-treatment modified Rankin Scale (mRs) and National Institute of Health Stroke Scale (NIHSS) scores.[22] Refer to Table 12 for recommendations regarding MESUs.

Table 12: Minimally Equipped Stroke Unit Recommendation	
Equipment	• At least three monitored beds separated from ward • Monitoring should include pulse oximeter, BP monitor, oxygen saturation, cardiac rhythm monitor
Staff	• Nursing staff trained for stroke patients- At least 1:2 care • Physicians trained in care of stroke patients • Physiotherapist • +/- Nutritionist
Written protocols for monitoring and management for the following are recommended in all stroke units	• Heart rate and rhythm, oxygen saturation, blood pressure • Neurological status- GCS, NIHSS • Blood pressure • Blood glucose • Dysphagia Screening and aspiration precautions • Repositioning for prevention of bedsores • Early mobilization and DVT prophylaxis

EVALUATION OF STROKE ETIOLOGY TO GUIDE SECONDARY STROKE PREVENTION

All patients admitted with acute ischemic stroke or TIA should undergo investigations to determine the underlying stroke etiology and to assess their risk factors (Table 13).

Table 13: Evaluation of etiology of stroke	
Brain Parenchymal Imaging	• CT brain OR • MRI brain (indicated if CT is not negative or small vessel disease is suspected or in case of wake-up stroke in hyper acute setting. MRI is also indicated for evaluating rare etiologies like vasculitis and in patients with TIA)
Vascular Imaging for extracranial and intracranial vessels	• CT Angiogram • MR Angiogram • Ultrasound carotid Doppler
Cardiac Work up	• 12-lead ECG, at least 24 hours of cardiac monitoring for admitted patients is recommended
	• Trans-thoracic Echocardiogram • Holter 24-72 hours* • Trans esophageal echocardiogram* * in selected patients suspected of Cardioembolic stroke
Blood Work up	• CBC, PT, PTT, creatinine • Glucose, HbA1c • Fasting Lipid Profile • Additional work up may be warranted in younger patients and in patients suspected of having etiologies such as vasculitis and other hypercoagulable states. These include vasculitis markers, antiphospholipid antibodies, homocysteine levels, infection markers and others. Clinical scenario should guide this testing.

DISCHARGE PLANNING

By the time the patient leaves the acute care hospital, the physician should ensure that the patient understands the etiology of his/her stroke. For this, it is important that

- Essential work up has been completed to decide best secondary prevention strategies
- Risk factor management has been optimized to prevent a second stroke
- The risk of complications after discharge has been assessed and measures have been taken to mitigate them
- Rehabilitation has started and there is a plan of continuing rehab post discharge
- Caregivers have received adequate information to manage the patient
- A follow up is lined up post discharge

MANAGING ACUTE ISCHEMIC STROKE IN RURAL AREAS WITH NO FACILITY OF NEUROIMAGING

Only large cities in Pakistan have the facility of neuroimaging which makes it difficult to differentiate between ischemia and intracerebral hemorrhage (ICH). The following points should be considered when managing acute onset neurological deficits in rural areas where facility of neuroimaging is not available.

1) Check airway, breathing and circulation. Manage appropriately.
2) Take history and do careful full neurological examination.
3) Try to differentiate between ischemia and ICH based on history, though it is very difficult to differentiate only based on history but severe headache, loss of consciousness and very low GCS are relatively more common in ICH.
4) Check blood glucose immediately and treat hypoglycemia which is a very important stroke mimic.
5) When managing BP in the first 24 hours after acute onset neurological deficit, targeting a maximum SBP of 180mmHg while avoiding a minimum mean arterial pressure (MAP) of <65mmHG is safe for both ischemia and ICH. If patients show worsening neurological deficits with BP reduction, the BP goal can be increased and a trial of BP augmentation with IV fluid can be considered23.
6) When CT scan is not available then clinician should decide to start aspirin in the acute setting and continue it for chronic secondary prevention after stroke of unknown type (SOUT) thus providing aspirin within 48 hours of symptom onset for all patients with SOUT would decrease in-hospital mortality by 4 per 1000 patients and recurrent stroke by 8 per 1000 patients. In SOUT if clinical suspicion is high for ICH, then it is better to withhold aspirin for 48 hours.
7) Dedicate beds for acute stroke management.
8) Pass NG tube if patient has dysphagia and start physiotherapy.
9) All care provided in a minimally equipped stroke unit may be provided in a rural set up to these patients.

SECONDARY PREVENTION GUIDELINES FOR ISCHEMIC STROKE AND TIA

A) Lifestyle modifications:

1) Smoking/ Tobacco

Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit active smoking, chewing tobacco like paan, gutka, naswar and avoid environmental tobacco smoke.[24] Counseling, nicotine products, and oral smoking cessation medications all are effective in helping smokers to quit.[25]

2) Physical activity

For patients with ischemic stroke or TIA should participate in at least three to four sessions per week of moderate- to vigorous-intensity aerobic physical exercise to reduce stroke risk factors. Sessions should last for about 40 minutes. Moderate-intensity exercise is typically defined as sufficient to break a sweat or noticeably raise heart rate (e.g., walking briskly, using an exercise bicycle). Vigorous-intensity exercise includes activities such as jogging[26.]

3) Obesity

All patients with TIA or stroke should be screened for obesity with measurement of BMI and waist to hip ratio. Life style modifications, healthy dietary habits, exercise and medicines should be considered to reduce weight[27.]

4) Diet

It is important to counsel patients with a history of stroke or TIA to follow diet rich in vegetables, fruits, whole grains, low-fat dairy products, poultry, fish, legumes, olive oil, and nuts and to limit intake of sweets and red meats. Two such diets are Mediterranean-type diet and DASH diet[28.] Patients with a history of stroke or TIA should also reduce their sodium intake to less than ≈2.4 g/d.

5) Air pollution and climate change

The environment has recently been identified as a strong risk factor for ischemic stroke. The brain is most affected by the body organ due to the environment. Strong advocacy efforts are needed at community and society level to decrease air pollution (acceptable air quality index less than 50) and limit use of greenhouse gases for climate change.

6) Obstructive Sleep Apnea (OSA)

In patients with an ischemic stroke or TIA and OSA, treatment with continuous positive airway pressure (CPAP) can be beneficial for improved sleep apnea, hypertension control, prevention of arrhythmias, sleepiness, and other apnea related outcomes.

B) Antiplatelet:

For long-term prevention of vascular events in people with non-cardioembolic ischemic stroke or TIA, antiplatelet agents should be started within the first 12 to 24 hours of symptom onset. If the patient has received thrombolysis, this should be delayed for 24 hours till a repeat CT has been done. Any of the following may be used for secondary stroke prevention, Aspirin 50 mg to 325 mg daily, Clopidogrel 75 mg daily, or Aspirin 25 mg plus extended release dipyridamole 200 mg twice daily.

In patients with non-cardioembolic minor stroke (NIHSS <3) or high-risk TIA (ABCD2 score >4), it is recommended to start dual antiplatelet early (Aspirin and Clopidogrel) within 24 hours and up to 7 days of symptom onset, and to continue for 21 to 90 days followed by single antiplatelet (Table 14).

Table 14: Recommendation for Antiplatelet in Non-Cardioembolic ischemic stroke or TIA

When to Start	• Non-thrombolysed patient: within 12-24 hours of symptom onset • Thrombolysed patient: after 24 hours, once repeat imaging has been done
Agents	• Aspirin 50-325 mg daily or Clopidogrel 75 mg daily or Aspirin 25mg + extended-release Dipyridamole 200mg twice daily to continue
	Dual Antiplatelet to be considered for the following patients (ideally within 24 hours of stroke onset and at least within 7 days): • Minor Stroke (NIHSS <3), High Risk TIA (ABCD2 >4) Aspirin 75-300 mg Day 1, continue 75 mg thereafter
	+ Clopidogrel 300 mg Day 1, continue 75 mg Day 2 to 21, then stop OR (if clopidogrel resistance is suspected) Ticagrelor 180 mg loading, continue 90 mg twice daily for 21 days
	• Moderate Stroke (NIHSS <5), High Risk TIA (ABCD2 >4) Aspirin 75-300 mg Day 1, continue 75 mg thereafter
	+ Ticagrelor 180 mg loading, continue 90 mg twice daily for 30 days
	• Ischemic Stroke and TIA with underlying 50-99% stenosis of a major intracranial artery
	Aspirin 325 mg daily to continue
	+ Clopidogrel 75 mg daily for up to 90 days
	It is not advisable to continue dual antiplatelet indefinitely for prolonged time periods unless there is another indication e.g. coronary heart disease

Recurrent Stroke while on Antiplatelets	In patients with recurrent stroke on antiplatelet treatment the following factors should be taken into considerations • Compliance to medication should be ensured • Control of other risk factors should be evaluated • Stroke Etiology should be re-evaluated • For patients on Aspirin at the time of non-Cardioembolic stroke, the effectiveness of increasing the dose of aspirin or of switching to another antiplatelet is not well established. • If patient is on Clopidogrel, clopidogrel resistance should be considered. It is recommended to check for CYP2C19 genetic testing and if testing is not available, to switch to another antiplatelet agent.

C) Hypertension:

In patients with acute ischemic stroke or TIA, and who are known with hypertension, anti-hypertensive medications should be resumed or started to achieve a clinic blood pressure target of <130/80 mm Hg. In patients with no history of hypertension, treatment should be considered if blood pressure readings are consistently above 130/80 mm Hg. For admitted patients with stroke or TIA, we recommend starting treatment prior to discharge, in order to ensure this important risk factor management is not missed (Table 15).

Choice of specific antihypertensive drugs and BP targets should be individualized on the basis of specific patient characteristics like extra cranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and diabetes. Availability of medicine and cost effectiveness should be kept in mind to prevent noncompliance.

People on antihypertensive treatment should have blood pressure monitoring done regularly, either with their general physician or with validated home BP monitoring devices.

Table 15: Recommendations for Hypertension Management

When to start	Anti-hypertensive medications may be started after the first 24 to 48 hours of acute ischemic stroke
Target	<130/80 in all patients with stroke and TIA Exception: In patients with severe carotid stenosis, a higher systolic BP 140-150 mm Hg may be tolerated till a definitive revascularization procedure is undertaken
Agents	The magnitude of BP lowering is more important than the class of agent used. Individual patient characteristics should be considered when selecting the agent. All of the below are reasonable first options • thiazide diuretic, • calcium channel blocker • angiotensin-converting enzyme inhibitor, or • angiotensin II receptor blockers
Monitoring and Follow up	BP lowering treatment should be monitored and doses should be adjusted to achieve required target. This can be done by the general physician. Monitoring may also be done using home devices but these must be validated and methods must be standardized using appropriate cuffs.

D) Diabetes Mellitus

After acute ischemic stroke (AIS), it is reasonable to screen all patients for diabetes mellitus using fasting plasma glucose, hemoglobin A1c (HbA1c) or an oral glucose tolerance test. In general, HbA1c is a more convenient method and does not require fasting. Diet, exercise, oral hypoglycemic drugs, and insulin are proven methods to achieve glycemic control. Target of HbA1C of ≤7 percent should be achieved for most of patients (Table 16).[29] Pioglitazone therapy in patient with stroke and type 2 diabetes is associated with reduction in recurrent stroke.[30] In a person living with diabetes and stroke, the management of vascular risk factors, including blood pressure, lipid lowering and appropriate antithrombotic therapy should be considered.[31] Endocrinologist should be consulted.

Table 16: Recommendations for Diabetes Management

Screening for DM	All patients with ischemic stroke or TIA should undergo screening for prediabetes/Diabetes using HbA1c, fasting plasma glucose, oral glucose tolerance.
Target	Achieving a goal of HbA1c < 7% is recommended for patients with diabetes and having stroke or TIA
Agents	Treatment of diabetes should include glucose-lowering agents with proven cardiovascular benefit to reduce the risk for future major adverse cardiovascular events (ie, stroke, MI, cardiovascular death).
	Treatment must also include other measures to improve glycemic control like diet, weight loss and improving physical activity levels
Monitoring and follow	Glycemic status should be monitored using HbA1c or continuous glucose monitoring at upleast twice a year. More frequent assessment is recommended for patients who are not meeting targets or in whom therapy has recently changed.

E) Lipid Management

Elevated lipid levels, especially cholesterol is an important modifiable risk factor for cardiovascular events including stroke. Patients with ischemic stroke or TIA should be screened for elevated lipid levels and advice should be given regarding lifestyle modifications including diet, weight loss as well as medications for lipid lowering. Statins are effective agents to lower LDL cholesterol as well as triglycerides and moderate to high intensity statins are recommended (Table 17). For extreme elevations of triglycerides, it is recommended to refer patients to metabolic specialists, to assist in managing them.

Table 17: Recommendation for Lipid Management	
Screening for Dyslipidemia	All patients with ischemic stroke or TIA should undergo screening for dyslipidemia with either a fasting or non-fasting plasma lipid profile.
Target	LDL Cholesterol <100 mg/dL LDL Cholesterol <70 mg/dL is recommended for patients with ischemic stroke or TIA and atherosclerotic disease (intracranial, carotid, aortic, or coronary)
Agents	Atorvastatin 80 mg daily Rosuvastatin 20-40 mg daily
	Ezetimibe 10 mg daily may be added to a statin if LDL target is unmet or high dose statin is not tolerated
	If LDL target is still not met, addition of PCSK9 therapy may be considered in patients with high atherosclerotic risk, although the cost must be kept in mind
	Fibrates are indicated for elevated TG >500
Monitoring and follow up	Adherence to lifestyle recommendations and medications should be assessed at 4-12 weeks by fasting lipid measurement and every 3-12 months thereafter Muscle and liver enzymes may be monitored to assess safety of statin therapy at these time points

MANAGEMENT OF SPECIFIC ETIOLOGIES

1) Cardioembolism

Table 18 deals with recommendations for various cardiac causes of embolic strokes.

Table 18: Recommendations for cardioembolic stroke	
Atrial Fibrillation	All patients with ischemic stroke or TIA with paroxysmal, persistent or permanent Valvular or non-Valvular atrial fibrillation or atrial flutter should receive long term oral anticoagulation for stroke prevention
Timing	• Should be initiated immediately after a TIA once brain imaging has excluded hemorrhage • For mild stroke, can be initiated within 3 to 5 days of stroke onset • For moderate to severe stroke can be initiated between 5 to 14 days of stroke onset
Agents	Non-Valvular AF: Direct Oral Anticoagulants DOACs* (Rivaroxaban, Apixaban, Dabigatran, Edoxaban) or Warfarin (dose adjusted to achieve INR 2.0-3.0)
	Valvular (Moderate to severe mitral stenosis, or prosthetic heart valves) AF: Warfarin (dose adjusted to achieve INR 2.0-3.0 for MS, 2.5-3.5 for prosthetic heart valves)
	In the setting of nonvalvular AF, if patients have contraindications to lifelong anticoagulation but can tolerate at least 45 days, it may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce the chance of recurrent stroke and bleeding

Monitoring and follow up	Patients on Warfarin require frequent monitoring of INR to ensure it is within the therapeutic range
	*DOAC doses may have to be adjusted depending on patient's age, GFR, and BMI
Valvular Heart Disease	• In patients with ischemic stroke or TIA and Valvular AF (moderate to severe MS or any mechanical valve)- Warfarin to reduce risk of recurrent stroke • In patients with mechanical mitral valve and history of stroke or TIA before valve replacement, Aspirin (75-100 mg/d) in addition to Warfarin (INR target 2.5-3.5) • In patients with native or nonrheumatic mitral valve disease (mitral valve prolapse, annular calcifications) without AF, Antiplatelet therapy is recommended • In patients with bio prosthetic aortic or mitral valves, and a history of stroke or TIA before valve replacement, long term antiplatelet therapy is recommended beyond 3-6 months from valve replacement • In patients with mechanical aortic valve, INR target of 2.5–3.5 or the addition of aspirin (75–100 mg/d) can be beneficial to reduce the risk of thromboembolic events
Infective Endocarditis	• In patients with ischemic stroke or TIA, with left side IE and mobile vegetation >10 mm in size, early surgery should be considered if there is no intracranial hemorrhage • Early surgery may also be considered in patients with recurrent embolic strokes despite being on antibiotic therapy • In patients with major stroke or intracranial hemorrhage, valve surgery may be delayed for at least 4 weeks
LV or LA Thrombus	• In patients with stroke or TIA and LV or LA thrombus, anticoagulation with warfarin, to achieve INR 2.0-3.0 is recommended for at least 3 months
Cardiomyopathy	• In patients with stroke or TIA, in sinus rhythm, with reduced EF without evidence of LA or LV thrombus, the effectiveness of anticoagulation over antiplatelet therapy is not well established. • In patients with stroke or TIA, in the setting of a mechanical assist device, treatment with combination of warfarin and aspirin may be beneficial to reduce risk of recurrent stroke
CE stroke in setting of acute MI	• In patients with stroke or TIA in the setting of acute anterior MI with reduced • ejection fraction, anticoagulation with warfarin may be considered for 3 months

Patent Foramen Ovale	• In patients with non-lacunar ischemic stroke identified to have a PFO on cardiac echocardiogram we recommend
	  • Multidisciplinary approach to determine the causal role of the PFO that involves the patient, cardiologist and the neurologist
	  • Optimal secondary prevention treatment including antiplatelet therapy, blood pressure and lipid lowering treatment and lifestyle modification should be done. Anticoagulation is not recommended unless there is another indication for it
	  • Selected patients below 60 years of age, with a high ROPE score (>7) and high risk PFO features (large size, presence of Atrial septal aneurysm) can be considered for PFO closure. This should be decided by the multidisciplinary team in conjunction with the patient.

Cardiac Tumors	• In patients with stroke or TIA found to have left sided cardiac tumors, resection of the tumor is recommended to reduce risk of recurrent ischemic events

2) Large Artery Disease

Recommendations to manage large artery disease are provided in Table 19.

Table 19: Recommendations for large artery disease

Extracranial Carotid Atherosclerosis	• In patients with TIA or non-disabling ischemic stroke within the past 6 months, carotid revascularization with carotid endarterectomy (CEA) or carotid artery stenting (CAS) is recommended for
	  • Ipsilateral severe (70-99%) stenosis
	  • Ipsilateral moderate (50-69%) stenosis
	• This is in addition to intensive medical therapy, with antiplatelet therapy, lipid-lowering therapy, and treatment of hypertension, to reduce stroke risk
	• CEA or CAS should be performed by operators with established peri-procedural complication rates of <6%
	• Procedure should ideally be performed within 2 weeks of the index event to get the maximum benefit of recurrent stroke prevention
	• CEA is preferred over CAS in
	  • In older patients >70 years of age
	  • If revascularization is planned within one week of index stroke
	• In patients with <50% stenosis of the symptomatic vessel, medical management is recommended over revascularization procedures.

Extracranial Vertebral Artery Disease	• In patients with recently symptomatic extracranial vertebral artery stenosis, intensive medical therapy (antiplatelet therapy, lipid lowering, BP control) is recommended to reduce stroke risk • The role of stenting or surgical procedures is not well established
Intracranial Atherosclerotic Disease	• In patients with stroke or TIA due to 50-99% stenosis of a major intracranial vessel, Aspirin 325 mg daily is recommended In patients with recent stroke or TIA due to 70-99% stenosis of a major intracranial • vessel, Clopidogrel 75 mg daily may be added up to 90 days to further reduce risk of recurrent stroke • Patients with stroke or TIA due to stenosis of a major intracranial vessel, should have aggressive risk factor management with high intensity statin, maintenance of systolic BP below 140 mmHg, and at least moderate physical activity. • The usefulness of angioplasty and/or stenting in patients with symptomatic intracranial disease is not well established and should not be considered as an initial treatment.
Extracranial Dissection	• In patients with ischemic stroke or TIA, following an extracranial carotid or vertebral artery dissection, treatment with either aspirin or anticoagulation is recommended for at least 3 months to prevent recurrent events • For anticoagulation, warfarin or a DOAC may be used.

3) Hypercoagulable States

Table 20 deals with hypercoagulable states

Table 20: Recommendations for hypercoagulable states	
Hematological Traits	• In patients with ischemic stroke and TIA and any of the following traits: Prothrombin gene mutation, Protein C, S, Anti-thrombin 3 deficiency, Activated Protein C resistance, elevated factor VIII levels Antiplatelet are reasonable as secondary prevention measure

Anti-phospholipid Antibodies	• In patients with ischemic stroke and TIA and
	  • an isolated APLA antibody, antiplatelet therapy alone is recommended
	  • confirmed APLA syndrome, anticoagulation with warfarin to achieve a target INR 2.0-3.0 is recommended

Hyperhomocysteinemia	• Elevated homocysteine levels increase risk of ischemic stroke • However, supplementation with folate, vitamin B6, and vitamin B12 has not shown to be effective for preventing subsequent stroke

4) Vasculitis

Recommendations for vasculitis are provided in Table 21.

Table 21: Recommendations for various vasculitides	
Autoimmune Vasculitis	• In patients with ischemic stroke or TIA and suspected giant cell arteritis, high dose glucocorticoids should be initiated without delay to reduce recurrent stroke risk • Other adjunctive medications like methotrexate may be considered alongside • In patients with ischemic stroke or TIA and diagnosis of primary CNS vasculitis, glucocorticoids should be initiated followed by steroid sparing therapy for long term use.
Infectious Vasculitis	• In patients with ischemic stroke or TIA with underlying infectious vasculitis, it is recommended to treat the underlying infection with appropriate antimicrobial agent. Such etiologies include vasculitis associated with varicella zoster, syphilis, and various causes of bacterial meningitis including TB meningitis. • In patients with HIV vasculopathy, aspirin may be added to anti-retroviral therapy

5) Other Etiologies

Table 22 provided recommendations for other etiologies.

Table 22: Recommendations for other etiologies	
Carotid Web	• Antiplatelet therapy is recommended for a symptomatic carotid web • Carotid artery stenting or endarterectomy may be considered in patients refractory to medical management
Fibromuscular Dysplasia	• In patients with FMD and history of ischemic stroke or TIA, antiplatelet and management of other risk factors is recommended to prevent a recurrent event • Stenting for cervical carotid artery may be considered in patients with recurrent ischemic events despite optimal medical management
Embolic Stroke of Undetermined Source	• In patients with no identified cause for their embolic stroke, despite the recommended standard work up, antiplatelet therapy is recommended for secondary stroke prevention

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