

ISCHEMIC STROKE CARE GUIDELINES FOR PAKISTAN

Official guidelines of Pakistan Society of Neurology (approved in December 2009)

Authors:

Ayeesha Kamran Kamal MD, FAHA, ABVN, ABPN

Ahmed Itrat MBBS

Imama Naqvi MBBS

Maria Khan MBBS

Roomasa Channa MBBS

Ismail Khatri MD

Mohammad Wasay MD, FRCP, FAAN

Affiliations:

Department of Medicine (section of Neurology), Aga Khan University, Karachi

Department of Neurology, Shifa International hospital, Islamabad

Corresponding author's address:

Ayeesha Kamran Kamal MD, FAHA, ABVN, ABPN

Department of Medicine/ Neurology

The Aga Khan University

Stadium Road

Karachi 74800

Pakistan

Phone: (9221) 4930051 Ext. 4669, 4681

Fax: (9221) 4934294

E-mail: ayeesha.kamal@aku.edu

Pakistan is the sixth most populous country in the world, with an estimated population of 165 million.¹ Non communicable disease including stroke now accounts for 41% of the total disease burden of Pakistan.² In a population dense country like Pakistan, an estimated 4.8% may be suffering from stroke³; this translates to 7.2 million individuals, compared to 700,000 annually in the United States.⁴

Data on the known modifiable risk factors for stroke from developed world populations show an alarmingly high prevalence within the population of Pakistan. Hypertension- the single most preventable cause of stroke- affects one in three adults aged greater than 45 and 19% of the population aged 15 and above.⁵ The National Health Survey of Pakistan showed that Diabetes mellitus is present in 35% > than 45 years of age.⁶ Coronary artery disease can cause cardio embolic stroke and is a surrogate for atherosclerosis in the cerebrovascular system: a population based cross sectional survey showed a prevalence of 1 in 4 middle aged adults with men and women at equal risk.⁷ Presence of CAD was defined as a composite of abnormal ECG + history of clinical event. The overall prevalence of obesity is 28 % in women and 22 % in men.⁸ The prevalence of tobacco use is 40% in men and 12% in women.⁹

The projected increase in stroke and coronary heart disease (CHD) is expected to be much greater in South Asia than in any other region worldwide, as regions like Pakistan experience epidemiologic transition.¹⁰ The idea that stroke is a disease of the developed world restricted to the aged and is largely inevitable leads to nihilistic self fulfilling prophecies. An estimated 94% of deaths from stroke in South Asia occur in people younger than 70 years in contrast to only 6% in the countries with established economies owing to a greater loss in the disability adjusted life years (DALYs).¹¹ The stroke epidemic of the developing world disables individuals in their prime of life and requires a concerted effort to combat with the rapid translation of known preventive measures into everyday practice.

Such a scenario calls for a systematic, need based and cost-effective guideline for diagnosis, acute management and secondary prevention of stroke which is cognizant of the resource limitations of Pakistan. These guidelines are a step in that direction.

PROPOSAL AND DESIGN:

Methods:

The primary author (AK) reviewed all the data on current stroke identification, management and secondary prevention as well as international guidelines. These guidelines focus on ischemic stroke only. For the purposes developing these guidelines especial attention was given to studies in which Asians participated as subjects or those which had broad international implications for stroke care. Besides the review of current trials, weightage was given to Cochrane reviews since these meta analysis look at papers in all international journals and are not restricted to the English language only. The manuscript has then been reviewed by several national neurology practitioners that encounter stroke patients. Recommendations are based on local feasibility and relevance. Cost effectiveness and public health implications have also influenced the strength of these recommendations- therefore the clarification being that individual patient care and sophisticated testing is still left to the discretion of the treating physician. These guidelines emphasize the basic tenets of good stroke care.

These recommendations are divided into three sections

- a) Prehospital stroke care
- b) Inhospital Management of Stroke
- c) Primary and Secondary Prevention

PREHOSPITAL STROKE CARE

Recognition and Triage:

In the current extended family set up with intense population density, stroke is often recognized immediately.¹² However delays in presentation to care may happen after the phase of recognition and may involve financial constraints, lack of knowledge of therapeutic options and inappropriate triage/delay by the primary physician. There are several quick historical tools that enable the effective recognition of stroke- and are included in the appendix.¹³⁻¹⁵ Table 1 shows these instruments that are relatively easy to grasp.

TABLE 1. Prehospital Stroke Identification Instruments

Los Angeles Prehospital Stroke Screen			
Last time patient known to be symptom free, Date _____	Time _____		
Screening criteria			
Age >45 y	Yes	Unknown	No
No history of seizures or epilepsy	Yes	Unknown	No
Symptoms present <24 h	Yes	Unknown	No
Not previously bedridden or wheelchair bound	Yes	Unknown	No
If unknown or yes			
Blood glucose 60 to 400 mg/dL	Yes	No	
Examination			
Facial smile grimace	Normal	Right droop	left droop
Grip	Normal	Right weak	left weak
		No grip	No grip
Arm strength	Normal	Right drift	left drip
Based on examination, patient has unilateral weakness	Yes	No	
If items are yes or unknown, meets criteria for stroke			
Cincinnati Prehospital Stroke Scale			
Facial droop			
Normal-both sides of face move equally			
Abnormal-one side of face does not move as well as the other			
Arm drift			
Normal-both arms move the same or both arms do not move at all			
Abnormal-one arm either does not move or drifts down compared to the other			
Speech			
Normal-says correct words with no slurring			
Abnormal-slurs words, says the wrong words, or is unable to speak			

Physicians and nurses are encouraged to familiarize themselves with these and utilize them to effectively triage stroke patients. In the absence of stroke centers, these patients are best directed to hospitals with a track record of admitting and managing stroke patients.

IDENTIFICATION:

History:

Stroke is defined as rapidly developing signs of focal disturbance of cerebral function lasting more than 24 hours with no apparent nonvascular cause.¹⁶ This is a clinical definition, and is considered to be reliable. We recommend including the following questions as part of history for any patient presenting with focal neurological signs:

Age, Onset of symptoms – here the onset would have to be defined as the last time when the patients were at their previous symptom-free state. If the patient was asleep, this would be defined as the time when the patient was last awake and symptom free or ‘normal’ subjectively. What are the symptoms? Are the symptoms persisting or resolved? Are there any pre-existing medical conditions and risk factors such as diabetes, HTN, previous CVA, previous/recent CAD, smoking or atrial fibrillation? Is there any use of anticoagulants and insulin? Is there any surgical history?

TABLE 2. Key Components of History

Onset of symptoms
Recent events
Stroke
Myocardial infarction
Trauma
Surgery
Bleeding
Comorbid diseases
Hypertension
Diabetes mellitus
Use of medications
Anticoagulants
Insulin
Antihypertensives

What is not a stroke?

In addition to correct recognition, primary care physicians should be equally equipped to rule out what is not a stroke. Several key components from a history and physical exam can help delineate stroke from other presentations that may mimic stroke. Correlation of symptoms with vascular distribution is strongly advised. Following features decrease the likelihood of stroke.

However, they are not absolute.

1. Bilateral symptoms
2. Symptoms unexplainable by vascular anatomy
3. Seizures in a patient with known seizure disorder
4. Absence of any major risk factors for stroke

Some common symptoms that may mimic stroke are given in Table 3 along with their distinguishing features.

TABLE 3 .Stroke Mimics and Clinical Features

Conversion disorder	Lack of cranial nerve findings, neurological findings in a nonvascular distribution, inconsistent examination
Hypertensive encephalopathy	Headache, delirium, significant hypertension, cerebral edema
Hypoglycemia	History of diabetes, serum glucose low, decreased level of consciousness
Complicated migraine	History of similar events, preceding aura, headache
Seizures	History of seizures, witnessed seizure activity, postictal period

PHYSICAL EXAMINATION:

A general physical examination with emphasis on vital signs is more important at the Primary care level than a complete neurological exam. A primary inspection and conversation with the patient should be enough to give a qualitative assessment of severity of symptoms. Those interested in proper neurologic examination are referred to a website – the National Institute of Neurologic Disorders and Stroke where they are encouraged to certify and train.¹⁷ The tertiary centre should be responsible for detailed neurological examination and workup; hence it requires re-emphasizing that the primary physician’s role is just to ‘bridge’ the gap between the patient and the tertiary centre and extract as much information in the process as possible.

Redundant investigations at the local practitioner’s office e.g. EKG etc would only add to the injury as it will delay timely management. However, a blood sugar measurement via a fingerstick performed at this time can have benefits, as it is less time consuming and cost effective. Hypoglycemia mimics stroke, while hyperglycemia is associated with a poor prognosis post stroke.^{18, 19}

RECOMMENDATIONS FOR PREHOSPITAL MANAGEMENT OF STROKE:

- In the acute setting of stroke, timely intervention to prevent further complications and hence deterioration is the most important aspect. Therefore, at primary care, the focus should be rapid assessment of patients’ condition and timely referral to a larger centre.
- The history should be brief and include age, symptoms, time of onset, time of symptoms, co-morbidities, risk factor profile, recent anticoagulant use and any surgical history. The history, physical exam and investigation should not take more than 15 minutes.
- Radial pulse, blood pressure measurements, precordial and carotid auscultation should be performed as part of the physical examination, followed by a brief neurological screening exam. Fingerstick glucose should be the only investigation performed at the office. All positive and negative findings should be noted, and a copy of this note should be sent along if transferring to a hospital.
- A stroke unit should take priority for transfer if it is available within a hundred miles of the outpatient clinic. There are stroke centers in certain urban cities of Pakistan.

Otherwise, any hospital with an inpatient service and trained physicians with a track record of care should be the facility of choice.

FUTURE DIRECTIONS AND NEED

- Prehospital recognition and triage by primary care physicians need to be quick and clear. More education is required to effect this change in behavior.
- More hospitals should have designated stroke centers and have protocol based care. Efforts to support these endeavors should be made at the educational, governmental and private sector.

IN HOSPITAL MANAGEMENT OF STROKE

Emergency Department:

Any patient received in the ED with suspicion of stroke 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, followed by initiation of high flow oxygen, if hypoxemic.²⁰ Once stabilized, an assessment of neurological deficits should be performed, which would require a history and physical examination.

If no documented piece of history is available, information should be obtained on the time of onset which is defined as last seen normal, brief description of symptoms, previous similar episodes, presence of risk factors for cerebrovascular disease, as well as any history of drug abuse, migraine, seizure, infection, trauma, or pregnancy.²¹ This should be followed by a physical examination. The NIHSS stroke scale score lends itself well to a directed neurologic examination and can quantify the degree of neurologic deficit- those with an NIHSS stroke scale greater than 20 have a greater chance of harboring a lesion amenable to lysis.²² This is included in the Appendix (1).

The emergency department management of suspected stroke should be comprehensive, but it should be prompt and if recombinant tissue plasminogen activator (rt-PA) is available at the facility, should follow the NINDS recommendations for stroke chain of survival: 10 minutes for the emergency physician

TABLE 4. Immediate Diagnostic Studies: Evaluation of a Patient with Suspected Acute Ischemic Stroke

All patients
Noncontrast brain CT or brain MRI
Blood glucose
Serum electrolytes/renal function tests
ECG
Markers of cardiac ischemia
Complete blood count, including platelet count*
Prothrombin time/international normalized ratio (INR)*
Activated partial thromboplastin time*
Oxygen saturation
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)

evaluation, specialist (neurologist) assessment within 10 minutes, and 25 minutes to CT scan, allowing rt-PA administration within 45 minutes to an hour.

Several tests are performed routinely performed in stroke patients to identify systemic conditions that may mimic stroke or affect therapeutic decisions. These tests include blood glucose, electrolytes, and complete blood count with platelet count, PT and aPPT. Of these tests, hypoglycemia may cause focal symptoms that mimic stroke and hyperglycemia is associated with unfavorable outcomes. Determination of platelet count and abnormal INR is essential for those patients who have a stroke while on warfarin or those with known liver dysfunction. A clinical cardiovascular examination and a 12 lead EKG are strongly recommended, acute myocardial infarction can lead to stroke and stroke can lead to myocardial ischemia. In addition, cardiac arrhythmias can occur among patients with acute ischemic stroke. Atrial fibrillation, an important potential cause of cardioembolic stroke can be detected in the acute setting.

Imaging of the brain is recommended in some form before initiating stroke specific therapy. An emergency non contrast head CT accurately identifies most cases of intracranial hemorrhage and helps discriminate non vascular causes of acute neurologic symptoms e.g. brain tumour.²³ The CT is also adequate pretesting for rt-PA prior to infusion and shows certain important prognostic signs.²⁴⁻²⁷ Although multimodal MRI are available in certain centers they are expensive and add little to the clinical management of stroke patients in this region if no neurointerventional therapy is planned or offered.^{28, 29}

MANAGEMENT ISSUES AND RECOMMENDATIONS

Arterial Hypertension

An elevated arterial blood pressure is often detected in the first hours after stroke. According to consensus, target blood pressure in patients who are not candidates for rt-PA should be a systolic of less than 220 mm Hg and a diastolic of less than 120 mm Hg. A blood pressure less than these values do NOT warrant anti-hypertensive medicine. In addition, the administration of sublingual nitrates or nifedepine to precipitously lower blood pressure is also contraindicated for any patient if he or she presents with hypertension and focal neurological symptoms³⁰. Those that receive intravenous rt-PA require need strict control of blood pressure to below 185/110.^{24, 31}

Thrombolysis

The current FDA approved treatment for acute stroke presenting within 3 hours of symptom onset is intravenous recombinant tissue type plasminogen activator (rt-PA).³² This recommendation is based on the observed outcomes of the NINDS trial, performed in 1996, which assessed early and late neurological outcomes in a group of patients treated with rt-PA once a hemorrhage was ruled-out on a CT scan. In this trial there was a relative risk reduction of 33% at 3 months and a symptomatic ICH rate of 6.8%. The dose of rt-PA was 0.9 mg/kg.²⁴ A lower dose of 0.6 mg/kg has been used successfully in a Japanese trial and requires testing in Asian populations.³³ A care pathway is provided here (Appendix 2).

TABLE 5. Characteristics of Patients with Ischemic Stroke Who Could Be treated With rt PA

<p>Diagnosis of ischemic stroke causing measurable neurological deficit</p> <p>The neurological signs should not be clearing spontaneously.</p> <p>The neurological signs should not be minor and isolated.</p> <p>Caution should be exercised in treating a patient with major deficits.</p> <p>The symptoms of stroke should not be suggestive of subarachnoid hemorrhage.</p> <p>Onset of symptoms <3 hours before beginning treatment</p> <p>No head trauma or prior stroke in previous 3 months</p> <p>No myocardial infarction in the previous 3 months</p> <p>No gastrointestinal or urinary tract hemorrhage in previous 21 days</p> <p>No major surgery in the previous 14 days</p> <p>No arterial puncture at a noncompressible site in the previous 7 days</p> <p>No history of previous intracranial hemorrhage</p> <p>Blood pressure not elevated (systolic <185 mm Hg and diastolic <110 mm Hg)</p> <p>No evidence of active bleeding or acute trauma (fracture) on examination Not taking an oral anticoagulant or, if anticoagulant being taken, INR ≤ 1.7 If receiving heparin in previous 48 hours, aPTT must be in normal range. Platelet count ≥ 100000 mm³</p> <p>Blood glucose concentration ≥ 50 mg/dL (2.7 mmol/L)</p> <p>No seizure with postictal residual neurological impairments</p> <p>CT does not show a multi lobar infarction (hypodensity $>1/3$ cerebral hemisphere).</p> <p>The patient or family members understand the potential risks and benefits from treatment.</p>

INR indicates international normalized ratio; aPTT, activated partial thromboplastin time.

TABLE 6. Treatment of Acute Ischemic Stroke: Intravenous Administration of rtPA

<p>Infuse 0.9 mg/kg (maximum dose 90 mg) over 60 minutes with 10% of the dose given as a bolus over 1 minute.</p> <p>Admit the patient to an intensive care or stroke unit for monitoring. Perform neurological assessments every 15 minutes during the infusion and every 30 minutes thereafter for the next 6 hours, then hourly until 24 hours after treatment.</p> <p>If the patient develops severe headache, acute hypertension, nausea, or vomiting, discontinue the infusion (if rtPA is being administered) and obtain emergency CT scan.</p> <p>Measure blood pressure every 15 minutes for the first 2 hours and subsequently every 30 minutes for the next 6 hours, then hourly until 24 hours after treatment.</p> <p>Increase the frequency of blood pressure measurements if a systolic blood pressure is ≥ 180 mm Hg or if a diastolic blood pressure is ≥ 105 mm Hg; administer antihypertensive medications to maintain blood pressure at or below these levels (see Table 10).</p> <p>Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters.</p> <p>Obtain a follow-up CT scan at 24 h before starting anticoagulants or anti platelet agents.</p>

Temperature

Increased body temperature in the setting of acute stroke is associated with poor neurologic outcomes. Although trials testing acute hypothermia as a neuroprotective therapy in stroke are underway³⁴⁻³⁷, it seems prudent to avoid hyperthermia and treat temperature elevations aggressively after stroke. Common reasons are aspiration pneumonia, IV line phlebitis and urinary tract infection, these may worsen outcomes therefore aggressive search for the source of infection and early institution of antibiotics is suggested. Avoid the cannulation of a paralyzed extremity to reduce the chances of iatrogenic infections.

Hyperglycemia

Hyperglycemia has detrimental outcomes after stroke. It increases the chances of hemorrhagic conversion.³⁸ Persistent hyperglycemia at the rate of > 200 mg / dl independently predicts stroke expansion.¹⁸ A reasonable approach is to initiate treatment to reduce blood glucose when the glucose level exceeds 200 mg/dL, the desired level of glucose should be between 80- 140 mg / dl. It is encouraged to have glucometers in hospital units and train staff to manage insulin infusions in a systematized manner. An aggressive glucose management protocol is provided (Appendix 3).

Anticoagulation

The early administration of either dose adjusted IV heparin or a low molecular weight heparin is associated with an increased risk of bleeding (intracerebral and extra cranial) complications.³⁹ These medications increase the risk of symptomatic hemorrhagic transformation in those with severe stroke. **Urgent anticoagulation with the goal of preventing early recurrent stroke, halting worsening, or improving outcomes after ischemic stroke is not recommended.**⁴⁰ This is regardless of etiology of stroke e.g. cardio embolic stroke. Anticoagulation is contraindicated within 24 hours of administration of rt-PA.²⁴ Anticoagulation may be used as a bridging agent to warfarinization to avoid skin necrosis – but these objectives should be clear.

Antiplatelet Agents

Antiplatelet therapy with aspirin 160 to 325 mg daily, given orally (or per rectum in patients who cannot swallow), and started within 48 hours of onset of presumed ischemic stroke reduces the risk of early recurrent ischemic stroke without a major risk of early hemorrhagic complications and improves long-term outcome⁴¹. The acute administration of clopidrogel, ticlid or any other alternate antiplatelet agent has not been tested in acute stroke.⁴² Large trials such as International Stroke Trial (IST)³⁹ and Chinese Acute Stroke Trial (CAST)⁴³ have proved the benefits of long term daily aspirin in prevention of major vascular events post stroke, with the latter being exclusively an Asian study, and hence complementing our population better.

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.

Aspiration

A wet gurgling voice after stroke, a marked facial weakness, marked cognitive slowing or inattention, suggests the need to screen for silent aspiration. The presence of a gag reflex doesn't equate with an organized swallowing capacity. A patient with stroke should be screened for the presence of swallowing problems with the water swallowing tests and modifications in the diet should be made accordingly. A screening protocol is provided (Appendix 2). Aspiration is the major risk factor for pneumonia after stroke.⁴⁴

Prevention of bed sores

All patients unable to mobilize independently are at risk of developing pressure sores. They should ideally be provided with a pressure relieving mattress as an alternative to a standard hospital mattress. Also there should be standing instructions for re-positioning these patients every two hours to avoid pressure sores.

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.⁴⁵⁻⁴⁷ Intermittent compression devices are recommended in those where the risk of ICH is high.^{48, 49}

Early Rehabilitation

Patients with stroke should be mobilized rapidly. There is very frequently a delay and this would avoid significant complications.

Steroids

Contrary to the popular practice, steroids do not appear to have any beneficial role in management of patients with presumed acute stroke. According to the last Cochrane database systemic review of seven trials in 2002, treatment with corticosteroids did not appear to show any improvement in functional outcomes of stroke survivors.⁵⁰ Furthermore, usage of steroids in these cases may elicit unwanted adverse effects such as hyperglycemia and infections.

Neuroprotection and Neurotonics

No single trial has shown convincing benefit of stroke neuroprotection and efficacy of intervention is doubtful.^{51, 52} At the same time, the widespread practice of administration of these agents remains in vogue in Pakistan. These must be stopped because of the economic toll on patients and their families are not justified.

RECOMMENDATIONS FOR IN HOSPITAL MANAGEMENT OF STROKE

Intravenous thrombolysis should be considered and offered to patients who present within 3 hours of the onset of stroke symptoms, the correct dose in Asians should be investigated as there are significant financial constraints imposed on families in the current fee for service system where this is offered.

Care pathways should follow standardized protocols especially for aspiration, Insulin use and the management of patients who have received rt-PA.

All patients should receive a basic non contrast head CT before the initiation of any specific therapy.

Ancillary testing (at least a 12 lead EKG and carotid dopplers in a high quality center) focused on discovering the proximate cause of stroke is encouraged to address atrial fibrillation, Carotid Stenosis and cardioembolic causes of stroke in the individual patient.

In those who are not candidates for thrombolysis the administration of aspirin in a dose of 325 mg is recommended.

IV Heparin or Subcutaneous Heparinoid does not improve outcomes in the acute phase of established stroke.

There is no benefit of steroids in the treatment of stroke.

There is no benefit of neuroprotectants and brain tonics in the acute and chronic phase of stroke.

Future Directions And Need

Protocol based supportive multidisplinary care is needed to support stroke care and those hospitals that may want to upgrade their centers.

Research is required into pragmatic early management and rehabilitation in these low cost, high volume settings that is relevant and applicable – examples are family assisted rehabilitation, use of low dose and alternate thrombolytic agents, Studying the yield and cost effectiveness of stroke tests.

POST HOSPITAL STROKE MANAGEMENT

All stroke survivors are at a high risk of stroke recurrence, by mechanisms which may be dependent on the pathophysiology of the primary stroke. The following discussion focuses on measures that are globally beneficial.

TABLE 7. Standardized Measures for Stroke

tPA considered
Screen for dysphagia
Deep vein thrombosis prophylaxis
Lipid profile during hospitalization
Smoking cessation
Education about stroke
Plan for rehabilitation considered
Antithrombotic medications started within 48 hours

Antithrombotic medications prescribed at discharge
 Anticoagulants prescribed to patients with atrial fibrillation

ANTITHROMBOTIC THERAPY

In general any antiplatelet agent initiated after stroke has an odds ratio of 28% in the reduction of nonfatal stroke and a 16% reduction in fatal stroke.⁵³ In general, aspirin in a dose ranging from 75 to 300 mg is efficacious in stroke prevention.^{54, 55} There is no evidence that increasing the dose of aspirin provides additional benefit in those patients who have a stroke while on aspirin. The higher dose ranges are associated with a greater risk of gastrointestinal hemorrhage.^{53, 56} Clopidogrel is marginally better at increased cost and is therefore suggested in those with concomitant peripheral vascular disease and / or intolerance to aspirin.⁵⁷⁻⁵⁹ The combination of aspirin and dipyridamole may offer additional protection.⁵⁴ However there are concerns in patients with angina (a frequent co morbid) and this combination must be avoided in those patients. Combination therapy in stroke patients with aspirin and clopidogrel has reportedly higher risks of symptomatic ICH.⁶⁰ The use of these agents in combination for TIA is not known, with early reports suggesting benefit.^{54, 60-63} Dose adjusted warfarin is suggested in an INR 2-3 for those who have intermittent or continuous atrial fibrillation.

Blood Pressure Control

The association between both systolic and diastolic blood pressures (BPs) and the risk of ischemic stroke is continuous.^{64, 65} As compared to compelling evidence of role of blood pressure control for primary prevention of stroke, data on secondary prevention is lacking. It is known that a mean blood pressure fall of 5 mm Hg leads to a one third reduction of stroke.⁶⁶ This association should hold true, if not stronger, for individuals who have had a cerebrovascular event before. Effective blood pressure control as defined by The Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) would be the management of choice for stroke patients.⁶⁷ This would mean a target blood pressure control of <120 systolic and <80 diastolic, along with lifestyle changes and dietary modification. This target would be irrespective of co-morbid. Table 7 summarizes the JNC 7 recommendations. The only large trial assessing efficacy of antihypertensives for secondary prevention of stroke was the PROGRESS trial, looking at the outcomes of patients receiving an ACE-I (perindopril) with a diuretic (indapamide).⁶⁸ This combination led to a 43% reduction in recurrence of stroke. It appears that for at least 70% of patients with hypertension >160/90 a two drug regimen would be necessary.⁶⁷

Table 7 Classification and Treatment of Blood Pressure (JNC 7)

Classification	Systolic Blood Pressure, mm Hg	Diastolic Blood Pressure, mm Hg	No Compelling Indication	With Compelling Indication*
Normal	<120	and <80	No antihypertensive drug	No antihypertensive drug
Prehypertension	120-139	or 80-90	No antihypertensive drug	Drugs for the compelling indication
Stage 1	140-159	or 90-99	Thiazide-type diuretics for most.	Drugs for the compelling

hypertension				May consider ACEls, ARBs, β blockers Calcium channel blockers, or combination	Other drugs (diuretics, ACEls, ARBs, β blockers as needed.
Stage 2 hypertension.	≥ 16	or	≥ 100	Two drug combination for most \dagger Usually thiazide-type diuretic and ACEI Or ARB or β -blockers or calcium channel blocker).	Drugs for the compelling indication other drugs (diuretics, ACEls, ARBs, β Blocker calcium Channel blockers) as needed.

*Lifestyle modifications are encouraged for all and include (1) weight reduction if overweight (2) limitation of ethyl alcohol intake, (3) increased aerobic physical activity (30-45 minutes daily), (4) reduction of sodium intake (<2.34 g), (5) maintenance of adequate dietary potassium (>120 mmol/d), (6) smoking cessation, and (7) DASH diet (rich in fruit, vegetables, and low-fat dairy products and reduced in saturated and total fat). Compelling indications include (1) congestive heart failure, (2) MI, (3) diabetes, (4) chronic renal failure, and (5) prior stroke. \dagger initial combined therapy should be used cautiously in those at risk for orthostatic hypotension.

Recommending these two classes of antihypertensives based on evidence appears to be a safe option; randomized controlled studies for Asian population are warranted nonetheless where the population attributable risk of hypertension as a cause of stroke may be very high.

Lipid Control

Unlike coronary heart disease, association of dyslipidemias with stroke occurrence as well as recurrence is weak. However, recent trials have shown the benefits of using statins for prevention of stroke in those with Coronary artery disease.⁶⁹⁻⁷² Simvastatin and Pravastatin were the drugs used in these trials. This effect may not hold true for patients with cerebrovascular disease, where despite significant reduction in incidence of coronary events, the reduction in incidence of recurrent strokes was not significant, as concluded by the Heart Protection Study (HPS).⁷³

In contradistinction, Stroke Prevention by Aggressive Reduction of Cholesterol Levels (SPARCL) study has shown that Atorvastatin 80 mg/day significantly reduced the risk of stroke in patients who previously had a stroke or transient ischemic attack (TIA) and who had no known cardiovascular disease.⁷⁴ The proposed underlying mechanisms by which statins reduce this incidence are poorly understood, but it is widely believed that the results are more dramatic than simple fall of cholesterol levels might suggest. Therefore, statins may have a multifactorial effect in prevention against cerebrovascular diseases. It appears that statins may reduce the risk of stroke in those with previous stroke or TIA and therefore these may be considered an independent atherosclerotic equivalent for the initiation of statins in selected patients.

Therefore, patients with ischemic stroke or TIA with elevated cholesterol, comorbid coronary artery disease, or evidence of an atherosclerotic origin should be counselled regarding lifestyle modification, dietary guidelines, and medication recommendations. Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL and LDL-C of <70 mg/dL for very-high-risk persons with multiple risk factors.

Also patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid coronary artery

disease, or no evidence of atherosclerosis) are reasonable candidates for treatment with a statin agent to reduce the risk of vascular events.

Diabetes mellitus

Diabetes being a factor associated with primary stroke is well known⁷⁵⁻⁷⁹, but there is insufficient data to support its role in recurrence.⁷⁶ The recommendations for glucose control, hence, should be the same for patients with and without a prior stroke. The benefits of using an anti-diabetic agent specifically for prevention of secondary strokes are currently under study in the IRIS trial, using pioglitazone 45 mg/d long term to assess reduction in recurrence.⁸⁰ Current evidence is inadequate to support its use.

Control of other modifiable cardiovascular risk factors in a patient with diabetes is one of the most essential and challenging issues. Aggressive blood pressure control in these patients is critical for decrease in recurrence. Furthermore, aggressive lipid control is also warranted for such patients.

As for patients with a coronary artery disease, LDL- C levels of < 70md/dL is recommended for patients who have had a stroke, though there is a lack of evidence for patients with cerebrovascular events.⁸¹ Clinical trials using statins in diabetic patients have shown reductions in cardiovascular and cerebrovascular events.⁸²⁻⁸⁴

sAll classes of anti-hypertensives are approved for use in diabetes, though it is largely agreed that more than one agent should be used, and also that one of the agents should either be an ACE-I or ARB. This recommendation holds for patients with cardiovascular as well as cerebrovascular events.

TABLE 2. Recommendations for Treatable Vascular Risk Factors

Risk Factor	Recommendations	Class/ level of Evidence
Hypertension	<p>Antihypertensive treatment is recommended for prevention of recurrent stroke and other vascular events in persons who have had an ischemic stroke and are beyond the hyperacute period.</p> <p>Because this benefit extends to persons with and without a history of hypertension, this recommendation should be considered for all ischemic stroke and TIA patients.</p> <p>An absolute target BP Level And reduction are uncertain and should be individualized, but benefit has been associated with an average reduction of =10/5 mm Hg and normal BP levels have been defined as <120/80 by JNC-7.</p> <p>Several lifestyle modifications have been associated with BP reductions and should be included as part of a comprehensive approach antihypertensive therapy.</p>	<p>Class I, Level A</p> <p>Class IIa, Level B</p> <p>Class IIa, Level B</p> <p>Class IIb, Level C</p>

	<p>Optimal drug regimen remains uncertain; however, available data support the use of diuretics and the combination of diuretics and an ACEI. Choice of specific drugs and targets should be individualized on the basis of reviewed data and consideration, as well as specific patient characteristics (eg, extracranial cerebrovascular occlusive disease, renal impairment, cardiac disease, and DM).</p>	Class I, Level A
Diabetes	<p>More rigorous control of blood pressure and lipids should be considered in patients with diabetes.</p> <p>Although all major classes of antihypertensives are suitable for the control of BP, most patients will require > 1 agent. ACEIs and ARBs are more effective in reducing the progression of renal disease and are recommended as first-choice medications for patients with DM.</p> <p>Glucose control is recommended to near-normoglycemic levels among diabetics with ischemic stroke or TIA to reduce microvascular complications.</p> <p>The goal for Hb A1c should be $\leq 7\%$.</p>	<p>Class IIa, Level B</p> <p>Class I, Level A</p> <p>Class I, Level A</p> <p>Class IIa, Level B</p>
Cholesterol	<p>Ischemic stroke or TIA patients with elevated cholesterol, comorbid CAD, or evidence of an atherosclerotic origin should be managed according to NCEP III guidelines, which include lifestyle modification, dietary guidelines, and medication recommendations.</p> <p>Statin agents are recommended, and the target goal for cholesterol lowering for those with CHD or symptomatic atherosclerotic disease is an LDL-C of <100 mg/dL and LDL-C <70 mg/dL for very-high-risk persons with multiple risk factors.</p> <p>Patients with ischemic stroke or TIA presumed to be due to an atherosclerotic origin but with no preexisting indications for statins (normal cholesterol levels, no comorbid CAD, or no evidence of atherosclerosis) are reasonable to consider for treatment with a statin agent to reduce the risk of vascular events.</p> <p>Ischemic stroke or TIA patients with low HDL-C may be considered for treatment with niacin or gemfibrozil.</p>	<p>Class I, Level A</p> <p>Class I, Level A</p> <p>Class IIa, Level B</p> <p>Class IIa, Level B</p>

Smoking

Smoking has been repeatedly identified as a significant risk factor for the occurrence of ischemic stroke.⁸⁵⁻⁸⁹ The most important Asian study assessing relationship between smoking and incidence of stroke in this population was one of the arms of Japan Public Health Centre –based prospective study on cancer and cardiovascular diseases (JPHC Study) cohort 1.⁹⁰ This looked at almost 40,000 Japanese middle aged men and women followed up over a period of 12 years to see development of strokes, and confirmed a positive relationship between smoking and risk of total stroke and subarachnoid hemorrhage after adjustment for known cardiovascular risk factors and selected lifestyles.

In the presence of such convincing evidence against the use of tobacco, physicians should ask their patients repeatedly to quit smoking for both primary and secondary prevention.

A detailed smoke cessation guide is available at the NIH smoking cessation website. This guide is a good reference for patients to ease the difficulties they face while attempting to quit. (http://www.smokefree.gov/pubs/clearing_the_air.pdf). Nicotine products and oral medications have been shown to be useful in helping patients quit smoking. Patients should be counseled to quit smoking in clear uncertain terms. Nicotine products and oral medications have been shown to be useful in helping patients quit smoking.

A detailed smoke cessation guide is available at the NIH smoking cessation website.⁹¹ This guide is a good reference for patients to ease the difficulties they face while attempting to quit.

Obesity

The prevalence of obesity in Pakistan is determined to be as high as 23% among urban males and 40% among urban females, while rural areas report lower prevalence.⁹² This was based on BMI calculation using the Asia-pacific criteria.^{93, 94} However, it is now believed that abdominal obesity, rather than generalized obesity, has a stronger association with cardiovascular morbidity. Abdominal Obesity, defined by a waist circumference more than 102 cm (40 in) in men and 88 cm (35 in) in women, was shown to be an independent risk factor for ischemic stroke in the Northern Manhattan Stroke Study, with the odds of ischemic stroke 2-3 times greater among those with WHR in the third quartile or over.⁹⁵ Optimum cut-offs for abdominal obesity for South Asian population have been proposed by Misra et al comparing waist circumference (WC) to standardized Asia-Pacific BMI cut-offs and equating cardiovascular risk factors.⁹⁶ This study proposes all adult males with WC > 78 cm and adult females with WC > 72 cm as having equal risks as those categorized ‘overweight’ by their BMI., while risks equate to those categorized ‘obese’ by their BMI if WC > 90 cm for males and >80 cm for females. Even though no consensus exists in principle accepting or rejecting this proposal, it should be understood that South Asian population has far severe implications for each unit of weight gained compared to the western populations, hence calling for a more aggressive dietary control. Although no evidence exists at present suggesting decrease in stroke recurrence by weight reduction, the indirect effect of weight reduction on blood pressure, blood glucose and lipids has a definitive effect on decreasing stroke recurrence.

Exercise- regular physical activity

This has an indirect effect on stroke prevention through lowering of blood pressure. A meta-analysis by Whelton et al. in which the experience of 1,108 normotensive persons enrolled in 27 randomized controlled trials was included, identified a 4.04 mmHg (95 percent CI, 2.75–5.32) reduction in systolic blood pressure in those assigned to aerobic exercise compared with the control group. The magnitude of the intervention effect appears to be independent of the intensity of the exercise program. It is recommended that persons exercise for at least 30 minutes on most, if not all, days of the week.

Dietary salt restriction

This again has impact on stroke risk indirectly through its impact on lowering blood pressure. At least three meta-analysis of the efficacy of reduced sodium intake in lowering blood pressure have been published since 1993. In all three reports, sodium reduction was associated with a small but significant reduction in systolic blood pressure in normotensive persons. In the NHANES I Epidemiologic Follow-up Study, He et al. reported that a 100 mmol higher level of sodium intake in overweight persons was associated with a 32 percent increase in stroke incidence, a 89 percent increase in stroke mortality, a 44 percent increase in CHD mortality, a 61 percent increase in CVD mortality, and a 39 percent increase in mortality from all causes. These data support the premise that a lower intake of dietary sodium reduces the risk of subsequent CVD.

Depression

The prevalence of depression in Pakistan has been estimated to be as high as 34%.⁹⁷ Stroke survivors are at a greater risk of developing depression, and this affects their recovery from stroke.^{98, 99} Data from a local hospital revealed prevalence of post-stroke depression to be 37.9 % using DSM IV criteria among 174 patients presenting to the outpatient clinics, with most patients presenting within three months of the primary stroke.¹⁰⁰ Factors contributing to increased risk after stroke include increased stroke severity, female sex, left sided lesions and a young age.^{101, 102} Early identification and management of depression post stroke is vital to ensure early recovery, and preventing cognitive impairment. Conventional tricyclic antidepressants are contra-indicated among stroke patients due to their adverse effects.¹⁰³ SSRIs have a low adverse effect profile and a good efficacy, making them invaluable in patients with multiple comorbidities.

TABLE 9. Recommendations for Modifiable Behavioral Risk Factors

Risk Factor	Recommendations
Smoking	All ischemic stroke or TIA patients who have smoked in the past year should be strongly encouraged not to smoke Avoid environmental smoke. Counseling, nicotine products, and oral smoking cessation medications have been found to be effective for smokers.
Alcohol	Patients with prior ischemic stroke or TIA who are heavy drinkers should eliminate or reduce their consumption of alcohol. Light to moderate levels of ≤ 2 drinks per day for men and 1 drink per day for nonpregnant women may be considered.
Obesity	Weight reduction may be considered for all overweight ischemic stroke or TIA patients to maintain the goal of a BMI of 18.5 to 24.9 kg/m ² and a waist circumference of <35 in for women and <40 in for men. Clinicians should encourage weight management through an appropriate balance of caloric intake, physical activity, and behavioral counseling.
Physical activity	For those with ischemic stroke or TIA who are capable of engaging in physical activity, at least 30 minutes of moderate-intensity physical exercise most days may be considered to reduce risk factors and comorbid conditions that increase the likelihood of recurrence of stroke. For those with disability after ischemic stroke, a supervised therapeutic exercise regimen is recommended.

Recommendations for Post Hospital Management of Stroke

Initiate a cost effective and safe anti platelet agent after ischemic stroke.

Initiate and maintain warfarin at an INR 2-3 in those who have atrial fibrillation.

Hypertension control is important and imperative in all patients especially diabetics. It is expected that hypertension control will require two agents in the majority of patients.

Quit smoking counseling should be performed in clear and unambiguous terms. For those few, who can afford it, supportive counseling and medications should be offered.

The use of statins in individual patients is suggested but its population based intervention still requires investigation in Asian populations.

Sensitive and early clinical screening for depression and its treatment will alleviate significant co morbidity after stroke

Future Directions and Need

Pragmatic Population based interventional risk reduction programs are needed to reduce the burden of stroke in vulnerable populations.

Research into the known and emerging risk factors for stroke is required to enhance the cost effectiveness and relevance of these interventions.

REFERENCES:

1. <https://www.cia.gov/library/publications/the-world-factbook/print/pk.html>.
2. Nishtar S. The national action plan for the prevention and control of non-communicable diseases and health promotion in Pakistan--prelude and finale. *J Pak Med Assoc.* 2004;54:S1-8
3. Jafar TH. Blood pressure, diabetes, and increased dietary salt associated with stroke--results from a community-based study in Pakistan. *J Hum Hypertens.* 2006;20:83-85
4. American Heart Association. Heart Disease and Stroke Statistics-2004 Update. Dallas TAHA.
5. Jafar TH. The growing burden of chronic kidney disease in Pakistan. *N Engl J Med.* 2006;354:995- 997.
6. National health survey of Pakistan 1990–1994 Pakistan medical research council 1998
7. Jafar TH, Jafary FH, Jessani S, Chaturvedi N. Heart disease epidemic in Pakistan: Women and men at equal risk. *Am Heart J.* 2005;150:221-226
8. Jafar TH, Chaturvedi N, Pappas G. Prevalence of overweight and obesity and their association with hypertension and diabetes mellitus in an Indo-Asian population. *Cmaj.* 2006;175:1071-1077
9. Nasir K, Rehan N. Epidemiology of cigarette smoking in Pakistan. *Addiction.* 2001;96:1847-1854
10. Omran AR. The epidemiologic transition: A theory of the epidemiology of population change. *Milbank Mem Fund Q.* 1971;49:509-538.
11. Strong K, Mathers C, Bonita R. Preventing stroke: Saving lives around the world. *Lancet Neurol.* 2007;6:182-187
12. Feldmann E, Gordon N, Brooks JM, Brass LM, Fayad PB, Sawaya KL, Nazareno F, Levine SR. Factors associated with early presentation of acute stroke. *Stroke.* 1993;24:1805-1810

13. Kothari RU, Pancioli A, Liu T, Brott T, Broderick J. Cincinnati prehospital stroke scale: Reproducibility and validity. *Ann Emerg Med.* 1999;33:373-378
14. <http://www.strokecenter.org/trials/scales/cincinnati.html>.
15. 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
16. Thorvaldsen P, Kuulasmaa K, Rajakangas AM, Rastenyte D, Sarti C, Wilhelmsen L. Stroke trends in the WHO MONICA project. *Stroke.* 1997;28:500-506
17. <http://www.ninds.nih.gov/>.
18. Baird TA, Parsons MW, Phan T, Butcher KS, Desmond PM, Tress BM, Colman PG, Chambers BR, Davis SM. Persistent post stroke hyperglycemia is independently associated with infarct expansion and worse clinical outcome. *Stroke.* 2003;34:2208-2214
19. Lindsberg PJ, Roine RO. Hyperglycemia in acute stroke. *Stroke.* 2004;35:363-364
20. Veazie MA, Galloway JM, Matson-Koffman D, LaBarthe DR, Brownstein JN, Emr M, Bolton E, Freund E, Jr., Fulwood R, Guyton-Krishnan J, Hong Y, Lebowitz M, Ochiai E, Schoeberl M, Robertson RM. Taking the initiative: Implementing the American heart association guide for improving cardiovascular health at the community level: Healthy people 2010 heart disease and stroke partnership community guideline implementation and best practices workgroup. *Circulation.* 2005;112:2538-2554
21. Nor AM, Davis J, Sen B, Shipsey D, Louw SJ, Dyker AG, Davis M, Ford GA. The recognition of stroke in the emergency room (rosier) scale: Development and validation of a stroke recognition instrument. *Lancet Neurol.* 2005;4:727-734
22. Cheung CM, Tsoi TH, Hon SF, Au-Yeung M, Shiu KL, Lee CN, Huang CY. Using the national institutes of health stroke scale (NIHSS) to predict the mortality and outcome of patients with intracerebral hemorrhage. *Hong Kong Med J.* 2008; 14:367-370
23. Adams HP, Jr., Brott TG, Furlan AJ, Gomez CR, Grotta J, Helgason CM, Kwiatkowski T, Lyden PD, Marler JR, Torner J, Feinberg W, Mayberg M, Thies W. Guidelines for thrombolytic therapy for acute stroke: A supplement to the guidelines for the management of patients with acute ischemic stroke. A statement for healthcare professionals from a special writing group of the stroke council, American Heart Association. *Circulation.* 1996; 94:1167-1174
24. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *N Engl J Med.* 1995; 333:1581-1587

25. Patel SC, Levine SR, Tilley BC, Grotta JC, Lu M, Frankel M, Haley EC, Jr., Brott TG, Broderick JP, Horowitz S, Lyden PD, Lewandowski CA, Marler JR, Welch KM. Lack of clinical significance of early ischemic changes on computed tomography in acute stroke. *JAMA*. 2001;286:2830-2838
26. Hacke W, Kaste M, Fieschi C, Toni D, Lesaffre E, von Kummer R, Boysen G, Bluhmki E, Hoxter G, Mahagne MH, et al. Intravenous thrombolysis with recombinant tissue plasminogen activator for acute hemispheric stroke. The European cooperative acute stroke study (ECASS). *JAMA*. 1995;274:1017-1025
27. Larrue V, von Kummer R, del Zoppo G, Bluhmki E. Hemorrhagic transformation in acute ischemic stroke. Potential contributing factors in the European cooperative acute stroke study. *Stroke*. 1997;28:957-960
28. Fiebach JB, Schellinger PD, Gass A, Kucinski T, Siebler M, Villringer A, Olkers P, Hirsch JG, Heiland S, Wilde P, Jansen O, Rother J, Hacke W, Sartor K. Stroke magnetic resonance imaging is accurate in hyperacute intracerebral hemorrhage: A multicenter study on the validity of stroke imaging. *Stroke*. 2004; 35:502-506
29. Kidwell CS, Saver JL, Villablanca JP, Duckwiler G, Fredieu A, Gough K, Leary MC, Starkman S, Gobin YP, Jahan R, Vespa P, Liebeskind DS, Alger JR, Vinuela F. Magnetic resonance imaging detection of microbleeds before thrombolysis: An emerging application. *Stroke*. 2002; 33:95-98
30. Grossman E, Messerli FH, Grodzicki T, Kowey P. Should a moratorium be placed on sublingual nifedipine capsules given for hypertensive emergencies and pseudoemergencies? *JAMA*. 1996; 276:1328-1331
31. Brott T, Lu M, Kothari R, Fagan SC, Frankel M, Grotta JC, Broderick J, Kwiatkowski T, Lewandowski C, Haley EC, Marler JR, Tilley BC. Hypertension and its treatment in the ninds rt-pa stroke trial. *Stroke*. 1998; 29:1504-1509
32. Lyden PD. Thromolytic therapy for acute stroke. 2005
33. Yamaguchi T, Mori E, Minematsu K, Nakagawara J, Hashi K, Saito I, Shinohara Y. Alteplase at 0.6 mg/kg for acute ischemic stroke within 3 hours of onset: Japan alteplase clinical trial (j-act). *Stroke*. 2006;37:1810-1815
34. Hammer MD, Krieger DW. Hypothermia for acute ischemic stroke: Not just another neuroprotectant. *Neurologist*. 2003; 9:280-289
35. Bernard SA, Buist M. Induced hypothermia in critical care medicine: A review. *Crit Care Med*. 2003; 31:2041-2051
36. Bernard SA, Gray TW, Buist MD, Jones BM, Silvester W, Gutteridge G, Smith K. Treatment of comatose survivors of out-of-hospital cardiac arrest with induced hypothermia. *N Engl J Med*. 2002; 346:557-563

37. The hypothermia after cardiac arrest study group. Mild hypothermia to improve the neurologic outcome after cardiac arrest. *N Engl J Med.* 2002;346:2041-2051
38. Kase CS, Furlan AJ, Wechsler LR, Higashida RT, Rowley HA, Hart RG, Molinari GF, Frederick LS, Roberts HC, Gebel JM, Sila CA, Schulz GA, Roberts RS, Gent M. Cerebral hemorrhage after intra-arterial thrombolysis for ischemic stroke: The proact ii trial. *Neurology.* 2001; 57:1603-1610
39. The international stroke trial (ist): A randomized trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischemic stroke. International stroke trial collaborative group. *Lancet.* 1997; 349:1569-1581
40. Gubitz G, Counsell C, Sandercock P, Signorini D. Anticoagulants for acute ischemic stroke. *Cochrane Database Syst Rev.* 2000:CD000024
41. Sandercock P, Gubitz G, Foley P, Counsell C. Antiplatelet therapy for acute ischemic stroke. *Cochrane Database Syst Rev.* 2003:CD000029
42. Albers GW, Amarenco P, Easton JD, Sacco RL, Teal P. Antithrombotic and thrombolytic therapy for ischemic stroke: The seventh ACCP conference on antithrombotic and thrombolytic therapy. *Chest.* 2004; 126:483S-512S
43. Cast: Randomized placebo-controlled trial of early aspirin use in 20,000 patients with acute ischaemic stroke. CAST (Chinese Acute Stroke Trial) collaborative group. *Lancet.* 1997; 349:1641-1649
44. Martino R, Foley N, Bhogal S, Diamant N, Speechley M, Teasell R. Dysphagia after stroke: Incidence, diagnosis, and pulmonary complications. *Stroke.* 2005; 36:2756-2763
45. Gould MK, Dembitzer AD, Doyle RL, Hastie TJ, Garber AM. Low-molecular-weight heparins compared with unfractionated heparin for treatment of acute deep venous thrombosis. A meta-analysis of randomized, controlled trials. *Ann Intern Med.* 1999; 130:800-809
46. Hyers TM, Agnelli G, Hull RD, Weg JG, Morris TA, Samama M, Tapson V. Antithrombotic therapy for venous thromboembolic disease. *Chest.* 1998; 114:561S-578S
47. Sandercock PA, van den Belt AG, Lindley RI, Slattery J. Antithrombotic therapy in acute ischemic stroke: An overview of the completed randomized trials. *J Neurol Neurosurg Psychiatry.* 1993; 56:17-25
48. Kamphuisen PW, Agnelli G, Sebastianelli M. Prevention of venous thromboembolism after acute ischemic stroke. *J Thromb Haemost.* 2005; 3:1187-1194
49. Davis SM, Donnan GA. Effective prophylaxis for deep venous thrombosis after stroke: Both low-dose anticoagulation and stockings for most cases. *Stroke.* 2004; 35:2910

50. Qizilbash N, Lewington SL, Lopez-Arrieta JM. Corticosteroids for acute ischaemic stroke. *Cochrane Database Syst Rev.* 2002;CD000064
51. Lutsep HL, Clark WM. Neuroprotection in acute ischemic stroke. Current status and future potential. *Drugs R D.* 1999; 1:3-8
52. Wahlgren NG, Ahmed N. Neuroprotection in cerebral ischemia: Facts and fancies--the need for new approaches. *Cerebrovasc Dis.* 2004; 17 Suppl 1:153-166
53. Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ.* 2002; 324:71-86
54. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European stroke prevention study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci.* 1996; 143:1-13
55. Collaborative overview of randomized trials of antiplatelet therapy--iii: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet trialists' collaboration. *BMJ.* 1994; 308:235-246
56. Hansson L, Zanchetti A, Carruthers SG, Dahlof B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: Principal results of the hypertension optimal treatment (hot) randomized trial. Hot study group. *Lancet.* 1998; 351:1755-1762
57. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (caprie). Caprie steering committee. *Lancet.* 1996; 348:1329-1339
58. Bhatt DL, Marso SP, Hirsch AT, Ringleb PA, Hacke W, Topol EJ. Amplified benefit of clopidogrel versus aspirin in patients with diabetes mellitus. *Am J Cardiol.* 2002; 90:625-628
59. Ringleb PA, Bhatt DL, Hirsch AT, Topol EJ, Hacke W. Benefit of clopidogrel over aspirin is amplified in patients with a history of ischemic events. *Stroke.* 2004; 35:528-532
60. Diener HC, Bogousslavsky J, Brass LM, Cimminiello C, Csiba L, Kaste M, Leys D, Matias-Guiu J, Rupprecht HJ. Aspirin and clopidogrel compared with clopidogrel alone after recent ischemic stroke or transient ischemic attack in high-risk patients (match): Randomized, double-blind, placebo-controlled trial. *Lancet.* 2004; 364:331-337
61. Kennedy J, Hill MD, Ryckborst KJ, Eliasziw M, Demchuk AM, Buchan AM. Fast assessment of stroke and transient ischemic attack to prevent early recurrence (faster): A randomized controlled pilot trial. *Lancet Neurol.* 2007; 6:961-969
62. Levine RL, Dixit SN, Dulli DA, Khasru MA. Aspirin "Failures," Clopidogrel added to aspirin, and secondary stroke prevention in veterans presenting with tia or mild-to-moderate ischemic stroke. *J Stroke Cerebrovasc Dis.* 2003; 12:37-43

63. Diener HC, Nitschmann S. [consequent preventive therapy protects against stroke: Express study (early use of existing preventive strategies for stroke)]. *Internist (Berl)*. 2008; 49:635-636
64. Rodgers A, MacMahon S, Gamble G, Slattery J, Sandercock P, Warlow C. Blood pressure and risk of stroke in patients with cerebrovascular disease. The United Kingdom transient ischemic attack collaborative group. *BMJ*. 1996;313:147
65. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med*. 2000; 342:145-153
66. Lawes CM, Bennett DA, Feigin VL, Rodgers A. Blood pressure and stroke: An overview of published reviews. *Stroke*. 2004; 35:1024
67. Chobanian AV, Bakris GL, Black HR, Cushman WC, Green LA, Izzo JL, Jr., Jones DW, Materson BJ, Oparil S, Wright JT, Jr., Roccella EJ. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: The JNC 7 report. *JAMA*. 2003; 289:2560-2572
68. Randomized trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischemic attack. *Lancet*. 2001;358:1033-1041
69. Collins R, Armitage J, Parish S, Sleight P, Peto R. Mrc/bhf heart protection study of cholesterol-lowering with simvastatin in 5963 people with diabetes: A randomized placebo-controlled trial. *Lancet*. 2003; 361:2005-2016
70. Sacks FM, Pfeffer MA, Moye LA, Rouleau JL, Rutherford JD, Cole TG, Brown L, Warnica JW, Arnold JM, Wun CC, Davis BR, Braunwald E. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. Cholesterol and recurrent events trial investigators. *N Engl J Med*. 1996; 335:1001-1009
71. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: The scandinavian simvastatin survival study (4s). *Lancet*. 1994; 344:1383-1389
72. Ovbiagele B, Kidwell CS, Saver JL. Expanding indications for statins in cerebral ischemia: A quantitative study. *Arch Neurol*. 2005; 62:67-72
73. Collins R, Armitage J, Parish S, Sleight P, Peto R. Effects of cholesterol-lowering with simvastatin on stroke and other major vascular events in 20536 people with cerebrovascular disease or other high-risk conditions. *Lancet*. 2004; 363:757-767
74. Amarenco P, Bogousslavsky J, Callahan AS, Goldstein L, Hennerici M, Sillsen H, Welch MA, Zivin J. Design and baseline characteristics of the stroke prevention by aggressive reduction in cholesterol levels (sparcl) study. *Cerebrovasc Dis*. 2003;16:389-395

75. Petty GW, Brown RD, Jr., Whisnant JP, Sicks JD, O'Fallon WM, Wiebers DO. Survival and recurrence after first cerebral infarction: A population-based study in Rochester, Minnesota, 1975 through 1989. *Neurology*. 1998;50:208-216
76. Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CD. Cause of stroke recurrence is multifactorial: Patterns, risk factors, and outcomes of stroke recurrence in the south London stroke register. *Stroke*. 2003; 34:1457-1463
77. Hier DB, Foulkes MA, Swiontoniowski M, Sacco RL, Gorelick PB, Mohr JP, Price TR, Wolf PA. Stroke recurrence within 2 years after ischemic infarction. *Stroke*. 1991; 22:155-161
78. Mast H, Thompson JL, Lee SH, Mohr JP, Sacco RL. Hypertension and diabetes mellitus as determinants of multiple lacunar infarcts. *Stroke*. 1995;26:30-33
79. Arauz A, Murillo L, Cantu C, Barinagarrementeria F, Higuera J. Prospective study of single and multiple lacunar infarcts using magnetic resonance imaging: Risk factors, recurrence, and outcome in 175 consecutive cases. *Stroke*. 2003; 34:2453-2458
80. Schondorf T, Forst T, Hohberg C, Pahler S, Link C, Roth W, Pfutzner A, Lubben G. The iris iii study: Pioglitazone improves metabolic control and blood pressure in patients with type 2 diabetes without increasing body weight. *Diabetes Obes Metab*. 2007; 9:132-133
81. Grundy SM, Cleeman JI, Merz CN, Brewer HB, Jr., Clark LT, Hunninghake DB, Pasternak RC, Smith SC, Jr., Stone NJ. Implications of recent clinical trials for the national cholesterol education program adult treatment panel iii guidelines. *Circulation*. 2004; 110:227-239
82. Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The long-term intervention with pravastatin in ischaemic disease (LIPID) study group. *N Engl J Med*. 1998;339:1349-1357
83. Pyorala K, Pedersen TR, Kjekshus J, Faergeman O, Olsson AG, Thorgeirsson G. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease. A subgroup analysis of the Scandinavian simvastatin survival study (4s). *Diabetes Care*. 1997; 20:614-620
84. Goldberg RB, Mellies MJ, Sacks FM, Moye LA, Howard BV, Howard WJ, Davis BR, Cole TG, Pfeffer MA, Braunwald E. Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: Subgroup analyses in the cholesterol and recurrent events (care) trial. The care investigators. *Circulation*. 1998;98:2513-2519

85. Kawachi I, Colditz GA, Stampfer MJ, Willett WC, Manson JE, Rosner B, Speizer FE, Hennekens CH. Smoking cessation and decreased risk of stroke in women. *JAMA*. 1993; 269:232-236
86. Mast H, Thompson JL, Lin IF, Hofmeister C, Hartmann A, Marx P, Mohr JP, Sacco RL. Cigarette smoking as a determinant of high-grade carotid artery stenosis in hispanic, black, and white patients with stroke or transient ischemic attack. *Stroke*. 1998;29:908-912
87. Robbins AS, Manson JE, Lee IM, Satterfield S, Hennekens CH. Cigarette smoking and stroke in a cohort of U.S. Male physicians. *Ann Intern Med*. 1994;120:458-462
88. Shinton R, Beevers G. Meta-analysis of relation between cigarette smoking and stroke. *BMJ*. 1989; 298:789-794
89. Wolf PA, D'Agostino RB, Kannel WB, Bonita R, Belanger AJ. Cigarette smoking as a risk factor for stroke. The Framingham study. *JAMA*. 1988; 259:1025-1029
90. Mannami T, Iso H, Baba S, Sasaki S, Okada K, Konishi M, Tsugane S. Cigarette smoking and risk of stroke and its subtypes among middle-aged Japanese men and women: The JPHC study cohort i. *Stroke*. 2004;35:1248-1253
91. http://www.smokefree.gov/pubs/clearing_the_air.pdf.
92. Nanan DJ. The obesity pandemic-implications for Pakistan. *J Pak Med Assoc*. 2002; 52:342-346
93. Choo V. Who reassesses appropriate body-mass index for Asian populations. *Lancet*. 2002; 360:235
94. World Health Organization. The Asia-pacific perspective: Redefining obesity and its treatment. Sydney, Australia: Health communications Australia Pty limited; 2000. Available: www.diabetes.com.au/pdf/obesity_report.pdf.
95. Suk SH, Sacco RL, Boden-Albala B, Cheun JF, Pittman JG, Elkind MS, Paik MC. Abdominal obesity and risk of ischemic stroke: The northern Manhattan stroke study. *Stroke*. 2003;34:1586-1592
96. Misra A, Vikram NK, Gupta R, Pandey RM, Wasir JS, Gupta VP. Waist circumference cutoff points and action levels for Asian Indians for identification of abdominal obesity. *Int J Obes (Lond)*. 2006;30:106-111
97. Mirza I, Jenkins R. Risk factors, prevalence, and treatment of anxiety and depressive disorders in Pakistan: Systematic review. *BMJ*. 2004;328:794
98. Robinson RG, Morris PL, Fedoroff JP. Depression and cerebrovascular disease. *J Clin Psychiatry*. 1990; 51 Suppl:26-31; discussion 32-23

99. Astrom M, Adolfsson R, Asplund K. Major depression in stroke patients. A 3-year longitudinal study. *Stroke*. 1993; 24:976-982
100. Chaudhary UJ, Osman SS, Iqtadar S, Zafar W, Shakil S, Zahoor Z, Akram J. Study of frequency and responsible factors for post stroke depression in stroke patients coming to Mayo Hospital Lahore. *Ann King Edward Med Coll*. 2006; 12:299-301
101. Barker-Collo SL. Depression and anxiety 3 months post stroke: Prevalence and correlates. *Arch Clin Neuropsychol*. 2007; 22:519-531
102. Kotila M, Numminen H, Waltimo O, Kaste M. Depression after stroke: Results of the Finnstroke study. *Stroke*. 1998; 29:368-372
103. Torta R, Cicolin A, Keller R. Stroke and depression: Clinical features and treatment. *Ital J Neurol Sci*. 1998; 19 Suppl 1:S20-24