ASIAN SYNOPSIS OF STROKE

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Preface

Dedicated to stroke victims without optimal management in developing countries

Innumerable advances in technology, diagnosis, treatment and understanding of various cerebrovascular disease processes have occurred in recent decades. I attempt to bring readers up to date with these advances. Recent major advances are introduced for the clinicians working in the developing countries. I have tried to retain a single consistent approach to stroke diagnosis and care. Studies on cerebral localization and correlation with functional anatomy (stroke syndromes) are interesting to neuroscientists, but not of immediate value applicable to the individual patients. Thus only practical points about stroke syndromes are written in this book. Despite very high costs and other barriers of intra-venous and intra-arterial thrombolysis in developing countries, this handbook includes these subjects. Many of the stroke patients are treated by internists and non-neurologists in the developed and developing countries. The author endeavors has been to write a practical book understandable for neurologists and non-neurologists with special concern to conditions of medical practice in the developing countries. Some of the evidence-based guidelines of stroke management driven from American and European Stroke Associations are not suitable and practical for stroke management in the developing countries. Guidelines are continuously developed and updated in the developed world but their practicality for use in developing regions is unrealistic. The author provided recommendations and guidelines for stroke practice in the developing countries. This handbook is written for residents of Neurology, Neurosurgery, Internal Medicine, Cardiology, Vascular Surgery and Stroke Fellows in the developing countries. Review of stroke literature reveals that almost all of stroke texts are provided in the developed countries especially in north America and Europe. This handbook is provided for physicians residing in Asia. I would appreciate cooperation of research chancellor and publication committee of Mashhad University of Medical Sciences for publication and distribution of this monograph.

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January, 1, 2012
Asian Synopsis of Stroke

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Clinical Diagnosis of TIA and Stroke

The traditional diagnosis of Transient Ischemic Attack (TIA) is clinical and not based on any specific diagnostic test. TIA is an impressive warning of stroke and its recognition provides the opportunity for therapeutic intervention. TIA usually occurs when a physician is not available to examine the patient. By definition all patients with a TIA or stroke will have had focal neurological symptoms which are those that arise from a disturbance in an identifiable and localized area of the brain. Localized cerebral ischemia causes focal neurological symptoms. There are some focal neurological symptoms which if they occur in isolation (such as rotational vertigo, transient amnesia, deafness, dysarthria, dysphagia, ataxia and diplopia) should probably not be considered because they all occur more commonly in non-vascular conditions. Non-focal symptoms such as faintness, dizziness, tinnitus, confusion, generalized weakness or sensory disturbance and incontinence are seldom due to focal cerebral ischemia but may be due to generalized brain ischemia as well as non-vascular causes. TIA is a clinical syndrome characterized by an acute loss of focal cerebral or monocular function with symptoms lasting less than 24 hours and which is thought to be due to inadequate cerebral or ocular blood supply. When the patient says; I got better in 24 hours, does not necessarily mean, I got completely back to normal and it is the later to which we are referring when defining a TIA. Almost half of cerebral TIs persist less than 5 minutes, another quarter subside within an hour and the remainder are gone within 24 hours. The prognosis for subsecuent stroke appears to be the same whether
the spell is brief or long in duration. Monocular TIAs usually persist less than 10 minutes. The symptoms duration of 24 hours was chosen to distinguish TIA from stroke. This time limit has been widely accepted. The patient must have no abnormal neurologic symptoms between attacks, unless there has been previous infarction. Following symptomatic recovery of TIA patients, a few physical signs such as reflex asymmetry or extensor plantar reflex may be present after 24 hours.

**Diagnostic criteria for TIA**

1. **Quality of symptoms**: TIA has negative symptoms, representing a loss of focal cerebral or monocular function (i.e. weakness, numbness, dysphasia, loss of vision). The neural dysfunction must be localized to a specific vascular territory.

2. **Onset**: TIA symptoms initiates abruptly, starting in different parts of the body (i.e. face, arm and leg) at the same time without intensification or spread (march). The deficit is maximal within a few seconds.

3. **Offset**: TIA symptoms resolve more gradually but completely, usually within 1 hour and always before 24 hours. Very brief attacks lasting only few seconds are unusual except in monocular TIAs.

4. **Absence of associated symptoms**: TIA usually occur without warning or associated symptoms. Headache, nausea or epigastric discomfort usually indicate migraine or epilepsy. Loss of consciousness is almost never due to a TIA, it usually suggests syncope or epilepsy. Generally, the visual loss in TIA is painless which helps to differentiate it from migraine with visual aura.

5. **Frequency of attacks**: TIAs often recur but very frequent (every day or every other day) stereotyped attacks for many years without development of stroke are not TIAs and raise the possibility of partial seizures.

The standard definition of TIA allows abnormal but functionally unimportant focal neurological signs such as reflex asymmetry or an extensor plantar response to persist for longer than 24 hours, provided the symptoms have resolved (this occurs in about 5% of the TIA patients).

The risk of stroke after monocular TIAs is less than cerebral TIAs. Monocular TIA is a brief monocular obscuration described by patients as a fog, cloud, shade or curtain in whole or part of the visual field of one eye. Patients with severe Internal Carotid Artery (ICA) stenosis or occlusion infrequently may experience recurrent, involuntary, irregular and wavering movements on the contralateral arm and/or leg. These rare limb shaking
TIAs occur during ischemic dysfunction of basal ganglia and are position dependent. Patients with severe carotid stenosis or occlusion infrequently have watershed TIAs with march of symptoms which are usually position dependent, despite migraine and partial seizures. These watershed TIAs could also occur during transient decrease of systemic blood pressure.

New definition of TIA

Some stroke experts defined TIA as a brief neurological dysfunction induced by a focal brain or retinal ischemic lesion, whose symptoms last in general close to one hour without any infarction in the neuroimaging. Two-thirds of TIAs last less than 1 hour and the probability that symptoms lasting more than 1 hour disappear within 24 hours is 15%. In addition, the prevalence of ischemic lesions on MRI increases with symptom duration. Although classic definition of TIA may induce a delay in thrombolysis therapy, however, classic definition has epidemiologic points of interest.

Case report: A 65 years old male had episodes of left leg numbness spreading to left upper limb during a few minutes and lasting for 15-30 minutes. All of these episodes occurred during mechanical activities. He had severe proximal right ICA stenosis. The last episode lasted for 20 hours and CT showed infarct in watershed area between superficial and deep branches of the Middle Cerebral Artery (MCA).

Stroke Definition

Stroke is a clinical syndrome characterized by an acute loss of focal cerebral function with symptoms lasting more than 24 hours or leading to death, and is thought to be due to either spontaneous hemorrhage in the brain or inadequate blood supply to a part of the brain. Silent brain infarction is defined as evidence of a new brain infarct in neuroimaging without corresponding manifestations. Brain CT in ischemic stroke patients rules out hemorrhagic stroke, but it does not need to confirm the presence of a brain infarction if clinical symptomatology is sufficient for stroke diagnosis. Patients with TIA and mild ischemic stroke have many similarities; they have a similar age and sex distribution, a similar prevalence of vascular risk factors and pathogenesis and they share the same long-term risk of serious vascular events. Thus, from the view of secondary prevention, there seems no pressing need to differentiate them. Distinction between stroke and TIA is arbitrary, does not have any pathophysiological basis and is of little value to the physician seeing the patient with persisting symptoms a few hours after onset. The problem is how to use these time-
based definitions of stroke or TIA in patients who are going to be potential candidates of expensive and dangerous therapies, i.e. intra-venous or intra-arterial thrombolysis, within a few hours of the onset of the symptoms². Whether this ischemic attack will turn out to be a TIA or a stroke may be an important question in these candidates of thrombolysis. Whenever physicians visit these patients in the acute phase, there are basically two groups of the patients, those with symptoms that have resolved at the time of assessment and those without significant recovery³. Some times vascular nature of the acute or sudden focal neurologic deficits is questionable. Presence of a definite cardiac source of embolism or a sever corresponding atherosclerotic stenosis or other vascular lesion, i.e. dissection, makes the syndrome very likely to be vascular². Because it is the suddenness of onset that usually stamps the event as vascular, it is useful to ask patients, what they were doing at that time. Sometimes stroke symptoms evolve steadily over minutes or hours, or may develop in a saltatory or stepwise fashion over several hours. This type of stroke initiation is named stroke in evolution or progressive stroke². In patients with sever extracranial ICA stenosis or occlusion watershed strokes due to distal flow insufficiency may occur. Proximal predominancy of the neurological deficit and development of ischemic event during fall of the blood pressure could guide to diagnosis of borderzone or watershed brain infarction². Evaluation of relationship between weakness region and topography of cerebral infarction based on brain CT in Persian stroke patients revealed that there is no topographic predominance based on the distribution and severity of weakness⁷. Global, Broca and Wernicke subtypes of aphasia constitute 52%, 40%, and 6% of language disturbances in Persian stroke cases with aphasia⁸. Based on the usual nourishment of Broca and Wernicke areas by superior and inferior branches of MCA, 79% of Global, 47% of Broca and 50% of Wernicke aphasias have a compatible infarct topography⁹. Specific cerebrovascular topography for subtypes of aphasia is not found⁹.

**Silent Brain Infarction (SBI)**

Each cubic millimeter of brain is vulnerable to ischemia and infarction, but ischemia in only about one-third of the brain is associated with any symptom or sign¹⁰. Neurologists often neglect the importance of SBI. SBI are frequently seen on neuroimaging in healthy elderly people and sometimes incidentally revealed by CT scan executed for other purposes. SBI are 5 times as prevalent as symptomatic brain infarcts in the general population¹⁰. The presence of SBI increases the risk of symptomatic stroke
3 folds, independently of other risk factors\textsuperscript{10}. Symptoms of SBI are not noticed or recognized by the patient. There are mainly two reasons leading to silence of the brain infarct: 1-The size and/or location of the lesion did not lead to to symptoms. 2-Symptoms produced by the SBI have not been recognized or have been forgotten by the patient. The later category is related to cerebral infarcts with transient symptoms, which result from an infarct visible by neuroimaging. A double-center study revealed that in age group more than 65 years, north American people are significantly more preponderant to SBI than Persians\textsuperscript{5}. The significantly higher preponderance of female gender to SBI was not related to age and race effect\textsuperscript{5}. Lacunar infarcts were found in 87\% of our patients with SBI\textsuperscript{5}. This finding may explain why these lesions are asymptomatic. Because the majority of lacunes occur in areas such as the lentiform nucleus and are thought to be asymptomatic or at least unrecognized.

**Differential diagnosis of TIA and Stroke**

The initial diagnosis of stroke or TIA may be revised particularly if a stroke patient deteriorates or fails to improve in a typical way after acute stroke. It is surprising how often in young patients multiple sclerosis can be confused with stroke and at any age how migraine aura without headache can be confused with TIAs. In general the problem is seldom the lack of a key investigation but often the lack of a good clinical history.

**Migraine with Aura**

Presence of positive neurological symptoms (i.e. flashing lights or dysesthesia) supports diagnosis of migraine\textsuperscript{1}. Neurological symptoms of migraine has gradual onset with intensification and spread or march from one body part to adjacent body parts over several minutes and resolve gradually\textsuperscript{2}. Headache and nausea are usually associated with neurological symptoms of migraine. It is not unusual for patients who had migraine aura to suffer identical auras at other times but without headache and nausea particularly as they get older\textsuperscript{1,2}. The onset of migraine attacks is usually in young to middle aged adults with few or no vascular risk factors and normal heart. Family history of migraine is common in these patients and attachs could be reduced with migraine prophylactic medication\textsuperscript{3}. Despite migraine, transient monocular blindness rarely occurs simultaneous with cerebral neurologic deficit as TIA. Transient monocular visual symptoms followed by pulsatile ipsilateral ocular pain is named ocular or retinal migraine\textsuperscript{2,3}. Gradual onset of monocular scotoma or incomplete blindness, positive
visual symptoms, i.e. scintillations lasting up to an hour is characteristic of retinal migraine\(^3\). Retinal vasospasm on fundoscopy of these patients may be seen during visual aura and recovered by calcium channel blockers\(^1\).

**Partial Seizure**

Symptoms of partial seizures are usually positive, i.e. limb jerking and paresthesia. Negative symptoms such as post ictal Todds paralysis may follow a partial motor seizure with secondary generalization but this should be obvious from the history unless the patient was asleep or is aphasic with no witness\(^1\). Seizure symptoms arise quickly over seconds to minutes but not suddenly and spread or march to adjacent parts of the body. Impaired awareness and consciousness with secondary generalization of seizure may occur. Onset of seizure attacks is usually in young to middle aged adults with few or no vascular risk factors\(^2\). Very frequent stereotyped attacks and therapeutic response to antiepileptic drugs suggests partial seizures.

**Tumor Attacks**

Both benign and malignant intracranial neoplasms occasionally cause sudden and transient loss of focal neurological function and simulate TIA\(^1\). Tumor attacks with pure sensory symptoms or aphasia are sometimes present in patients with meningioma or glioma\(^1\). Gradually, more characteristic epileptic manifestations, i.e focal jerking and loss of consciousness declare itself. Neurologic manifestations of a brain tumor sometimes simulates a cerebrovascular lesion. Slow progression of focal neurological deficit over days to weeks, history of recent headache, epileptic seizures and papilledema makes easy to diagnose brain tumors\(^2\). Hemorrhage within a tumor without previous focal symptoms may cause sudden onset of focal neurological deficit\(^3\). Brain tumors and extracerebral hematomas constitute most of pseudostrokes identified by CT.

**Chronic Subdural Hematoma**

This should be suspected in clinical practice if there is subacute onset of focal neurological symptoms, persistent headache, more confusion than expected from the neurological deficit and a progressive or fluctuating clinical course\(^1\). Chronic subdural hematoma is rare after 3 months of head trauma.

**Psychological Disorder**

Occurrence of manifestations in a young adult especially females without underlying vascular risk factors often with emotional context are in favor of
psychological disorders\textsuperscript{1}. Sometimes there is a family member or a friend (model) with stroke or TIA. There is inconsistency in what patient can do and can not do, i.e. the patient may not be able to lift either leg off the bed but can still sit up and walk\textsuperscript{6}.

**Encephalitis, Brain Abscess and Subdural Empyema**

If a patient with focal neurological deficit has altered consciousness and fever then localized brain infection needs to be considered particularly if there is no other cause for the fever such as pneumonia, urinary tract infection or deep venous thrombosis\textsuperscript{1}. Subacute evolution of focal neurological deficit and presence of fever, seizure, sinusitis and mastoiditis suggests these infectious processes\textsuperscript{3}.

**Multiple Sclerosis**

These patients are usually young women without vascular risk factors and with a normal heart. There are usually more neurological signs than symptoms and evidence of lesions in other parts of central nervous system\textsuperscript{6}.

**Mononeuropathy and Radiculopathy**

Peripheral nerve lesions occasionally have sudden onset or sudden awareness of persisting focal sensory or motor symptoms on waking up from sleep. However, lower motor neuron signs or sensory loss or pain in a dermatomal or nerve distribution area are suggestive of this diagnosis\textsuperscript{1}.

**Hypoglycemia**

Transient or permanent focal neurological deficits can occur even without adrenergic symptoms in hypoglycemia. Consciousness is often normal in these circumstances and the blood glucose may have returned to normal during sample withdrawal\textsuperscript{2}. These episodes are usually caused by hypoglycemic drugs rather than insulinoma\textsuperscript{1}.

**Rare etiologies of TIA or brain infarction**

Embolization of an embolus from an aneurysm or dissection, vascular steal and small intraparenchymal hemorrhage associated with an arteriovenous malformation may cause TIA or stroke\textsuperscript{1}.

**Clinical Stroke Subtyping**

Clinical criteria that have been developed to help differentiate infarct
from hemorrhage rely on decreased consciousness, severe headache, vomiting as predictors of hemorrhage. Since small hematomas can present with circumscribed focal deficits and can easily lead those relying on the clinical syndrome alone to diagnose infarction mistakenly, these criteria can never be relied on for a definite diagnosis. The advent of Computerized Tomography (CT) has led to correction of these potential misdiagnoses. It is often difficult to classify patients by different mechanisms of cerebral infarction on clinical criteria alone. Diagnostic workup is required as the presenting clinical syndrome is usually not distinctive enough to infer the cause and could not lead a definite determination of infarct subtype without confirming laboratory data. A sudden onset of stroke manifestations may occur in cardioembolic, large and small artery atherosclerotic disease and miscellaneous causes. Despite traditional beliefs, fluctuating onset may be seen in documented embolic strokes and small artery atherosclerotic disease. A mild weakness in stroke patient may evolve to a total paralysis by a gradual or steplike intensification within several hours. The progressive stroke is not characteristic for any stroke subtype. Multiple cortical and subcortical infarcts in different vascular territories are suggestive of brain embolism from a cardiac or aortic source, however embolic material may go infrequently to the same side on repeated occasions. Although history of TIA is common in patients with large artery atherosclerosis however it may be found in other subtypes of brain infarction. Recurring TIAs in the same vascular territory are frequent precursors of atherosclerotic strokes. TIAs tend to cluster in time and stroke tends to occur early after a TIA and affects the same arterial territory. TIA in patients with small artery atherosclerotic disease occurs in a stereotyped fashion and is limited to a period of days. Because it takes shorter for a small vessel to be occluded than a large vessel. In large vessel disease the TIAs may be less stereotyped, i.e. weakness of right hand in one attack and aphasia in another. The larger the vascular territory, the more opportunity for variety in clinical presentation. Lacunes typically present with highly focal symptoms. Lacunar TIAs are very stereotyped and numerous. Cardioembolic TIAs tend to be less frequent but last longer than atherosclerotic events and often involve multiple vascular territories. The term crescendo TIAs describes the occurrence of multiple TIAs over a few hours to a few days increasing in duration and severity. Many syndromes such as isolated hemianopsia, Broca aphasia and Wernicke aphasia were considered almost specific for embolism. It was assumed that these infarcts are so focal and associated with distal involvement of the arterial tree that local atherothrombosis is not
a serious possibility. Surprisingly, CT has shown that any of these syndromes my arise rarely from a hematoma. It is clear that brain infarcts of all sizes and all locations (i.e. lacunar infarcts) can be caused by cardiogenic emboli. History of systemic embolism is valuable but infrequent in patients with cardioembolic stroke. The presence of an irregular arrhythmia or heart murmur is important in clinical diagnosis of cardioembolic stroke. Patients with brain infarction and early stupor or depressed level of consciousness have more chance of a cardiac source of large embolism. A shrinking deficit can occur when the embolus is introduced into the ICA, causing a profound full hemisphere syndrome, after which it passes up the ICA to its final branches leaving only a mild deficit after a few days. Mohr described spectacular shrinking deficit with sudden complete or nearly complete clearing of initially severe neurologic deficit. Most often these patients have cardioembolic occlusion of the main stem of MCA or Basilar Artery (BA) with rapid recanalization. Shrinking deficit is also seen in small vessel atherosclerotic disease and other causes of cerebral infarction. Presence of decreased alertness, headache or seizure argue against a lacunar stroke. Lacunes typically present with highly focal symptoms. Only 52.8% of patients with lacunar syndrome demonstrate corresponding lacunar infarction on CT. Convulsion in acute stroke is more common in sinovenous occlusion and cortical arterial infarction. Genetic factors play at least some part in the development of some stroke risk factors; i.e, hypertension and diabetes. Fibromuscular Dysplasia (FMD), homocysteinuria, Antithrombin III and proteins C,S deficiencies. Dissection is an important cause of stroke in young adults especially following trauma. FMD is most often found incidentally in angiographies performed for other purposes.

**Cerebral Venous Thrombosis (CVT)**

Cortical vein thrombosis and venous infarction present with a characteristic syndrome. After a few days of increasing headache an explosive onset of seizure occurs with asymmetric motor weakness, pyramidal signs and deteriorating level of consciousness. Focal seizure with or without generalization often is followed by focal neurologic deficit in these patients. Usually the evolution of the clinical course in patients with CVT is slower and more indolent than in patients with arterial occlusion. Increased intracranial pressure presenting with headache and papilledema without sever neurological deficit suggests sinovenous occlusive disease. Headache in patients with sinovenous thrombosis is caused by the...
local process within the veins and dural sinuses and development of increased intracranial pressure. Pseudotumor cerebri could be presentation of isolated dural venous thrombosis without cerebral venous infarction. Pseudotumor cerebri is more frequent in patients with lateral sinus thrombosis\textsuperscript{2,6}. There is often a combination of contributing factors in pathogenesis of CVT in the patient; i.e. post-partum period, pregnancy, oral contraceptive consumption, proteins C or S deficiency, factor V Leiden mutation, dehydration and Behcet disease. Short term oral contraceptive consumption is the most common cause of CVT in Iran\textsuperscript{14}. Therefore we ask about oral contraceptive consumption in any young lady who comes with a new onset persisting headache.

**Vascular Dementia**

Vascular dementia is classified as cortical and subcortical\textsuperscript{6}. Cortical form is associated with large or medium sized infarcts. Lacunar infarcts and white matter disease (often termed as Binswanger disease, lacunar state or subcortical arteriosclerotic encephalopathy) make subcortical dementia\textsuperscript{6,11}. Various combinations of aphasia, apraxia, agnosia and visuospatial deficit characterize cortical vascular dementia due to multiple cortical infarcts\textsuperscript{12}. Subcortical vascular dementia is characterized by progressive gait disturbance, bilateral pyramidal and extrapyramidal signs, pseudobulbar syndrome and emotional lability\textsuperscript{11}. Among 342 Persian ischemic stroke patients, 21 patients (6.1\%) had vascular or multi-infarct dementia. Cortical, subcortical and mixed subtypes consisted 33.\%, 38\% and 28.6\% of vascular dementia topographies\textsuperscript{15}. Vascular dementia was significantly more frequent in patients with simultaneous carotid and vertebrobasilar territories involvement, df=1, p<0.001\textsuperscript{15}. Vascular dementia was found in 13.6\% of our patients with cardioembolic mechanism and 3.8\% of other stroke patients which has a significant difference, df=1, p=0.001 OR=3.94\textsuperscript{15}.

**Clinical Points in Neurovascular Examination of stroke patient**

The symptoms of non-dominant hemisphere such as sensory and visual extinction is less important for the patients and should not be forgotten by physicians. Patients often use the terms numbness, heaviness and paralysis interchangeably because many persons do not realize that paralysis can occur without loss of sensation\textsuperscript{1}. Since patients often do not cover one eye during an attack of monocular TIA, most of the patients are unable to say whether just one eye or half of both visual fields were involved\textsuperscript{1}. Because central vision is usually preserved in stroke, hemianopsia or
quadrantanopsia may be undetected by the patient until it leads to an unusual number of mishaps, i.e. stumbling into objects on the blind side or automobile accident. Diplopia alone is not considered as TIA and diplopia in vertebrobasilar TIAs seldom last longer than 5 minutes. Although transient vertigo alone is not considered as TIA, in patients with severe cervical spondylosis and osteophytes adjacent to vertebral artery, attacks of vertigo are precipitated by changing the position of the head on the neck. Looking up a tall building or rotation of the head to one side while backing up a car or shaving may cause these types of true vertigo. Pules of the pedal and other limb arteries should be palpated in the stroke patient. Tenderness of the superficial temporal artery points toward the giant cell arteritis. Normally the ICA pulse is too deep and rostral to be felt in the neck. The arterial pulse in neck comes from Common Carotid Artery (CCA). The CCA bifurcation must be auscultated beneath angle of the jaw. A bruit over this area is not a sensitive and specific sign for ICA stenosis. Because very severe ICA stenosis may not cause a bruit and external carotid artery stenosis can also cause a bruit in the same place. Inexperienced examiners sometimes create bruits by compressing the carotid by their stethoscope. Intensity of the bruit correlates poorly with the degree of stenosis. Bruits become audible after the lumen has been reduced about 50%. With increasing stenosis the pitch becomes higher, however the volume increases until the luminal surface reduced by two-thirds and after that it decreases. Duration of the bruit prolongs with increasing degree of stenosis. Murmurs that continue into diastole suggests at least 90% reduction of the luminal surface. In severe ICA stenosis or occlusion proximal to the origin of ophthalmic artery, collateral channels may open and a bruit may be heard over the ipsilateral globe. After listening to the carotid arteries, supraclavicular fossa and mastoid region should be auscultated for Vertebral Artery (VA) bruits. Sometimes a unilateral VA bruit is a reflection of augmented flow to compensate for a contralateral VA occlusion. The bruit is then on the wrong side for the symptoms. In fundoscopic exam, subhyaloid hemorrhage almost always indicate subarachnoid or large intracerebral hemorrhage with sudden and severe increase of intracranial pressure. In long-lasting severe ICA stenosis, the reduced pressure in the ophthalmic artery may minimize hypertensive retinal changes ipsilateral to the stenosis. If consciousness is impaired and yet the stroke itself seems mild consider chronic subdural hematoma, cerebral vasculitis, dural venous thrombosis and non-bacterial endocarditis. Patient with endocarditis has illness, malaise and weight loss. If the
consciousness is impaired with mild focal neurologic deficit, also consider comorbidities such as pneumonia, dysglycemia, uremia and addiction\textsuperscript{2,6,16}. Fever is unusual in the first few hours of stroke onset unless the patient has bacterial endocarditis, myxoma, vasculitis, infectious dural sinus thrombosis and infectious differential diagnosis, i.e. herpes encephalitis\textsuperscript{2,3}. History of recurrent deep venous thrombosis in the patient or his/her family suggests thrombophilia\textsuperscript{4}. A classic scenario for extracranial dissection is ischemic stroke accompanied by intense neck or head pain. It could be an ipsilateral throbbing headache or sharp neck pain\textsuperscript{2}. Enlargement of the dissected artery by the intraluminal clot or a pseudoaneurysm impinges on adjacent structures. Extracranial ICA dissection may cause a partial Horner syndrome (characterized by ptosis and miosis with preserved facial sweating) and multiple lower cranial nerve palsies\textsuperscript{11}. VA dissection is usually associated with ipsilateral occipital headache or earache. Cerebral or cervical bruit, frequently audible to the patient, could be found in cases with ArterioVenous Malformation (AVM), FibroMuscular Displasia (FMD), carotidocavernous fistula, distal ICA stenosis, ICA dissection, carotid loops and glomus tumor\textsuperscript{12}. The syndrome of cerebellar infarction is often difficult to diagnose when gait exam is missed. Symptoms of cerebellar stroke can resemble labyrinthitis and may appear slight\textsuperscript{2,3}. Sever peripheral vertigo and vomiting may be the cardinal manifestation of cerebellar infarcts simulating vestibular neuritis or labyrinthitis\textsuperscript{2,3}. It is important to ask the patient about presence of vascular risk factors and other manifestations of vascular disease such as ischemic heart disease and leg claudication. Examination of the head and neck may reveal signs of trauma or seizure activity; e.g., contusions and tongue lacerations\textsuperscript{16}. Early seizures within 7 days of stroke onset occurs in 6.1\% of patients with ischemic stroke\textsuperscript{17}. Partial seizures with or without secondary generalization constitutes 60\% of these early seizures\textsuperscript{17}. Ischemic lesions with cortical involvement are 2.43 times more preponderant to early seizures\textsuperscript{17}. Frequency of early seizures is not significantly related to extension of infarction\textsuperscript{17}. Headache is a common symptom in ischemic stroke patients, however headache is rare in lacunar infarction unless it occurs as a coexistence in these cases\textsuperscript{18}. Unilateral burning pain and dysesthesia is frequent in patients following vascular lesions of thalamus\textsuperscript{18}. Tremor, athetosis, dystonia and chorea develop sometimes during recovery of paretic limbs in patients with previous cerebrovascular accidents\textsuperscript{19}. Presence of these movement disorders reveals involvement of lentiform nucleus and striatum in the patient\textsuperscript{19}. 
Checklist of cerebrovascular symptoms
   1- Have you ever suddenly lost vision in one eye?.
   2- Have you ever suddenly had jumbled speech, slurred speech or difficulty in talking?.
   3- Have you ever had weakness or loss of feeling in the face, arm or leg?.
   4- Have you ever had clumsiness of the arm or leg?.
   5- Have you ever had unsteadiness in walking?.
   6- How long did the symptoms last?.
Chapter II

Mechanism and Pathophysiology of Ischemic Cerebrovascular Events

A crisis is created with occlusion of a major artery. Diminished blood flow in turn activates protective mechanisms for restoring it. Low pressure flow helps to draw blood from higher pressure regions through collateral vessels. Local tissue acidosis caused by release of lactic acid and other metabolites leads to vasodilation and increases regional blood flow. In ischemic brain, there are various grades of ischemia ranging from irreversible cell death in most deprived zone to a reversible situation of diminished electrical activity named the threatened ischemic pneumbral zone. The survival of ischemic regions depends on:

1- Adequacy of collateral circulation: Congenital deficiencies in the circle of Willis and prior occlusion of potential collateral vessel decreases the available collateral supply.

2- State of the systemic circulation: Low systemic blood pressure, cardiac pump failure and hypovolemia reduces blood flow.

3- Serologic factors: Systemic hypoxia, increased blood viscosity and sugar enhance the risk of cell death.

4- Changes within the obstructive vascular region: Emboli do not adhere to the vessel wall of the recipient artery and frequently are fragmented by natural fibrinolytic activity and passes through the vascular bed. Propagation of the local clot and its embolization is important in atherothrombosis.

5- Flow resistance in collateral vessels is affected by risk factors of atherosclerosis which cause thickening of the vessel wall.

Normally, cerebral blood flow is about 50mL/100g brain tissue/minute.
Neuronal function is affected in two stages during ischemia\textsuperscript{16}. The first threshold is at a blood flow of about 20 mL blood/100g brain tissue/min, below which neuronal electrical function is compromised but is recoverable\textsuperscript{16}. If blood flow falls below the second critical threshold of 10 mL/100g brain tissue/min, then irreversible damage occurs\textsuperscript{16}. Cells in the ischemic penumbra are not functioning but they are still alive and could either recover function or die. It is not clear how long ischemic penumbra is salvagable by reperfusion or measures to protect neurons. Duration of the time window for effective therapeutic intervention is unknown\textsuperscript{11}. All of the following mechanisms could lead to temporary (TIA) or permanent (infarction) tissue injury. For optimal management of the stroke patient, the physician must identify the mechanism of stroke. Because it is not always possible to be absolutely certain of the true mechanism, the clinician often must consider the possibility of more than one mechanism such as atherothrombosis and cardioembolism and must evaluate for each. The mechanism of ischemic strokes can be any of these categories. Attributing an infarct to a particular pathogenesis purely on the basis of its site and size is often incorrect. A thorough diagnostic workup is required, as the presenting clinical syndromes are usually not distinctive enough to infer the cause. Discrimination between infarct subtypes on clinical grounds alone is difficult.

**Atherothrombosis**

Thrombosis refers to an obstruction of blood flow due to a localized occlusive process within one or more blood vessels. The lumen of the vessel is narrowed or occluded by an alteration in the vessel wall or by superimposed clot formation\textsuperscript{3}. The most common type of vascular pathology is atherosclerosis in which fibrinous and muscular tissues overgrow in the subintima and fatty materials form plaques that can encroach on the lumen\textsuperscript{3}. Next, platelets adhere to plaque and form clumps that serve as nidi for deposition of fibrin, thrombin and clot leading to formation of an occlusive thrombus\textsuperscript{3}. Hemorrhage into a plaque leads to acute luminal compromise. Atherosclerosis mainly affects large (i.e. aortic arch) and medium sized arteries at places of arterial branching (i.e. carotid bifurcation), tortuosity (i.e. carotid siphon) and confluence (i.e. BA)\textsuperscript{3}. These are sites of hemodynamic sheer stress. Atherosclerotic narrowing is often at the origin of extracranial ICA, carotid siphon, main stem of MCA, origin of extracranial VA, distal VA, BA and aortic arch. Intracranial atherosclerosis is more common in blacks, Asians, women and diabetics\textsuperscript{2,3}. The frequency
Chapter II: Mechanism and Pathophysiology...

of extracranial atherosclerotic stenosis in Persian stroke patients is similar to the north American stroke patients, however intracranial atherosclerotic stenosis is significantly more frequent in Persian patients\textsuperscript{20}. Similar results has been reported in comparison of Eastern Asian and Western Caucasian races\textsuperscript{20}. Aortic atheroma greater than 4 mm in thickness or ulcerated Aortic atheroma with mobile component is an important source of artery-to-artery embolism. Aortic atheroma as well as cardiac source of embolism could cause infarcts in multiple cerebrovascular territories. This location of atherosclerosis is rare under 60 years of age\textsuperscript{11}. The mobile component is made of mobile thrombi or a piece of atheromatous plaque with high risk of embolization\textsuperscript{11}. Relations between atherosclerotic plaques characteristics and risk of ischemic events have been reported based on pathologic and imaging tests of carotid and other brain arteries\textsuperscript{11,12}. The degree of plaque stenosis bears the clearest relation with risk of stroke. Plaque ulceration and progression are correlated with increased risk of stroke\textsuperscript{12}. Plaque irregularity in angiogram represents ulceration and instability with thromboembolism\textsuperscript{1,11}. The risk of ischemic stroke ipsilateral to sever carotid stenosis is highest soon after a TIA and then declines. Risk of stroke distal to an asymptomatic stenosis is far less than distal to a recently symptomatic stenosis of the same severity\textsuperscript{11}. The nidi of loosely adherent platelets and fibrin can break off and embolize distally. Embolism from ICA in some individuals with a dominant posterior communicating artery or persistent trigeminal artery causes occlusion of the PCA\textsuperscript{16}. The vertebrobasilar arterial system has a high incidence of variations, anomalies and persistent fetal vessels\textsuperscript{21}. Two important anatomic facts explain why VA origin lesions seldom cause chronic hemodynamically significant low flow to the vertebrobasilar system. 1- The Vertebral Arteries (VAs) are paired vessels that unite to form a single basilar artery. 2- The extracranial VA gives off numerous muscular and other branches as it ascends in the neck. Thus in the VA system, there is much more potential for development of adequate collateral circulation. Even when there is bilateral occlusion of the VAs at their origins, patients do not often develop posterior circulation infarcts\textsuperscript{21}. VA-origin disease is more benign than ICA-origin disease from hemodynamic aspect. This important point could make influence in therapeutic interventional decisions in asymptomatic VA origin stenosis\textsuperscript{21}. The small penetrating brain arteries are more often damaged by hypertension than by atherosclerotic process. Increased arterial tension leads to hypertrophy of the media and deposition of fibrinoid material into the vessel wall, a process that gradually encroaches on the already small lumen\textsuperscript{3}. Atheromatous plaques, often
referred to as microatheromas, can obstruct the orifices of penetrating arteries. Since cortical and lacunar ischemic stroke patients have similar vascular risk profile, the same type of individual, i.e. diabetic or hypertensive develops either small vessel disease and so lacunar infarcts or large vessel atherothromboembolism and so cortical infarction. The difference in site of vascular disease reflects differing genetic susceptibility. However many atherosclerotic stroke patients have stroke in both of these vascular territories in different times. Perhaps the same individuals are susceptible for atherosclerosis of both vascular territories but one becomes symptomatic before the other.

**Risk Factors of Cerebrovascular Atherosclerosis**

A number of large epidemiological studies in North America and Europe have identified numerous risk factors for the development and progression of atherosclerosis. The prevalence of stroke and atherosclerosis risk factors vary by race-ethnicity. These differences are crucial to the etiology of stroke and to the design of stroke prevention programs. Comparisons of variability in the occurrence of stroke in different races are often confounded by factors other than racial differences. These include socioeconomic, lifestyle and nutritional factors as well as variations in risk factors abnormalities in different racial groups. In recent years attempts have been made to determine risk factor differences in different racial groups in a single geographic location. These researches determines the contribution of these risk factor differences to variations in the frequency of stroke. The prevalence and severity of cerebrovascular atherosclerosis increases with age independent of other risk factors. It has been shown that modification of several major risk factors for stroke can reduce stroke incidence. Hypertension is the principal risk factor for atherosclerotic strokes which also predisposes to the cardiac conditions promoting cardiogenic cerebral embolism. Relative risk of stroke among definitive hypertensives compared to normotensives is 3.1 in men and 2.9 in women. Even borderline levels of hypertension carry a 50% increased stroke risk. Incidence of stroke increases more with systolic than diastolic hypertension. There is no clear or consistent relationship between ischemic stroke and blood lipid levels. Although hyperlipidemia is a weaker risk factor for stroke than coronary artery disease, correlations between cholesterol levels particularly low density lipoproteins and cerebrovascular atherosclerosis has been shown. High HDL cholesterol and lower total cholesterol is associated with increased risk of intracerebral hemorrhage. Smoking and
diabetes are other important risk factors for cerebrovascular atherosclerosis\textsuperscript{11}. Diabetics have an increased susceptibility to atherosclerosis and an increased prevalence of other atherogenic risk factors. The Honolulu heart program of Japanese men living in Hawaii found that increasing degrees of glucose intolerance is associated with an increased risk of thromboembolic stroke which was independent of other risk factors\textsuperscript{23}. Case-control studies of stroke patients and prospective epidemiologic studies have confirmed an independent effect of diabetes with a relative risk of ischemic stroke in diabetics from 1.8 to 3 times than nondiabetics\textsuperscript{4}. Smoking independently increases the relative risk of stroke by about threefold. The risk is dose-dependent and is strongest for SAH and cortical ischemic stroke due to atherothromboembolism. Cigarette smoking has been clearly linked to brain infarction in the Honolulu epidemiologic study\textsuperscript{23}. In a meta-analysis of 32 studies, cigarette smoking was a significant contributor of stroke incidence in both men and women\textsuperscript{12}. The risk of ischemic stroke due to atherosclerosis is not significantly increased in non-smoker women without hypertension who use oral contraceptives\textsuperscript{11}. However women older than 45 years or who have above risk factors should not use oral contraceptives. Risk factors of atherosclerosis interact with each other in complex ways to increase stroke risk. Fibrinogen levels are closely correlated with other risk factors such as smoking, hypertension, diabetes and also obesity and hematocrit level\textsuperscript{11,12}. Plasma fibrinogen level has a strong association with stroke and heart attacks. There is no significant difference in frequency rate of atherosclerosis risk factors and obesity between north American and Persian stroke patients\textsuperscript{24,25}. However hypertension is significantly more frequent in Persian than north American males\textsuperscript{24}. Low mobility was reported in 29% of north American and 5% of Persian stroke patients, df=1, \( p=0.0001 \)\textsuperscript{25}. Industrialization and diet changes in recent decades in Iran could be the main reason of similarities in the frequency rate of the atherosclerosis risk factors between north American and Persian patients\textsuperscript{24,25}. Obesity is a significant independent contributor to stroke incidence in younger men and elderly women\textsuperscript{11}. Obesity has been a common stroke risk factor in both of our north American and Persian patients with insignificant differences based on the race and gender. Overweight correlates with several other risk factors for atherosclerosis; i.e hypertension and hypercholesterolemia\textsuperscript{11,12}. Obese persons have higher levels of blood pressure, blood glucose and atherogenic serum lipids, and on the account alone could be expected to have an increased stroke incidence\textsuperscript{11}. Vigorous exercise may exert a beneficial influence on risk factors of atherosclerosis. It could reduce elevated blood
pressure as a result of weight loss and by lowering the pulse rate\textsuperscript{11}. High physical activity raises the HDL, lowers the LDL cholesterol and improves glucose tolerance by increasing insulin sensitivity\textsuperscript{11}. Regular sport program and high physical activity promotes a lifestyle conductive to favorably changing detrimental health habits such as cigarette smoking and change of the harmful diet\textsuperscript{11}. Low mobility was significantly more frequent in our north American stroke patients, especially in the females. Although north American and other western nations have a better physical life style than Persian and other Middle East nations. However, old people in western countries are usually left alone or live in the institutions. Fortunately, Persian and other Middle East nations have especial respect to the old people based on their cultural believes. Thus, old people in Iran have usually acceptable physical activity by help of their children and relatives. In Framingham study, physical activity in subjects with mean age of 65 years was associated with a reduced stroke incidence \textsuperscript{26}. Moderate levels of activity tended to provide an intermediate level of protection\textsuperscript{26}. Our results confirms that Persian white race and north American white race have no difference in preponderance to the atherosclerosis risk factors and obesity, although these races live in two distant continents\textsuperscript{24,25}. However both of these races are subtypes of white Caucasians. Managing obesity and moderate levels of physical activity provides substantial benefit and is recommended as a sensible lifestyle modification to reduce risk of stroke. Elevated hematocrit is seen in 9.5\% of females and 5.4\% of males with ischemic stroke in Iran and it does not seems to be a significant risk factor in these cases\textsuperscript{27}. Depression, anxiety and stress may trigger onset of stroke in people already at risk of stroke\textsuperscript{6}. Stress, hyperlipidemia, inflammatory states and smoking enhance platelet aggregability. Stress causes elevation of fibrinogen and factor VIII\textsuperscript{11}. A procoagulant state related to increased levels of cytokines, acute phase reactants and fibrinogen with a decreased activity of proteins C and S could account for the association between recent non-specific infections and ischemic stroke\textsuperscript{11}. Infections; i.e. Helicobacter may contribute to the development of atheroma and plaque instability\textsuperscript{11}.

**Non-atherosclerotic arterial thrombosis**

Isolated cerebral arteritis, arteritis of brain vessels secondary to systemic vasculities and giant cell arteritis of superficial temporal artery cause luminal clot. Dissection with tearing of the vessel wall makes luminal or extraluminal clot. However arterial thrombus due to dissection usually involves distal extracranial ICA and VA\textsuperscript{6}. Sever focal vasoconstriction can
lead to decreased blood flow and thrombosis. This condition may occur in patients with subarachnoid hemorrhage, some drugs abuse and trauma. Congenital dilatation of blood vessels also alters local blood flow and clots often form in dilated segments. This condition named arterial dolicoectasia makes luminal clot which blocks the artery or lead to artery-to-artery embolism. Systemic hypercoagulable state, polycythemia and thrombocytosis occasionally cause clot formation. During pregnancy there is increase of fibrinogen and factors VII, VIII, IX and X. Fibromuscular Dysplasia (FMD) is an overgrowth of media and intimal elements that compromises vessel contractility and luminal size. Small clots may form in post stenotic dilation of FMD segments of brain arteries.

**Embolism**

In embolism, material formed elsewhere within the vascular system lodges in a cerebral vessel and blocks the blood flow. Emboli can block any artery depending on the size of the embolic material. The material arises proximally from the heart, major arteries and systemic veins. Cardiac sources of embolism include the heart valves, endocardium, clots and tumors within the atrial or ventricular cavities. Artery-to-artery emboli are composed of clot, platelet clumps and fragments of atherosclerotic plaques that break off from the proximal vessels. Clots from systemic veins travel to the brain through right to left heart shunts such as atrial septal defect or a patent foramen ovale, a process termed paradoxical embolism. Infrequently air, fat, bacterial clumps, tumor cells and injected drugs enter the vascular system and embolize to brain vessels. Upto half of stroke patients if fully evaluated including transesophageal echocardiography have a potential cardiac source of embolism. The frequency of cardioembolic sources for brain ischemia depends on how thoroughly patients are evaluated, what lesions are accepted as potentially emboligenic and the specific diagnostic criteria for heart disease. Not all cardiac sources of embolism are equal threats. A mechanical heart valve is more likely to be etiology of stroke than mitral valve prolaps or patent foramen ovale. Both of the laters present frequently in people without stroke and thus more likely to be unrelated to stroke etiology. Major risk cardioembolic sources include; atrial fibrillation, mitral stenosis, mechanical heart valve, left heart thrombus, atrial myxoma, endocarditis, dilative cardiomyopathy and recent myocardial infarction. Non-valvular and valvular atrial fibrillation are the most common cause of cardioembolism in developed and developing countries respectively. Fibrillating patients with rheumatic mitral disease, left
ventricular dysfunction, enlarged left atrium, hypertension, diabetes and aged more than 65 years have higher risk of cardioembolism. The average absolute risk of stroke in unanticoagulated non-valvular fibrillating patients is about 5% per year. Cardioembolism constituted 54% of all stroke etiologies in Persian young adults and rheumatic valvular heart disease was present in 32% of these cases and caused 2.5 preventable stroke cases per 100000 Persian young adults per year. Evaluation of all age groups of Persian stroke patients revealed that frequency of cardioembolic mechanisms of stroke in Iran is similar to other areas around the world, however rheumatic valvular disease and valvular fibrillation consist the most frequent sources of cardioembolism in Iran despite western countries. Rheumatic mitral stenosis was found in 45% of Iranian cardioembolic stroke patients and atrial fibrillation was present in 68% of these stroke patients with rheumatic mitral disease in whole age groups. The incidence of rheumatic valvular disease in whole of our stroke patients was 9.3% and significantly higher in females. The cause of this gender discrepancy is unknown. Early diagnosis and treatment of streptococcal throat infection and its complications including prevention of rheumatic valvular disease and its complications is inadequate in developing countries. Further improvement in the quality of manufacturing and storage of antibiotics is recommended in developing countries.

**Distal Flow Insufficiency**

Low systemic perfusion pressure could be pathophysiology of diminished flow to the brain tissue. Diminished flow to brain tissue is caused by low systemic perfusion pressure. Cardiac pump failure most often due to myocardial infarction, arrhythmia and systemic hypotension affects the brain bilaterally in borderzone regions of arterial territories. Asymmetric effects can result from pre-existing severe stenotic vascular lesions causing asymmetrical distribution of underperfusion. Persian patients with cortical borderzone brain infarction frequently have severe extracranial ICA stenosis or occlusion. The ischemia occurs not within but between major arterial territories because this is where perfusion pressure is likely to be most attenuated. There is also a subcortical borderzone in the corona radiata and centrum semiovale above the lateral ventricle. This area lies between the supply of lenticulostriate, Hubner arteries and cortical branches of MCA, ACA and PCA. There is much variations between individuals in borderzone areas and they may even change with time in the same individual. Two basic mechanisms could cause stroke in patients with severe
ICA stenosis. The first mechanism is artery to artery embolism causing intracranial arterial occlusion and subsequent perfusion failure. The second mechanism is distal flow insufficiency with borderzone infarction. Both mechanisms may even be operative in the same patient in different episodes. Diagnosis of low flow infarcts should be suspected if symptoms start on standing, during operation or hypotension. Boundary zone or watershed infarcts are frequent. There is no specific presentation for boundary zone infarcts.

**Apoptosis**

The process of programmed ischemic cell death is referred to as apoptosis. When neurons become ischemic, K+ ions move across the cell membrane into the extracellular space and Ca++ ions move into the cell which compromises controlling ion influx and leads to mitochondrial failure. Ca++ decreases oxygen availability and leads to production of oxygen-free radicals, causing severe cell dysfunction. Toxic response of ischemic neurons to increased local glutamate opens membranes and increases Na+ and Ca++ influx into cells. Large influx of Na+ are followed by entry of water causing edema. When an artery is occluded by thrombus, endogenous tissue plasminogen activator is released from the adjacent endothelium. It attaches to and activates fibrin-bound plasminogen. This mediates lysis of the thrombus and recanalizes the occluded artery. Often such spontaneous recanalization does not occur until the ischemic brain has become infarcted. Exogenous thrombolysis aims to rapidly restore blood flow by lysing embolus or in situ thrombi. Cells in the ischemic piaumbra are not functioning but are still alive and could either recover or die. It is not clear how long ischemic piaumbra be salvaged by the reperfusion or measures to protect neurons.

**Miscellaneous etiologies**

Venous infarction due to cerebral venous thrombosis, migraine induced stroke and extracranial carotid and vertebral dissection consists the most frequent miscellaneous causes of ischemic stroke in Persian patients.

**Presence of Multiple Stroke Mechanisms**

Frequency of brain infarct etiologies depends on how throughly patients are evaluated, what lesions are accepted as potential etiology and diagnostic criteria. Identification of a cardiac source of embolism is insufficient to confirm definite cardioembolic mechanism, as other possible etiologies...
frequently coexist, particularly in elderly patients. A patient with ischemic stroke and severe ipsilateral carotid stenosis is presumed to have suffered an episode of thromboembolism and would be a candidate for carotid endarterectomy. In a similar patient with atrial fibrillation the heart is the suspected source of thromboembolism, necessitating anticoagulant treatment. But what if a patient with ischemic stroke has corresponding severe carotid stenosis as well as atrial fibrillation? Some physicians may give precedence to the most distal (carotid) lesion, whereas others believe that severe carotid stenosis is more likely than atrial fibrillation to be coincidental. Yet in such patients it is difficult to be certain about the actual mechanism of stroke. Indeed you should consider and manage both of these mechanisms. About 30% of atrial fibrillation associated strokes are due to intrinsic small cerebrovascular disease or atheroma of large cerebral or neck arteries. It is impossible to be sure of actual cause of an ischemic stroke if several potential causes are present in the same individual. In one-third of stroke patients with cardiac source of embolism, the source is irrelevant because there is another, perhaps more likely cause of cerebral ischemia. Seventeen percent of Persian stroke patients have more than one potential cause of stroke. Etiologic overlaps were significantly more frequent in Persian stroke patients with small artery territory involvement, P=0.004. Twenty seven percent of our stroke patients with symptomatic atherosclerotic stenosis and 12.5% of those with cardiac source of embolism had small artery territory or lacunar infarct. Cardioembolism was significantly more frequent in our stroke patients with large artery territory involvement. When a small deep infarct occurs in an elderly hypertensive patient with a cardioembolic source, it is uncertain whether the infarct is due to cardioembolism or atherosclerotic small vessel disease. The presence of associated diffuse white matter changes or multiple pure lacunes support an intrinsic subcortical vasculopathy. Etiologic overlaps are frequent and should be considered for optimal management of the ischemic stroke patients.

**TIA Mechanisms**

Stroke patients with history of TIA have vascular risk factors similar to other stroke patients. The presence of TIA history does not confirm a special etiology of ischemic stroke. There was not significant difference in frequency of various stroke etiologies in Persian stroke patients with and without history of TIA, df=4, P=0.61. The frequency of hypertension, diabetes and ipsilateral ICA stenosis was not significantly different between
our stroke patients with and without TIA; df=1, p=0.61. Hypercholesterolemia and smoking were significantly more frequent in our stroke patients with TIA; df=1, p=0.011 and df=1, p=0.014 respectively. TIA was present in 16.5% of lacunar and 17.2% of large artery territory infarcts; df=1, p=0.084. All types of ischemic stroke are likely to be preceded by TIA and the risk factor profile of ischemic stroke and TIA are similar. The atherosclerotic artery to artery embolus is a common cause of TIA. TIA may occur as a result of short lived cardioembolic mechanism in different arteries. In these cases the deficit tends to last more than 1 hour. Severe arterial stenosis could cause perfusion failure TIAs with distal flow insufficiency. These TIAs appear under episodes of arterial hypotension or special postural conditions with the same clinical presentation and march. These low flow TIAs develop over minutes rather than seconds and sometimes consist of jerking and shaking of one arm or leg confusing with seizures. There may be monocular visual blurring often in bright light named retinal claudication. In patients with severe carotid stenosis transient monocular blindness may be precipitated by bright light, a change in posture or a heavy meal. Stroke tends to occur early after a TIA and often affect the same arterial territory. The risk of stroke ipsilateral to severe carotid stenosis is highest soon after TIA presentation and then declines, although the stenosis seldom regresses. TIAs could also be related to small penetrating arterial disease. Prior TIA episodes occur in 20% of lacunar stroke. TIA in lacunar infarcts has more episodes and a shorter latency between the first TIA and infarction. Capsular warning syndrome consists of clusters of stereotypic hemiparesis without any cognitive or language deficits, which follows within hours or days by a lacunar infarct in the internal capsule. Crescendo TIAs reflect recurrent thromboembolism from an ulcerated atherosclerotic plaque.

Mechanism of Sinovenous Thrombosis

Risk factors of intracranial sinovenous occlusive disease are quite different from those in patients with arterial occlusion. Patients with sinovenous occlusions are younger, usually female and have low frequencies of hypertension, diabetes, smoking and coronary artery disease when compared with patients suffering arterial occlusive disease. The conditions that should alert clinicians to the possibility of sinovenous occlusive disease are as follows:

1- Infants and babies with dehydration and sepsis.
2- Peurperal and pregnant women
3- Women who take oral contraceptive.
4- Acute or chronic otitis media, mastoiditis and sinusitis.
5- The presence of inflammatory disease such as Behçet and inflammatory bowel disease.
6- Patients with known cancer especially leukemia and lymphoma.
7- Past medical history of recurrent leg vein thrombosis.
8- Known hypercoagulable hematologic disorders.
9- Sepsis, dehydration, cachexia and malnutrition.
10- Intracranial meningioma and penetrating head truma.

When draining dural sinuses are occluded the intravascular pressure in the feeding arteries must increase to a level above sinovenous pressure to keep brain perfusion. Increased intracapillary pressure leads to extravascular leakage causing sever edema and multifocal hemorrhages. Infarction is often related to propagation and spread of thrombi to draining superficial and deep cerebral veins. Increase in the platelet count and fibrinogen levels during third trimester and increased adhesion of platelets during the postpartum period leads to peurperial CVTs. Hereditary hypercoagulable states (i.e. Antithrombin III, protein C and S deficiency or factor V Leiden mutation) should be looked for in the absence of an obvious cause. In some patients with these abnormalities, CVT may occur only when other precipitating factors such as pregnancy are superimposed. CVT may complicate or be the first manifestation of SLE, Antiphospholipid antibody syndrome, Behçet disease and inflammatory bowel disease. OCP consumption was found as risk factor in 56.8% of Persian females with CVT. This group of females have been used LD and HD types of OCP in 97% and 3% respectively. Forty one percent of Persian females with CVT have been on short term OCP consumption. In this later group of females, Ramadan and Hadj religious months were the reason of using short term OCP in 86% and 5% respectively. Short term OCP consumption is the most common cause of CVT in Persian women. Programs for public awareness should be conducted for reducing use of OCP in short term periods during Ramadan and Hadj months in Iran.

Hemorrhagic Arterial Brain Infarction (HABI)

Microvasculature within the ischemic tissue may be injured so that fragmentation of the embolus, reperfusion and recanalization, leads to leakage of blood into the ischemic tissue resulting in hemorrhagic infarction. Collateral flow may also be obtained through pial arteries
causing hemorrhagic transformation of brain infarct in persistence of initial arterial occlusion. HABI is mainly reported in cardioembolic stroke and decision making for anticoagulation therapy is difficult in HABI patients. Eighty eight percent of HABI in our stroke patients occurred within MCA territory\(^{38}\). The lenticulostiate artery is involved alone in 46% and with other MCA branches in 23% of these cases\(^{38,39}\). Clinical course in our patients with HABI is deterioration in 16%, improvement in 38% and stabilization in 46%\(^{38,39}\). Cardioembolism consists 40% of etiologies in patients with HABI\(^{39}\). Thus most of the patients with HABI do not have cardioembolic etiology. This later finding reduces the importance of Fisher-Adams hypothesis about reopening of the occluded artery after disruption of its endothelial layer during the occlusion time\(^{16}\).

**Stroke Registry**

The hospital-based stroke registry is useful for understanding diverse clinical characteristics for stroke related to geographical, racial or environmental differences. Stroke registry makes valuable epidemiologic information about stroke and have influence on therapeutic and prevention strategies regarding stroke in the country. Stroke registry could also provide an excellent data bank for clinical research in stroke. The causes, clinical presentations, risk factors and outcomes of brain infarction are heterogeneous. These factors are essential in determining initial stroke management. To treat stroke patient optimally, the physician must identify the correct mechanism of stroke. Ischemic stroke is a complex entity with multiple etiologies and variable clinical manifestations. A well-organized stroke data bank can help to provide much information and numerous insights into these problems. Variations in the distribution of stroke subtypes between stroke registries may be due to differences in patients population, classification criteria and the extent of diagnostic investigations. Large stroke data banks provide the best available information for the diagnosis, clinicoradiological correlations and outcome of patients with cerebrovascular disease.

**Khorasan Stroke Registry**

The Khorasan Stroke Registry (KSR) established for evaluation of incidence, clinical manifestations, risk factors, topography and etiology of ischemic stroke in southern Khorasan, Iran, during 2001-2005\(^{40}\). Consecutive stroke patients underwent a standard battery of diagnostic
investigations by a stroke neurologist. Topography and etiology of brain infarction determined by the Asian Stroke Criteria (ASC). The incidence of ischemic stroke in Persian population is 43.17 cases per 100000 people per year\(^{40}\). 1392 ischemic stroke patients (738 females, 654 males) were evaluated in the KSR. Atherosclerosis consisted 53.6% of etiologies followed by uncertain causes (19.9%), cardioembolism (11.8%) and miscellaneous etiologies (2.9%)\(^{40,41}\). 11.7% of our patients had both atherosclerosis and cardioembolic mechanisms. The women were significantly more susceptible to stroke with atherosclerotic mechanism and miscellaneous etiology; \(p<0.001\), \(P<0.001\) respectively. Men were significantly more preponderant for stroke with uncertain cause, \(p<0.001\). The distribution of stroke with cardioembolic mechanism was not significantly different based on gender, \(p=0.79\). Distribution of stroke with atherosclerotic, cardioembolic and uncertain mechanisms was not significantly different based on small versus large vessel territory involvement, \(p=0.689\), \(p=0.207\), \(p=0.078\) respectively\(^{40,41}\). Stroke with miscellaneous etiology was found in large vessel territory infarcts, \(p<0.001\). The distribution of stroke with atherosclerotic and cardioembolic mechanisms was not significantly different between carotid versus vertebrobasilar territory involvement, \(p=0.371\), \(p=0.297\) respectively. Miscellaneous etiology was present in carotid territory infarcts, \(p=0.013\). Stroke with uncertain causes was significantly more frequent in vertebrobasilar territory involvement, \(p=0.001\). Rheumatic valvular disease was present in 44.8% of cardioembolic strokes and caused 4.31 preventable stroke cases per 100000 Persian population per year\(^{40,41}\). Hypertension and history of ischemic cerebrovascular events were the most frequent risk factors, 53.1% and 22.3% respectively\(^{40,41}\). In-hospital mortality of our ischemic stroke patients was 7.3%. 336 patients with intracerebral hemorrhage (189 females, 147 males) were evaluated in the KSR. The incidence of intracerebral hemorrhage in Persian population is 10.43 cases per 100000 people per year\(^{40,41}\). Hypertension was extremely prevalent and is seen in 87% of these ICH cases. In terms of localization of ICH, 32% were putaminal, 29% lobar, 28% thalamic, 5% cerebellar, and 6% had a pontine location. During the first week after stroke 25.3% of ICH patients died in the hospital\(^{40,41}\). High frequency of atherosclerotic etiology in the KSR is the due to its classification criteria which does not separate small vessel territory infarcts as a different etiologic subtype. Rheumatic valvular disease is an important cause of stroke in Persian population.
Khorasan Posterior Circulation Stroke Registry (KPCSR)

Clinical information about stroke in the vertebrobasilar territory has lagged behind that for anterior circulation stroke. Posterior circulation syndrome often has been attributed to hemodynamically significant vertebrobasilar arteries stenosis leading to low flow ischemia or penetrating artery disease. KPCSR is the first reported posterior circulation stroke registry in Iran, which deals with clinical course and etiology of stroke based on the different topographies of the vertebrobasilar territory. Consecutive patients with vertebrobasilar territory brain infarction admitted in Ghaem hospital, Mashhad enrolled in a prospective study during 2005-2007. Diagnosis of ischemic stroke in the posterior circulation was made by a stroke neurologist based on the clinical manifestations and neuroimaging. The territory of infarct was determined by topographic maps of cerebrovascular territory. Vertebrobasilar territory infarcts were classified into five groups according to the location involved: brainstem, thalamus, cerebellum, cortical posterior cerebral artery and mixed categories. All of the stroke patients underwent a standard battery of diagnostic investigations and etiology of ischemic stroke was determined by the Asian Stroke Criteria. The 72-hour stroke course determined as regressive, stable and deterioration. 302 Patients (147 females, 155 males) with mean age years 62.5; SD: 7.8 were investigated. Cortical posterior cerebral artery, thalamus, brain stem, cerebellum and mixed categorizes consisted 31.3%, 4.3%, 32.8%, 17.9% and 13.9% of the stroke topographies. The influence of gender and age groups on distribution of infarct localization was not significant, p=0.65, p=0.127. Hypertension, hyperlipidemia, diabetes and smoking were found in 22.5%, 7.9%, 3.9% and 4.6% of the patients in isolation, and 37.4% of them had multiple stroke risk factors. Differences in frequency rate of risk factors among various stroke localizations were not significant, p=0.123. Atherosclerosis consisted 50.6% of etiologies in our patients followed by uncertain (25.5 %), cardioembolism (12.5%), both atherosclerosis and cardioembolism (6.3%) and miscellaneous causes (4.6%). Atherosclerotic stenosis was found in 42 (10.6%) patients in KPCSR. The V1, V2, V3, V4, basilar and posterior cerebral artery stenosis were found in 26, 1, 1, 8, 4, and 2 patients respectively. Atherosclerosis was the most common etiology in age groups 60-69 and 70-79 years. Coexistence of atherosclerosis and cardioembolism was found in 50% of the patients aged 80-89 years. Uncertain etiology consisted 38% of stroke subtypes in patients younger than 50 years. The distribution of stroke etiologies in age groups was significantly different, p=0.002. The effect of
gender in frequency rate of stroke etiologies was not significant, \( p=0.271 \). The distribution of stroke etiologies based on its localization was not significantly different, \( p=0.421 \). Atherosclerosis was the most common etiology in all localizations of stroke in the posterior circulation. Rheumatic mitral stenosis consisted 34.2% of the cardioembolic mechanism in our patients. Atrial fibrillation was present in 50% of patients with cardioembolic mechanism in KPCS. Stabilization consisted the most common early stroke course (57.7%) followed by deterioration (22.1%) and regression (20.2%)\(^{42}\). The effect of gender and age groups on distribution of course subtypes was not significant, \( p=0.121 \), \( p=0.081 \) respectively. The distribution of course subtypes was not significantly different based on the risk factors, \( p=0.606 \). The distribution of stroke course based on its etiologies was not significantly different, \( p=0.697 \). Mortality of our patients with posterior circulation stroke within the first week post event was 10.9%. Among patients with deteriorative course, 43.3% had atherosclerotic etiology and 35.8% of them had uncertain cause. A significant association between stroke localization in the vertebrobasilar territory and its course was not found, \( df=8 \), \( p=0.901 \). In summary, Atherosclerosis consists the most common cause of posterior circulation stroke in Iranian patients. The cause of stroke in the posterior circulation could not reliably be derived from infarct topography.

**Khorasan Pediatric Stroke Registry (KPSR)**

Ischemic stroke is rarely seen in childhood. Congenital stroke may pass unrecognized by parents during early infancy, until the child starts crawling or walking. At this stage asymmetry is noted or delay in the rate of acquired motor or cognitive skills is manifested. Stroke in children usually represents with acute onset hemiplegia. Recovery in children is more than adults because the developing brain has more plasticity\(^{43}\). Frequent striatocapsular involvement leads to more dystonic and choreathetotic sequelae in childhood strokes.

The pediatric causes of stroke are quite different than adult causes. Atherosclerosis is a rare cause of brain infarction in the children. Certain subgroups of children are at high risk of ischemic stroke; these include children with congenital heart disease, rheumatic valvular disease, sickle cell anemia, cancer, Moyamoya disease and Down syndrome. Homocystinuria, mitochondrial disease, prothrombotic states, migraine and truma are among other causes of ischemic stroke in childhood and early adolescents. A population based study was conducted for determination of incidence,
clinical manifestations and etiology of pediatric ischemic stroke in southern Khorasan, Iran, during 2002-2007. In this province, every child with possible diagnosis of stroke is referred to stroke neurologist and routinely admitted in Pediatric division of Valie-Asr tertiary care hospital. The diagnosis of ischemic stroke was made based on the clinical presentation and brain imaging. All of the patients underwent a standard battery of diagnostic investigations. Seventeen children with ischemic stroke (7 females, 10 males) with mean age of 5.5 years were evaluated. The incidence of pediatric ischemic stroke in our province is 1.8 cases per 100000 children population per year. Unilateral weakness was found in all of the patients. Ipsilateral extensor plantar response, heightened deep tendon reflexes, seizure, fever and altered consciousness were found in 41%, 35%, 47%, 35%, and 23% of the patients respectively. The onset of pediatric brain infarction in our registry was sudden in 35%, acute in 59% and subacute in 6% of cases. The infarctions were localized in carotid territory in 88% of the cases. Meningoencephalitis induced vasculopathy consisted 23.5% of determined etiologies followed by Fallot tetralogy (11.8%), head trauma (11.8%), dehydration (11.8%), migraine (11.8%), and hypercoagulable state (5.9%). Twenty three percent of our pediatric patients had uncertain cause of stroke. All of our pediatric stroke patients with infectious etiology were young children and half were referred from a rural area in summer 2004. The polymerase chain reaction for herpesvirus, and tuberculosis and bacterial culture of cerebrospinal fluid was negative in these cases. Special virology facilities was not available. In-hospital mortality of our pediatric ischemic stroke patients was 11.7%. The incidence and clinical characteristics of pediatric brain infarction in Iran is the same as other studies around the world. Meningoencephalitis induced vasculopathy is the most common determined etiology of pediatric ischemic stroke in Iranian population.

**Development of Pathophysiologic Classification of Stroke Territory (PCST): An academic concept**

We searched for all studies describing pathophysiologic classification of brain infarction. The following string of keywords was entered in to MEDLINE(OVID and PUBMED): [Pathophysiology] and [Classification] and [Stroke] and [Criteria] and [ Territory], with the final search performed February 24, 2011. Surprisingly, no pathophysiologic classification was found for ischemic stroke. The PCST was developed as an academic tool for categorization of brain infarction. The PCST was designed by the author and approved in the scientific committee of Khorasan association of
neurologists in 2009. The basis for development of PCST has been comparison of stroke territory based on the neuroimaging and etiology of stroke in the Khorasan Stroke Registry and Khorasan Posterior Circulation Stroke Registry. All of the ischemic stroke patients in these stroke registries underwent a standard battery of diagnostic investigations for detection of stroke etiology. Determination of stroke territory was made based on a computed tomographic guide to the identification of cerebral vascular territories. The PCST makes a primary view and impression about cause of stroke based on its territorial involvement. Stroke neurologists around the world are invited to help us in modification of PCST. The PCST is presented in Table 1.

**Table 1: Pathophysiologic Classification of Stroke Territory (PCST)**

| 1- | Total Internal Carotid Artery (ICA) territory infarct: ICA atherothrombosis, cardioembolism, ICA dissection all with non-functional anterior communicating artery. |
| 2- | Total or large Middle Cerebral Artery (MCA) territory infarct: ICA atherothrombosis or dissective occlusion with functional anterior communicating artery, cardioembolism, Aortocarotid to MCA embolism with atherosclerotic or dissective pathology, MCA stem atherothrombosis. |
| 3- | Large deep MCA territory infarct: Cardioembolism, Aortocarotid to MCA embolism involving MCA stem with recanalization or functional pial MCA collaterals. |
| 4- | Cortical MCA territory infarct: Cardioembolism, Aortocarotid to MCA embolism. |
| 5- | Anterior Cerebral Artery (ACA) territory infarct: Cardioembolism, Aortocarotid to ACA embolism, vasospasm. |
| 6- | Anterior choroidal artery territory infarcts: Cardioembolism, artery to artery embolism. |
| 7- | Posterior Cerebral Artery (PCA) territory infarct: Verteobasilar to PCA embolism, cardioembolism. |
| 8- | Vertebral Artery (VA) and Basilar Artery (BA) territorial infarcts; brain stem and cerebellum infarctions: Atherothrombosis in distal VA or BA, cardioembolism, Aortovertebral to distal arterial embolism. |
| 9- | Borderzone territory infarcts: Unilateral in severe proximal arterial stenosis with distal flow insufficiency, bilateral in cardiac arrest. |
| 10- | Small deep infarcts in small penetrating arterial territories (Lacunar infarcts): Often atherothrombosis, artery to artery embolism, cardioembolism. |
| 11- | Ischemia in more than one cerebrovascular territory: Multiple cardioembolic and Aortoembolic processes, diffuse arterial disease. |

**Clinical risk scores in patients with TIA**

Patients presenting with TIA are at high risk of early recurrent stroke (up
to 10% in the first 48 hours). Therefore they need urgent clinical diagnosis to treat associated risk factors and identify specific treatable causes, particularly arterial stenosis and other embolic sources. Simple clinical scoring systems can be used to identify patients at particularly high risk.

Several risk scoring systems have been developed for assessment of stroke risk after a TIA or minor stroke. The **ABCD2** score is the most famous system for predicting patients who are at risk of developing a stroke after a TIA\(^**\). This score is calculated as:

- **A**ge $\geq 60 = 1$,
- **B**P $> 140$ and/or $> 90 = 1$,
- **C**linical: unilateral weakness = 2, speech disturbances = 1,
- **D**uration of symptoms $> 1$ hour = 2, duration between 10-59 minutes = 1, duration $< 10$ minutes = 0,
- **D**iabetes = 1. A score $\geq 5$ predicts a seven days stroke risk of 10%\(^**\). Five hundreds TIA patients were prospectively evaluated in Oxford vascular study based on the ABCD2 score\(^**\). Eleven percent of them had a recurrent stroke and 10% had a recurrent TIA within 7 days. The ABCD2 score was highly predictive of major recurrent stroke, weakly predictive of minor recurrent stroke and inversely related to risk of recurrent TIA\(^**\). Five hundreds eleven Persian TIA or Minor Ischemic Stroke (MIS) patients were evaluated in a prospective cohort study\(^**\). Any TIA or stroke was recorded within 3 days and 3 months post event. All of the above items of ABCD2 scoring system were evaluated as risk factors. Influence of gender, isolated sensory symptoms, isolated monocular blindness, smoking, hyperlipidemia, past history of stroke, atrial fibrillation, ischemic heart disease, other high risk cardiac source of embolism, symptomatic $> 70\%$ ICA stenosis, multiple TIAs, Crescendo TIAs, observation of brain infarct in CT compatible to manifestations were also evaluated as risk factors of recurrent ischemic cerebrovascular events. Presence of TIA or MIS as the initial event was also investigated as risk factor of recurrent ischemic cerebrovascular events\(^**\). The results were analyzed by backward stepwise regression logistic analysis. 393 TIA patients (238 males, 155 females) and 118 MIS patients (77 males, 41 females) enrolled the study. 117 strokes (23.2%), 99 TIA (19.6%), and 11 vascular death (2.2%) occurred within 3 months post event in whole of our 511 patients with minor ischemic events. Crescendo TIAs and multiple TIAs were associated with greater risk of stroke at 3 days in a univariate analysis (OR= 5.120, $p=0.000$) and (OR=3.988, $p=0.003$) respectively. Crescendo TIAs and multiple TIAs were also associated with greater risk of stroke at 3 months in a univariate analysis (OR= 3.722, $p=0.000$) and (OR=3.081, $p=0.000$) respectively. Multiple and crescendo TIAs is the main predictive of stroke recurrence, derived in univariate analysis of our patients with minor ischemic events.
These clinical characteristics of TIA should be considered as indication of urgent admission and therapeutic interventions in TIA patients\textsuperscript{48}. This finding could reflect an unstable vascular condition with higher risk. Addition of multiple TIAs to ABCD\textsuperscript{2} score might augment its predictive accuracy. Our research work supports adding multiple or crescendo TIA to ABCD\textsuperscript{2} score and giving score of 4 to this clinical item as suggested by North Hertfordshire rapid access TIA service referral form (accessible online at http://www.enherts-tr.nhs.uk/gps-professionals/files/2010/04/Rapid-Access-TIA-service-referral-form.pdf). Patients with index MIS had 11.5% lower risk of recurrent stroke at 3 days than patients with index TIA in multivariate analysis (OR=0.115, \( p=0.039 \)). At the other words, presence of MIS comparing to TIA as initial event had a protective effect on recurrence of stroke in next 3 days. Paradoxically, the risk of a subsequent ischemic stroke may be less after a completed stroke than after a TIA\textsuperscript{49}. Thus patients with index TIA are actually more unstable in terms of a new stroke than those presenting with an index stroke. History of stroke was a nonsignificant risk factor of stroke recurrence within next 3 days in multivariate analysis, (OR=2.853, \( p=0.076 \)). Diabetes was independently associated with 3 months stroke recurrence of our patients with minor ischemic events in multivariate analysis, (OR=2.655, \( p=0.039 \)). Presence of MIS comparing to TIA as initial event had a nonsignificant protective effect on recurrence of stroke in next 3 months (OR=0.385, \( p=0.103 \)). The ABCD\textsuperscript{2} score had a weak predictive value for 3 months and 3 days recurrent stroke in our TIA patients (AUC= 0.599, AUC=0.591), but a high predictive value for 3 months and 3 days recurrent stroke in our MIS patients (AUC=0.727, AUC=0.728) respectively. The Area Under the Curve (AUC)=0.5 is by chance occurrence and AUC=1 shows perfect prediction of last event which is stroke. The ABCD\textsuperscript{2} score is highly predictive of short-term recurrent stroke in MIS patients but not TIA cases, despite it's creation for TIA cohorts.
Clinical Localization of Ischemic Cerebrovascular Events

Many of the classical vascular syndromes occur infrequently, at least in their pure forms and rarely have a particular cause. Thus they have limited practical value to the clinicians. Clinical localization of the brain lesions is primarily from the findings on neurologic examination. Many non-neurologists feel ill-equipped to detect neurologic signs. The most frequently missed signs of brain dysfunction are abnormalities of higher cortical function (i.e. hemineglect, visual neglect and aphasia), oculomotor abnormalities (i.e. eyes deviation) and gait disturbances. Some patients with cerebellar lesions have a normal examination when recumbent or seated but can not walk. These patients are too often discharged from the emergency room only to return later with worse prognosis. Cerebellar infarction may be misdiagnosed as labyrinthitis or upper gastrointestinal disease if nausea, vomiting and vertigo are their prominent presentation. Neuroanatomic findings can usually be placed in one of below seven general categories.

Approach to Stroke Localization

The process is simply one of pattern recognition matching patients neurological deficits. The main stroke localizations and their cardinal patterns is presented below.

1- Left hemispheric lesion in territory of ICA and its MCA or ACA branches: Right limbs weakness, right limbs sensory loss, aphasia, difficulty in reading, writing and calculating, right visual field defect and poor right conjugate gaze.

2- Right hemispheric lesion in territory of ICA, MCA or ACA: Left limbs weakness, left limbs sensory loss, left visual field defect, left hemineglect, extinction of the left stimulus of two simultaneously visual or tactile stimuli, difficulty in drawing and copying.
3- Left PCA territory lesion: Right visual field defect, difficulty in reading with retained writing ability, difficulty in naming colors and objects presented visually, numbness and sensory loss in the right limbs.

4- Right PCA territory lesion: Left visual field defect or neglect, left limbs numbness and sensory loss.

5- Vertebrobasilar territory lesion: Rotational vertigo, diplopia, weakness or numbness of all four limbs or bilateral regions, crossed motor or sensory findings (numbness or weakness of one side of the face and the opposite side of the body), bilateral blindness or visual field defects, nystagmus, dysconjugate gaze, gait or limb ataxia out of proportion to weakness, crossed syndrome (lower motor neuron type cranial nerve palsy with numbness or weakness of the opposite side of the body). In vertebrobasilar territory strokes bilateral weakness may be asymmetric on two sides and weakness should not be due to an old stroke or other defect in one of the sides. Motor and/or sensory deficits in vertebrobasilar TIAs sometimes affect different sides during different attacks. Ataxia, imbalance and unsteadiness should not be due to vertigo in vertebrobasilar territory lesion. Drop attacks, a rare presentation of vertebrobasilar TIAs is the consequence of episodic ischemia of the lower brain stem or upper cervical cord with a relatively benign course and prognosis.

6- Pure motor stroke due to internal capsule or base of pons lesions: Weakness of face, arm and leg on one side of the body without abnormalities of higher cortical function, sensory or visual dysfunctions and reduced alertness.

7- Pure sensory stroke due to thalamic lesion: Numbness or decreased sensation of face, arm and leg on one side of the body without weakness, incoordination, visual and higher cortical dysfunctions.

In some stroke patients, the clinical findings are quite limited and do not represent the full clinical syndrome, i.e. the abnormality may be limited to aphasia, yet this is sufficient to place the patient in the category of left hemisphere anterior circulation. Because no other pattern includes aphasia. Similarly, nystagmus and ataxia are diagnostic of brain stem or cerebellar lesions in the category of vertebrobasilar disease. In other patients the findings are not sufficient to allow definite localization but suggest a number of possibilities, i.e. weakness limited to a single limb could fit into a number of these categories (numbers 1, 2, 6 in the preceding list). Small deep infarcts typically present with highly focal symptoms such as pure motor stroke, pure sensory stroke, ataxic hemiparesis and dysarthria clumsy hand syndrome. Although mixed sensorimotor stroke is considered one of the
five classic lacunar syndromes, however it is difficult to differentiate this syndrome from large vessel territory infarction or deep hemorrhages except by neuroimaging\textsuperscript{\textsuperscript{1,12}}. Disorders of higher cerebral function, i.e. aphasia, agnosia, apraxia, amnesia, sensory or visual neglect, hemianopsia and other visual field defects are rare in small deep infarcts (lacunes)\textsuperscript{\textsuperscript{1,12}}. Depressed or loss of consciousness, seizure and headache are also rarely seen in patients with small deep infarcts. Hemichorea-hemiballismus is the most frequent movement disorder of vascular origin with small deep infarcts\textsuperscript{3}. Occlusion of the inferior division of MCA usually causes a homonymous hemianopsia or superior quadrantanopsia and fluent aphasia (in left hemisphere lesions). The predominance of motor and sensory deficits in the face and arm is common in infarcts of the entire cortical territory of MCA or its superior division, however this finding is not specific and may be seen in small deep infarcts\textsuperscript{7}. Hemiparesis predominantly in the lower limb is seen mainly in the ACA territory infarcts\textsuperscript{7}. The traditional teaching of cerebrovascular syndromes is based on the general assumption that particular symptoms and signs arise from restricted areas of damaged brain which receive their vascular supply in a predictable manner. Although these are of value to those interested in cerebral localization, however learning these vascular syndromes have very limited benefit for managing stroke patients in 21th century with available brain MRI technology. It seems reasonable to distinguish clinically anterior (carotid) circulation strokes and posterior (vertebrobasilar) circulation strokes because certain investigations, i.e. carotid duplex and treatments, i.e. carotid endarterectomy are only appropriate to ischemic events of anterior circulation\textsuperscript{1}. In general, based on clinical manifestations of stroke it can be impossible to be sure of which arterial territory is involved, because so often the symptoms are not entirely specific for one particular arterial territory\textsuperscript{16}. Individual variation in arterial anatomy and previous arterial disease affecting the collateral circulation may cause this discrepancy. In addition a brain function can be distributed through multiple arterial territories, i.e. the corticospinal tract is supplied in the brain by the anterior circulation and in the brain stem by the posterior circulation\textsuperscript{7}. Ninety six percent of patients with isolated homonymous hemianopsia have PCA occlusion\textsuperscript{12}. However homonymous hemianopsia could be due to occlusion of inferior cortical branch of MCA involving the optic radiation. Localization of involved vascular territories of cerebellum by neuroimaging could determine level of the vascular occlusive disease. An infarct in the posterior inferior cerebellar artery territory means a vascular lesion at the level of intracranial VA, whereas an anterior inferior
cerebellar artery territory infarct means a caudal BA lesion and a superior
cerebellar artery territory infarct means a lesion at the rostral end of the BA.

**Oxfordshire (Bamford) Clinical Localization of Stroke**

Based on Oxfordshire clinical localization of stroke below categories are
illustrated:\textsuperscript{1,50}:

**Posterior Circulation Syndromes**

At the time of maximal deficit any of below patterns\textsuperscript{1,50};
1- Ipsilateral cranial nerve (III-XII) single or multiple palsy with
contralateral motor and/or sensory deficit.
2- Bilateral motor and/or sensory deficit.
3- Disorder of conjugate horizontal or vertical eye movements.
4- Cerebellar dysfunction without ipsilateral long tract deficit (as seen in
ataxic hemiparesis)
5- Isolated hemianopsia or cortical blindness.

Note: Horner syndrome, nystagmus, vertigo, dysarthria and hearing
disturbances may be present in patients with posterior circulation syndrome
but are not of particular localizing value\textsuperscript{1}.

Note: There is tendency for posterior circulation syndrome to be
underdiagnosed from inattention to truncal or gait ataxia in examination.

**Total Anterior Circulation Syndrome**

All of below patterns should be present\textsuperscript{1,50}.
1- Hemiplegia contralateral to the cerebral lesion.
2- Hemianopsia contralateral to the cerebral lesion.
3- New disturbance of higher cerebral function, e.g aphasia and visuospatial
disturbance.

Term total is used in this context that all of the major aspects of
supratentorial cerebral function has been affected. This syndrome is usually
seen in large MCA territory and ICA territory infarcts. A quarter of all
patients with total anterior circulation syndrome have an underlying primary
intracerebral hemorrhage\textsuperscript{1}. Occasionally an otherwise typical posterior
circulation syndrome is associated with disturbance of higher cerebral
function, i.e. aphasia and agnosia because posterior circulation may supply
parts of supratentorial structures. Perhaps the biggest penalty of Bamford
localization system is the ability of the PCA territory ischemia to produce a
total anterior circulation syndrome. Such patients have a relatively mild
hemiparesis but marked aphasia and visual field defect\textsuperscript{1}. The motor deficit
in these cases occurs due to involvement of the small perforating arteries arising from the proximal PCA which supply midbrain or a thalamic infarction with involvement of the adjacent posterior limb of the internal capsule.

**Partial Anterior Circulation Syndrome**

Any of below patterns may be present\(^1\)\(^,\)\(^5\)\(^0\).

1. Motor/sensory deficit + new disturbance of higher cerebral function.
2. New disturbance of higher cerebral function + hemianopsia
3. Motor/sensory deficit + hemianopsia
4. Motor/sensory deficit alone less extensive than lacunar syndromes, i.e. monoparesis
5. New disturbance of higher cerebral function alone, i.e. aphasia

Note: When more than one type of deficit are present they must all reflect damage in the same cerebral hemisphere.

Partial anterior circulation syndrome has less extensive deficits than the total anterior syndrome and yet do not fulfill the specific criteria for lacunar syndromes, either due to the presence of higher cerebral dysfunction or because motor/sensory deficit is too restricted than lacunar syndromes\(^2\). Partial anterior circulation syndromes is caused by cortical MCA and ACA territory infarcts. Occasionally a patient who have MCA stem occlusion falls short of the full definition of total to partial anterior circulation syndrome because good collateral flow restricts the clinical syndrome. Borderzone infarcts caused by sever extracranial ICA stenosis could present as partial anterior syndrome\(^3\). In demented patients, evaluation of new cortical dysfunction and homonymous hemianopsia is impossible. Most of the patients with inappropriate infarct have multiple strokes. Primary intracerebral hemorrhage consists about 10% of posterior circulation syndromes, 25% of total and 6% of partial anterior circulation syndromes\(^5\)\(^0\). The Bamford clinical localization predicts the volume of cerebral infarction. Thus physician can predict which patients are at greatest risk of developing impairment of conscious level and may be at risk of aspiration pneumonia or herniation. An impaired level of consciousness is found in 14% of those with total anterior circulation syndrome and impaired consciousness is not seen in patients with lacunar syndrome unless due to other causes\(^1\).

**Lacunar Syndromes**

The term lacune is used to describe an area of infarction within the territory of a single perforating artery. Lacune is a pathologic term and
based on neuroimaging the term small deep infarct is preferred. Lacunes are small, deep infarcts that occur in the subcortical regions of the brain, including the deep white matter, basal ganglia, internal capsule, thalamus and brain stem. The majority of lacunes occur in areas that are clinically silent, however others occur at strategic sites such as internal capsule and pons, where clinically eloquent ascending and descending neural tracts are concentrated and an extensive clinical deficit can occur from an anatomically small lesion. About one-quarter of all ischemic strokes and TIA's are lacunar. Patients with lacune may present with a large number of clinical syndromes. Lacunes typically present with the highly focal symptoms. The clinical expression of lacunar infarcts relates to the site of infarction. It could be argued that any clinical pattern that has been linked convincingly to a pathological lacune or equivalent imaged small deep infarct, should be refered to as a lacunar syndrome. The advantage of defining and recognizing these syndromes in clinical practice is the high probability that these will be the clinical expression of underlying lacunar infarct. If one considers the basic neurovascular pattern it has no surprise that these small deep infarcts rarely have major impact on higher cognitive or visual functions. Patients with lacunar syndromes should not have aphasia, dysphasia, visuospatial disturbance, visual field defect, dyspraxia and other disturbances of higher cerebral function. Lacunes predominate in the basal ganglia, internal capsule, pons and corona radiata. Therefore cortical manifestations; i.e aphasia, apraxia, agnosia and neglect is not seen in these patients. Homonymous hemianopsia and seizure is very rare in patients with lacunar syndrome. These types of manifestations are assumed as exclusion criteria for diagnosis of lacunar stroke. When impairment of consciousness develops in a patient with lacunar syndrome, a search for alternative explanation in spite of brain edema is acceptable. Decreased level of consciousness and headache are rarely caused by lacunar infarction. Complete pure motor stroke is diagnosed when the weakness equally affects the face, arm and leg on the same side sparing the sensation. Partial pure motor stroke was defined as a brachio-facial or brachio-crural distribution of weakness or unequal involvement of the face, arm and leg. Complete pure sensory stroke is defined as equal sensory disturbance over the entire side of the body including the face, proximal as well as the distal parts of the upper and lower limbs, neck and trunk. Partial pure sensory stroke is diagnosed with involvement of less than the entire side of the body or unequal involvement of the face, arm and leg. The affected parts could feel stretched, hot and pins sticking with partial or
complete sensation deficit. Mixed sensory motor stroke is restricted to both sensory and motor involvement of face, arm and leg\textsuperscript{11,12}. Complete and partial mixed sensory motor stroke is defined similar to the above descriptions. As pure motor, pure sensory and sensorimotor stroke only deficits involving face and arm or the whole of the arm and leg should be accepted as lacunar syndromes and more restricted deficits are more likely to be of cortical origin\textsuperscript{11,12}. In lacunar syndromes at least two of the three parts: face, upper and lower limbs should be involved\textsuperscript{1}. Since motor or sensory involvement may be followed by each other within hours of the stroke onset, the lacunar syndromes are detected at completion of the motor or sensory manifestations after 24 hours of the stroke onset. Ataxic hemiparesis is diagnosed as homolateral ataxia with crural paresis. This syndrome usually presents as a mild to moderate weakness of the leg especially the ankle with little or no weakness of the upper limb and face and accompanied by ataxia of the arm and leg on the same side\textsuperscript{11}. However weakness may involve face and arm to the same degree as the leg\textsuperscript{11}. The degree of ataxia should be more striking than the weakness and exceeds that attributed to the weakness alone\textsuperscript{11}. Dysarthria clumsy hand syndrome is detected as dysarthria and ataxia of the upper limb\textsuperscript{11,12}. This syndrome also includes facial weakness, dysphagia and mild weakness of the hand and even the leg. The reflexes on the affected side are often exaggerated with extensor plantar response\textsuperscript{11,12}. Atypical lacunar syndromes consist of isolated hemichorea or hemiballismus, isolated internuclear ophthalmoplegia, one and half syndrome, isolated vertical gaze palsy and isolated horizontal gaze palsy\textsuperscript{13,51}. The 6\textsuperscript{th} nerve palsy with contralateral hemiparesis, Millard Gubler syndrome, Bendikt syndrome, Claude syndrome, Weber syndrome, Foville syndrome, internuclear ophthalmoplegia with contralateral hemiparesis, dysarthria with facial palsy, and isolated dysarthria are also included in the atypical lacunar syndromes\textsuperscript{13,51}. The presence of cortical signs, hemianopsia and seizure considered as exclusion criteria for diagnosis of lacunar syndromes\textsuperscript{2,7}. Consecutive Persian stroke patients registered in two Iranian registries during 2001-2007 enrolled in a prospective validation study. All of the patients who developed ischemic stroke had one or more brain CT scan 48 hours after the stroke\textsuperscript{13}. A lacune was considered as responsible for lacunar syndrome in CT scan when its location corresponded to the clinical manifestations. CT of these cases should demonstrate a new subcortical lesion <2 Cm, no new cortical lesion and no new lesion ≥ 2 Cm\textsuperscript{13}. In the brain stem, new lesion < 1.5 Cm was considered as lacune\textsuperscript{13}. Brain CT scan with no visible new lacunar infarction and without other new abnormalities
were also assumed as appropriate for neuroimaging detection of lacunar infarct\textsuperscript{13}. Lacunar syndromes are usually caused by small deep infarcts. Thus a visible lesion in neuroimaging may not be seen. Sensitivity, specificity, Positive Predictive Value (PPV) and Negative Predictive Value (NPV) of the lacunar syndromes was calculated in the whole and in separation. Lacunar syndromes were found in 625 patients; 21.3\% (286 females, 339 males); with mean age 68.05 SD: 8.9. Lacunar syndromes were significantly more frequent in males, p<0.05. Perhaps men are more serious regarding evaluation of their problems. Table 2 demonstrates the frequency of various lacunar syndromes in our 625 patients\textsuperscript{13}.

<table>
<thead>
<tr>
<th>Type of lacunar syndrome</th>
<th>Number</th>
<th>Males (N)</th>
<th>Females (N)</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure motor stroke</td>
<td>275</td>
<td>151</td>
<td>124</td>
<td>44%</td>
</tr>
<tr>
<td>Pure sensory stroke</td>
<td>60</td>
<td>33</td>
<td>27</td>
<td>9.6%</td>
</tr>
<tr>
<td>Mixed sensory motor stroke</td>
<td>141</td>
<td>78</td>
<td>63</td>
<td>22.5%</td>
</tr>
<tr>
<td>Ataxic hemiparesis</td>
<td>40</td>
<td>21</td>
<td>23</td>
<td>6.4%</td>
</tr>
<tr>
<td>Dysarthria clumsy hand</td>
<td>44</td>
<td>21</td>
<td>23</td>
<td>7.1%</td>
</tr>
<tr>
<td>Atypical</td>
<td>65</td>
<td>35</td>
<td>30</td>
<td>10.4%</td>
</tr>
<tr>
<td>Total</td>
<td>625</td>
<td>339</td>
<td>286</td>
<td>100%</td>
</tr>
</tbody>
</table>

Brain CT scan of 330 patients (52.8\%) with lacunar syndrome demonstrated lacunar infarct corresponding to the manifestations. 216 of these patients (34.6\%) had no new lesion in the brain CT scan. Thus neuroimaging of 546 cases (87.4\%) was appropriate to lacunar infarct and calculated as true positive. The brain CT scan of 79 cases (12.6\%) had discrepancy with lacunar infarction and classified them as false positive for lacunar syndrome. Cortical infarction, cortical and subcortical infarction, subcortical infarction $\geq$ 2 Cm and intracerebral hemorrhage consisted 17.7\%, 44.3\%, 26.6\% and 11.4\% of these 79 false positive cases respectively\textsuperscript{13}. Lacunar syndromes in whole had sensitivity of 83.7\%, specificity of 96.5\%, PPV of 87.8\% and NPV of 95.4\% (CI: 95\%)\textsuperscript{13}. Comparison of two genders revealed PPV of 91.6\% in females and PPV of 83.7\% in males with lacunar syndromes. Pure motor stroke had specificity of 97.9\% and PPV of 82.9\% (CI: 95\%) and partial pure motor syndrome consisted 65\% of these cases\textsuperscript{13}. Pure sensory stroke was detected with specificity of 99.9\% and PPV of 96.6\% (CI: 95\%) and 80\% of these cases.
had partial pure sensory syndrome. Mixed sensory motor syndrome was diagnosed with specificity of 98.8%, PPV of 81.5% (CI: 95%) and partial mixed sensory motor syndrome consisted 78% of these cases. Ataxic hemiparesis was diagnosed with specificity of 99.9% and PPV of 97.5% (CI: 95%). Dysarthria clumsy hand syndrome demonstrated specificity of 100% and PPV of 100% (CI: 95%). Atypical lacunar syndromes were associated with specificity of 99.8% and PPV of 95.4% (CI: 95%). 52.8% of our patients with lacunar syndrome had a corresponding small deep infarct in brain CT scan performed 48 hours after event. In our stroke registry 79 cases (12.6%); with lacunar syndrome had CT findings inappropriate to the lacunar syndrome. These findings are congruent with the other reported studies. Intracerebral hemorrhage consisted 1.4% of our lacunar syndromes and 3.8% of lacunar syndromes reported by Arboix. The specificity of all subtypes of lacunar syndrome in our registry was high and reached up to 100% in dysarthria clumsy hand. PPV as the most accurate diagnostic marker of lacunar subtypes was moderate in pure motor and mixed sensory motor syndromes and high in the other subtypes of lacunar syndromes. The previous studies confirmed that presence of a deficit involving the face, arm and leg was highly predictive of a lacunar or small deep infarct but noted that a facio-brachial deficit was much less predictive than a brachio-crural deficit. It has also been pointed out that the close anatomic and vascular relationships between the motor and sensory Rolandic cortices actually make the possibility of a mixed sensory motor stroke from a cortical infarction more likely than a cortical pure motor stroke. However there is no difference in this regard in our patients. It is clear that a large subcortical infarct can cause a mixed sensory motor stroke. About 10% of the stroke patients presenting with a lacunar syndrome will have a lesion other than a small deep infarct on the scan, which might explain the neurological symptoms. The proportion of such atypical patients does seem to be higher for mixed sensory motor stroke than other syndromes and particular care should be taken in this group. Miscellaneous or atypical subtypes consisted 10.4% of the 625 patients with lacunar syndromes. There is not a specific brain localization for lacunar syndromes. Infarcts presenting as sensorimotor stroke tends to be larger than infarcts with other lacunar syndromes. Table 3 represents frequency of atypical lacunar syndromes in our lacunar registry.
Table 3: Distribution of atypical lacunar syndromes in our lacunar registry

<table>
<thead>
<tr>
<th>Type of the syndrome</th>
<th>Number</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isolated Internuclear Ophthalmoplegia</td>
<td>20</td>
<td>30.8%</td>
</tr>
<tr>
<td>Internuclear Ophthalmoplegia and hemiparesis</td>
<td>4</td>
<td>6.2%</td>
</tr>
<tr>
<td>Isolated one and half syndrome</td>
<td>3</td>
<td>4.6%</td>
</tr>
<tr>
<td>Isolated vertical gaze palsy</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Isolated horizontal gaze palsy</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>6th nerve palsy and contralateral hemiparesis</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Millard Gubler Syndrome</td>
<td>4</td>
<td>6.2%</td>
</tr>
<tr>
<td>Weber Syndrome</td>
<td>10</td>
<td>15.4%</td>
</tr>
<tr>
<td>Bendikt syndrome</td>
<td>2</td>
<td>3.1%</td>
</tr>
<tr>
<td>Claude Syndrome</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Foville Syndrome</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Dysarthria and facial weakness</td>
<td>10</td>
<td>15.4%</td>
</tr>
<tr>
<td>Isolated dysarthria</td>
<td>5</td>
<td>7.7%</td>
</tr>
<tr>
<td>Hemiballismus</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Hemichorea</td>
<td>1</td>
<td>1.5%</td>
</tr>
<tr>
<td>Total</td>
<td>65</td>
<td>100%</td>
</tr>
</tbody>
</table>

In very elderly or demented patients it could be difficult to detect higher cerebral dysfunction or visual field defect and the result of neuroimaging may assist primary clinical classification. Small vessel lipohyalinosis or microatheroma formation is the common underlying pathologic lesion in lacunes. One-third of the lacunar infarcts occur in normotensive individuals. Despite the availability of effective antihypertensive drugs, the incidence of lacunar stroke has not changed in recent decades. Thus, the influence of hypertension as risk factor of lacunar brain infarction is attenuated. Other etiologies of lacunar infarctions include intracranial atherosclerotic disease of large or medium size arteries and embolism from heart, aorta and extracranial arterial trunks. Coexistence of multiple etiologies in some patients with lacunar infarction obscures determination of a precise cause. Microemboli might be the cause of an important minority of lacunar events. The issue is of key importance when an ipsilateral severe ICA stenosis is considered in a patient with corresponding lacunar infarction. Etiology of 348 Persian ischemic stroke patients including 96 lacunar stroke and 252 Large Artery Territory (LAT) brain infarction were evaluated prospectively. Hypertension was present in 60.4% of patients with lacunae and 50.4% of patients with LAT infarction, p=0.09. Diabetes and hypercholesterolemia were significantly more frequent in Persian patients with lacunar syndrome than LAT infarction, p=0.034 and p<0.001 respectively. Distribution of smoking and TIA was not significantly different comparing lacunar strokes.
and LAT infarctions, \( p=0.59 \) and \( p=0.37 \) respectively\(^{53}\). Atrial fibrillation was significantly more frequent in our patients with LAT infarction than lacunes, \( p<0.001 \). Surprisingly, distribution of ipsilateral ICA or VA stenosis corresponding to infarction was not significantly different comparing Persian stroke patients with lacune and LAT infarction, \( p=0.164\(^{53}\). The frequency of various etiologic mechanisms is not significantly different between lacunar stroke patients and patients with large vessel territory infarction\(^{53}\). Table 4 compares distribution of etiologies in our lacunar stroke and LAT infarction patients.

**Table 4:** Distribution of various etiologies in our 96 lacunar stroke and 252 LAT infarct patients.

<table>
<thead>
<tr>
<th>Etiology/Territory</th>
<th>Lacunae 96 patients</th>
<th>Large Artery Territory 252 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerosis</td>
<td>46 (50%)</td>
<td>138 (53.9%)</td>
</tr>
<tr>
<td>Atherosclerosis and cardioembolism</td>
<td>14 (15.2%)</td>
<td>26 (10.2%)</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>10 (10.9%)</td>
<td>34 (13.3%)</td>
</tr>
<tr>
<td>Uncertain</td>
<td>22 (23.9%)</td>
<td>48 (18.8%)</td>
</tr>
<tr>
<td>Miscellaneous</td>
<td>0 (0%)</td>
<td>10 (3.9%)</td>
</tr>
</tbody>
</table>

Our results suggest that hypertension is not more important in the pathogenesis of lacunar infarction than LAT infarction. The apparent excess of hypertension and diabetes in lacunar infarction was confined to studies in which the presence of hypertension and diabetes favored a diagnosis of lacunar infarction\(^{54}\). This raises the possibility of mechanisms other than small artery disease in non-hypertensive patients with lacunar stroke\(^{54}\). In lacunar stroke, carotid stenosis is more common on the ipsilateral side than on the contralateral side\(^{55}\). Carotid endarterectomy appears to reduce the subsequent risk of lacunar as well as LAT stroke in patients with severe carotid stenosis\(^{55}\). Sever ICA stenosis ipsilateral to the symptomatic lacune was found in 27.1\% of our lacunar patients. Patients with lacunar syndromes often have no abnormality in brain CT, carotid duplex and echocardiography which is important in cost-effectiveness of stroke work up\(^1\).
Chapter IV

Neurovascular Imaging of Stroke

Routine Brain Imaging in Stroke

Ideally any stroke investigation should be accurate, noninvasive, accessible, inexpensive and informative in the sense that the result will influence patient management and outcomes. Neuroimaging data including the size, location and involved vascular territory of infarction as well as the presence of bleeding affect both acute and long-term treatment decisions. The usual brain imaging test for stroke and TIA patients is Computerized Tomography (CT) around the world. The diagnostic yield and clinical utility of newer neuroimaging procedures must be weighted against the time cost, availability and financial costs of these tests. From a practical point of view, the first step in classification is the distinction of ischemic stroke from Primary Intra-Cerebral Hemorrhage (PICH). This distinguishes two groups of stroke with differing causes, prospects for survival and influences decisions about medical and surgical treatments. No clinical criteria can reliably differentiate ischemic stroke from PICH. Brain CT within a week of stroke is required for this differentiation. Appearance of presumed ischemic lesions in the relevant part of the brain in CT of the patients presenting with TIA, should not change the diagnosis of TIA to stroke based on the traditional definition of TIA. It is duration of symptoms that is relevant to the distinction. Ischemic brain lesions in CT of TIA patients is almost always found in patients with carotid territory TIAs and performing CT in patients with vertebrobasilar territory and monocular TIA is not necessary for this purpose. Repeating CT in the hope of demonstrating an infarct after an early normal scan is usually not indicated when the clinical condition remains unaltered. Clinical distinction between carotid and vertebrobasilar territory infarcts may be difficult, i.e. pure motor hemiparesis could be caused by cortical, internal capsule and pontine lesions and patient with the latter would not be considered for carotid surgery despite presence
of severe carotid stenosis. Repeating CT is indicated in these cases. Stroke patients with normal initial CT and high chance of death have a legal indication of repeating CT, if there is no respiratory failure with handling difficulty. Occasionally it is difficult to differentiate an infarct from a tumor or partially resolved hematoma on the initial CT scan. Therefore it may be necessary to repeat CT with contrast injection after weeks for observing evolution pattern of tumors. A simple routine brain CT scan, about 10 slices through the whole brain at 1 centimeter intervals without intravenous contrast is usually all that is required for imaging of acute stroke. CT will remain the first line imaging in acute stroke with reserving MRI for more complicated cases in the next few decades.

**Hyperacute infarct signs in CT**

Adventures of thrombolytic treatment and improvement of CT technology increased using CT to identify early infarct (first 6 hours) or arterial occlusion signs that affect decisions about treatment. Loss of visualization of the insular ribbon (definition of the grey-white interface at the lateral margins of the insula) and outline of the lentiform nucleus (blurring of the lentiform nucleus margins) have been reported within 3 hours of stroke onset in basal ganglia. Loss of normal grey-white matter differentiation at the cortex-white matter and basal ganglia-white matter interfaces are all forms of hypodensity in which the ischemic grey matter first becomes hypodense with respect to normal grey matter. Effacement of the overlying cortical sulci and compression of the lateral ventricle are early imaging signs of edema. The extent of mass effect in the early phase of edema is proportional to the size of the infarct. Early infarct signs shows areas of irreversible ischemic damage. Hypodensity or tissue of lower density than the adjacent white and grey matter is other early sign of infarction. Small infarcts appear later than large ones because there is less tissue to alter their density. These early signs may be detected within 6 hours of stroke onset in up to 80% of MCA territory infarcts. Isolated cortical swelling without hypodensity is rare but potentially reversible in patients with acute cerebral ischemia. Hyperdense artery sign, most often is seen in patients with MCA stem and BA occlusion, is another early but indirect sign of ischemic stroke. It represents visualization of arterial occlusion caused by thrombosis or embolus as an increased density in the artery. However absence of this sign is not a reliable indicator of a patent artery. Calcified artery walls in the elderly and increased hematocrit can produce a similar appearance although it is usually bilateral. Dot sign on the initial CT at silvian fissure means MCA branch occlusion.
The Alberta Stroke Program Early CT Score (ASPECTS) and Persian Early Computed Tomography Score (PECTS)

The presence of widespread signs of early infarction, i.e. hypodensity in more than one-third of MCA territory, is correlated with higher risk of hemorrhagic transformation following thrombolytic therapy. Since early signs of major MCA territory infarction is considered as an exclusion criteria in thrombolysis therapy, physicians must be able to reliably identify scans with this finding. However, estimation of ischemic tissue extent is hampered by modest interobserver agreement among experts, with reported k-values of 0.39-0.64. Additionally, it appears that clinicians have a tendency to rate very small and large infarcts well but have trouble with classifying moderately large infarcts. The Alberta Stroke Program Early CT Score (ASPECTS) system is used for estimation of large MCA territory infarcts which are ineligible to thrombolysis with tPA. The ASPECTS method is semiquantitative and localization weighted estimation of ischemic tissue volume within MCA territory. This method improves detection of early ischemic changes in the CT scan. A cross-sectional study was conducted in ischemic stroke patients admitted in Ghaem hospital, Mashhad during 2008. The CT images were chosen from Ghaem stroke data bank. The inclusion criteria were the presence of MCA territory infarction and availability of electronic and hard copies of CT scans performed within 6 hours after stroke onset. Patients were excluded if infarction outside the MCA territory was present on CT image. Uncertain time of stroke onset and poor scan quality were considered as exclusion criteria. CT of stroke patients with lacunar syndrome were excluded. All of the consecutive brain CT images that met the above inclusion criteria and had no exclusion criteria enrolled in this study. Axial CT scans were performed on a third-generation CT scanner (Siemens, ARTX, Germany) oriented along the supraorbital meatal line. Section thickness was 5 mm in the posterior fossa (130 kV, 150 mAs) and 10 mm superiorly (130 kV, 150 mAs). Films were made at window level 35 HU. All patient details were removed from the films. Early signs of ischemia was defined as X-ray hypoattenuation, loss of the gray-white boundary (which is due to X-ray hypoattenuation of the grey matter) and focal brain swelling. The later was defined as any focal narrowing of the cerebrospinal-fluid space due to compression by adjacent brain structures such as effacement of the cortical sulci or ventricular compression. Only new areas of ischemia were scored. The entire MCA territory is summarized by 10 regions of interest on two axial CT slices which involve basal ganglionic and supraganglionic structures in the
ASPECTS system (Picture 1)\(^{56,58}\). One point is deducted for partial or total involvement by ischemic tissue in any of the 10 designated regions\(^{56,58}\). An ASPECT score of \(\leq 7\) was associated with an increased rate of symptomatic hemorrhage following intravenous tPA therapy\(^{56,58}\). A normal CT scan has an ASPECTS value of 10 points. The PECTS system was designed by the author and approved by scientific committee of Khorasan Associations of Neurologists and Radiologists. The PECTS is calculated from two standard axial cuts, one at the level of the thalamus and basal ganglia, and one just rostral to the ganglionic structures. For PECTS, the territory of MCA is allotted 8 points\(^{57}\). PECTS is assessed by systematically scoring each of 7 regions (M1-M7) on the CT scan. The evaluated cortical regions M1 to M6 is the same as ASPECTS system (Picture1)\(^{57}\). The M7 region includes subcortical structures (internal capsule, lentiform nucleus, external capsule, insular ribbon) and insular cortex\(^{57}\). The caudate head is not included in PECTS because it has dual blood supply from the MCA and anterior cerebral artery. One point is deducted for partial or total involvement by ischemic tissue in any of the M1 through M6 designated regions and two points is deducted in partial or total M7 region involvement\(^{57}\). A score of 8 implies no evidence of new early signs of ischemia in the MCA territory. A progressively lower score indicates more extensive ischemic changes. A validation study was conducted for detection of interobserver agreement in estimating volume of MCA stroke based on two methods\(^{57}\). Four experienced academic radiologists independently evaluated the CT images based on the ASPECTS and PECTS methods at separate sessions. The readers were given only brief training, which included a set of written guidelines based on relevant published articles\(^{55,56}\) and 5 separate CT films (2 with extensive early ischemic changes) shown them as example. Rating for each method was performed 2 weeks apart. Training on the use of each method was provided prior to each reading. The readers were blind to all clinical information except symptom side. All images were reviewed on film. The PECTS and ASPECTS templates was provided to the readers. PECT and ASPECT scores were dichodorized at \(< 6\) or \(\geq 6\) and at \(> 7\) or \(\leq 7\) respectively \(^{56,57}\). Cochrane Q test and Kappa test served for statistical analysis to compare the readers agreement for quantification of early CT ischemic changes based on two mentioned methods\(^{57}\). Fifty brain CTs were available while 16 scans excluded for poor quality or uncertain time of onset. Ten patients had brain infarction outside the MCA territory and excluded.Twenty four patients (15 males) with mean age 61.8 years; SD: 8.5 with infarcts in the MCA territory were studied. The 24 scans were
examined by 4 raters yielding a total of 96 patient-scan examinations. Table 5 represents the interrater agreement of major MCA territory infarction based on the reading methods.\(^5\)

<table>
<thead>
<tr>
<th>Radiologist</th>
<th>ASPECTS ≤7 Number of scans</th>
<th>PECTS &lt;6 Number of scans</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rater 1</td>
<td>16</td>
<td>9</td>
</tr>
<tr>
<td>Rater 2</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>Rater 3</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Rater 4</td>
<td>6</td>
<td>15</td>
</tr>
</tbody>
</table>

Figure 1: represents ASPECTS and PECTS templates

Four radiologists agreed on dichotomized ≤7 and >7 scores based on the ASPECTS method of 4 (16.6%) and 4 (16.6%) patients respectively. 33.3% of the patients had whole raters agreement based on the ASPECTS method. Difference in distribution of dichotomized ≤7 and >7 ASPECT score between four raters was significant; \(Q=13.071, \text{df}=3, \ p=0.04\). Four radiologists agreed on dichotomized <6 and ≥6 scores based on the PECTS method in 4 patients (16.6%) and 7 patients (29.2%) respectively. 45.8% of the patients had whole raters agreement based on the PECTS method. Difference in distribution of dichotomized <6 and ≥6 scores based on PECTS method between 4 raters was not significant; \(Q=6.349, \text{df}=3, \ p=0.26\).
p=0.096. 96 patient-scan examinations by 4 raters were analysed for number of patients considered as eligible for thrombolysis based on the two methods. 52.1% and 51.1% of 96 patient-scan examinations were ineligible to tPA therapy based on the ASPECTS and PECTS methods respectively\textsuperscript{57}. Distribution of patients ineligible for thrombolysis was not significantly different comparing the ASPECTS and PECTS methods with each other; k=0.010, p=0.885. ASPECTS and PECTS were devised to provide a systematic approach of assessing and improving reliability of early ischemic changes in regions of the MCA territory. These systems provide a reliable semiquantitative, localization weighted estimation of ischemic tissue volume within the MCA territory\textsuperscript{57}. ASPECTS is a predictor for both functional outcome and symptomatic hemorrhage in patients treated by rTPA thrombolysis\textsuperscript{58,59}. In an individual with ASPECTS value of 7 or less, the risk of symptomatic intracerebral hemorrhage with rTPA is 14 times that of patients with a score greater than 7\textsuperscript{58,59}. Our study revealed superior reliability of PECTS than ASPECTS method. A significant difference in distribution of stroke patients ineligible to rTPA therapy was found between our four radiologists based on ASPECTS method, while this difference was not significant based on the PECTS system\textsuperscript{57}. 96 scan-patient examinations in our study group revealed insignificant difference in distribution of patients ineligible for rTPA thrombolysis comparing the ASPECTS and PECTS systems. These findings confirm that PECTS is an alternative to ASPECTS system which has higher reliability\textsuperscript{57}. The PECTS was developed to offer the reliability and utility of a standard CT examination with a reproducible grading system to assess early ischemic changes in the MCA territory. This CT score has shown to be simple, reliable and identifies stroke patients unlikely to make an independent recovery despite thrombolytic treatment. Posterior Circulation Acute Stroke Prognosis Early CT Score allots the posterior circulation 10 points. 1 point each is subtracted for hypodensity in left or right thalamus, cerebellum or PCA territory and 2 points each for hypodensity in midbrain or pons. Score less than 8 identifies posterior circulation stroke with poor prognosis\textsuperscript{42}. The above score like ASPECTS was designed in university of Calgary, Canada.

**Acute infarct signs in CT**

Infarctions usually appear in CT during 48 hours of stroke onset. Small infarcts in neuroimaging are sometimes presented as TIA\textsuperscript{1}. Within the first 3 hours of stroke, the reasonable time window for starting thrombolytic therapy, both CT and routine MRI are commonly insensitive for detection of
ischemia. A subsequent CT is obtained if the patient gets worsen neurologically and is especially helpful in identifying hemorrhagic transformation following thrombolytic therapy. Infarcts in the brain stem and cerebellum are particularly difficult to visualize with CT due to artifacts arising from the petrous bones. Infarct swelling is maximal around the third to fifth days and gradually subsides during the second and third weeks. The extent of mass effect of edema is proportional to the size of infarct. The infarct gradually increases in density during the second week and sometimes becomes isodense and indistinguishable from normal surrounding brain which is called the fogging effect. This phenomenon may last up to two weeks and then the infarct becomes progressively hypodense and black. Fogging effect is usually partial and appears as isodense superficial curvilinear bands in large infarcts. Brain CT shows the appropriate infarct in 60% of patients with an ischemic stroke overall. Thus a patient with a clinical diagnosis of stroke and an early CT which is either normal or shows a relevant hypodense lesion is classified as having an ischemic stroke. Patients with symptoms of more extensive stroke are more likely to have a visible relevant infarct in CT and early visible infarcts carries worse prognosis. A typical large artery infarct is a wedge shaped, sharply demarcated hypodensity and occupies all or part of a recognizable vascular territory. A lesion straddling different vascular territories is not likely to be an arterial infarction. When you are faced with a CT showing multiple holes in the brain and generalized atrophy, it may be impossible to decide which hole is the relevant one unless serial scans reveal a new hole or Gadolinnum enhanced T1 weighted MRI shows an enhancing lacune. Lacunes or small deep infarcts are rounded and less than 1.5-2 centimeters in diameter. CT demonstrates the symptomatic lacunar lesion in 50% and routine MRI in 80%. Borderzone or watershed infarcts lie in areas of brain at the edge of the large artery territories, i.e. parietoccipital funnels for MCA-PCA boundary zone and over the vertex as frontal parasagittal strips in ACA-MCA boundary zone. In old infarcts, atrophy is present on CT or MRI with enlarged sulci and ex vacuo dilatation of the adjacent ventricle. Neuroimaging within first day of stroke is recommended only in 1- Preparation of thrombolytic therapy. 2- When deteriorating consciousness may indicate surgical intervention in primary ICH. 3- Suspected cases of subarachnoid hemorrhage. 4- Suspected cerebellar stroke necessitating close clinical monitoring and standby neurosurgery team. 5- Suspected ICH secondary to anticoagulant therapy or coagulation disorders necessitating special therapies. 6- Patients with crescendo TIAs or stroke in evolution.
who are considered for heparin therapy. Focal encephalitis, i.e. herpes simplex encephalitis and purulent cerebritis can appear exactly like an infarct although the lesion is not wedge shaped and involves more white matter than cortex. If there is any doubt, i.e. fever and subacute onset, other specific diagnostic tests must be carried out. A hypodense lesion involving different vascular territories is not likely to be an arterial infarction. Edema in ischemic infarcts involves both gray and white matter, while in tumors, vasogenic edema is limited to the white matter. This selective involvement of subcortical regions in vasogenic edema makes the characteristic digitate pattern. Metastasis with extensive edema can also mimic infarction. Intravenous contrast may show up a cortical nodule in these cases. Infarcts usually get smaller in repeated scans after a few weeks, whereas brain tumors and metastasis stay the same or get bigger. Typical patterns of vasculitic infarcts on CT include multiple lacunar infarcts or bilateral borderzone infarcts in a young normotensive patient. Territorial patterns is less frequent unless in vasculitis due to meningitis.

**Leukoaraiosis**

Leukoaraiosis (LA) means thinning or rarefaction of cerebral white matter which is often located at periventricular and subcortical areas. LA is defined on baseline CT scan as symmetrical hypodensity in periventricular and subcortical white matter. These are poorly margined, patchy or punctuate and non-dysplacing lucencies. LA is more concentrated around frontal horns as well as the trigones of the lateral ventricles in mirror-image locations. LA is a common neuroradiologic finding in elderly people. LA is classified as a variant of atherosclerosis that selectively involves the penetrating arterioles of periventricular area, resulting in chronic ischemia. LA represents deeply placed watershed infarcts caused by hypoperfusion in the distal deep arterial territories. LA has prognostic implications because its presence increases the risk of stroke not only in patients with TIA or minor stroke but also in general population. Twenty one percent of north American and Persian stroke patients had LA without difference in races. There is no difference in frequency rate of LA between north American and Persian stroke patients. In age groups <65 years and ≥65 years, the frequency of LA in north American and Persian stroke patients was similar, p=0.072, p=0.588 respectively. LA was significantly more frequent in hypertensive patients, p=0.04. The effects of diabetes, hypercholesterolemia and smoking on frequency rate of LA were not significant, p=0.84, p=0.71, p=0.40 respectively. Elderly and female gender were other significant risk factors.
factors of LA, $p=0.049$, $p=0.002$ respectively\textsuperscript{61}. LA was 2.54 times more common in stroke patients aged $\geq 65$ years than younger patients\textsuperscript{61}.

**Diagnosis of venous infarcts based on CT**

Differences in clinical presentation, work up and management between venous and arterial infarcts makes their differentiation important in CT. Venous infarcts often do not quite fit the usual site of an arterial territory infarct\textsuperscript{11}. Venous infarcts can be differentiated from hemorrhagic arterial infarcts because of their extraterritorial site and multifocal findings\textsuperscript{11}. It may be multiple, bilateral and is more swollen than an equivalent-sized arterial infarct. Similar to arterial infarctions, venous infarctions are hypodense on CT and $T_1$ imaging and hyperdense on $T_2$ imaging with mass effect\textsuperscript{11}. Hemorrhages within the venous infarcts are very common and multiple. Unilateral or bilateral parasagittal bleeding occurs in superior sagittal sinus thrombosis and temporolateral bleeds occur following thrombosis of the transverse sinus. Venous infarcts have early obvious hypodensity with early distinct margin. The direct sign of recent sinus thrombosis consists of a small hyperdensity within the sinus representing the clot or hyperdense sinus sign\textsuperscript{12}. Frequently the thrombus is only recognized as a non-enhancing area or filling defect within the sinus on contrast CT or MRI. This empty triangle is called empty delta sign\textsuperscript{6,12}. The compensating increase in flow through the collateral venous network surrounding the sinus leads to good enhancement of the falx cerebri and tentorium cerebelli.

**Hemorrhagic transformation of infarct**

Hemorrhagic transformation of brain infarction is typically distinguished from primary ICH by the lack of homogeneity of the hemorrhagic area which lies within or on the edge of an area of low density confined to a single arterial territory\textsuperscript{38}. These are often patchy or petechial areas of increased density throughout the infarct. These infarcts appear heterogenous with alternating hypodense and hyperdense zones yielded by a mixture of necrotic tissue and blood\textsuperscript{38}. Indeed some hemorrhagic infarctions called intrainfarct hematomas can look like a primary ICH and without serial CTs the patient would have been labeled as primary ICH, however presence of concurrent intraventricular hemorrhage is an evidence for ruling out the hemorrhagic infarctions in these circumstances\textsuperscript{11,12,38}. The only definitive way of diagnosing hemorrhagic infarctions is to have identified a definite infarct or at least to have excluded primary ICH on an earlier CT and then to see hemorrhage in the same region on a follow up scan\textsuperscript{38,39}. A voluminous
hypodensity surrounds these hematomas which differs from the fine circular hypodense margins of primary ICH. Topography of these voluminous hypodense areas are within an arterial territory\textsuperscript{11,12,38,39}.

**Magnetic Resonance Imaging (MRI) in acute stroke**

Routine MRI including T\textsubscript{1} and T\textsubscript{2} weighted images are relatively insensitive to the changes of hyperacute ischemia within the first hours after stroke onset. These images will show abnormalities in less than half of the patients in this early period\textsuperscript{11}. The earliest ischemic changes detectable with routine MRI (T\textsubscript{1},T\textsubscript{2}) are loss of normal flow void in the symptomatic artery within minutes of stroke onset which is the MRI equivalent of hyperdense artery sign on CT\textsuperscript{11}. This provides direct information about location of blocked artery or vein. Swelling is seen in T\textsubscript{1} images without signal change on T\textsubscript{2} images within 3 hours. Signal change in T\textsubscript{2} images is observed within 6 hours. T\textsubscript{2} type of MRI is able to detect small deep infarcts clearly, furthermore in patients with several lacunes, Gadolinium enhancement often demonstrates the enhancing recent lacune\textsuperscript{11}. New lacunes on non-enhanced T\textsubscript{2} images are less hyperintense than old lacunes\textsuperscript{11,12}. Ischemic lesions are considered as lacune if on T\textsubscript{1}, T\textsubscript{2} or DWI they appear as round, ovoid or linear with less than 1.5 centimeter length\textsuperscript{62}. MRI is more sensitive to small lesions in the brain stem and posterior fossa than CT because there is no interference from brain artifacts. Circumstances that MRI is preferable to CT in patients with brain infarction include\textsuperscript{11,12}:

1- MRI is superior than CT for lacunar, posterior fossa and small cortical infarcts. 2- More than 10 days after stroke, CT may show a low density area that could have been infarction or resolving hematoma, while it is essential to differentiate infarction from ICH for secondary prevention. 3- When CT is negative and localization of infarct is important for therapeutic purposes. 4- When arterial dissection or CVT are suspected cause of infarction. However, MRI is certainly less practical and takes longer time and more cost. Since small cortical infarcts may be hidden in the gyral pattern of the convexity and would not be visualized in CT, MRI is a better tool in these cases. The T\textsubscript{2} images are best suited for demonstration of cerebral parenchymal damage and brain edema. It takes usually 6 to 8 hours for T\textsubscript{2} images to show infarction\textsuperscript{11}. It is clear that elevated signal on T\textsubscript{2} images is more sensitive (90%) for detection of early cerebral infarction than CT (60%) in the first 24 hours\textsuperscript{11,12}. On routine MRI, hemorrhagic infarctions are typically recognized during 48 hours by appearance of low intensity signal areas within a high signal intensity infarct in T\textsubscript{2} weighted image. In practice,
we request MRI in TIA or stroke only if it could change the management policy in the patient. It is not requested for diagnosis of lacune, cerebellar infarcts, small cortical infarcts and for defining anatomopathology of the lesion, although it is superior to CT. Sometimes MRI is performed for confirmation of ischemic stroke in posterior fossa in patients with non-diagnostic CT especially for legal purpose. Reserve MRI for difficult cases with specific questions. In patients with ICH, MRI demonstrates venous sinus thrombosis, multiple metastasis, primary tumors, parenchymal sequella of vasculitis and arteriovenous malformation which are more visible in MRI than CT. Pacemakers, mechanical heart valves, intracranial metallic clips, metallic prosthesis are absolute contraindications of MRI. First trimester of pregnancy is a relative contraindication of MRI.

**Fluid Attenuated Inversion Recovery Imaging (FLAIR)**

Infarcts are visible better and earlier around 4 hours and are hyperdense on FLAIR type of MRI. Despite T2 images, cerebrospinal fluid is not hyperintense on type of FLAIR. FLAIR is better for identifying the extent of infarct. FLAIR is useful for differentiating small cortical and periventricular infarcts which may be difficult to distinguish from adjacent cerebrospinal fluid in T2 images. New lacunes on FLAIR are hyperintense while old lacunes or old larger infarcts appear as hypointense.

**Diffusion Weighted Imaging (DWI)**

DWI type of MRI certainly shows appropriate hyperdense lesions within 30 minutes of stroke. DWI signals reflect the mobility of water molecules within tissues which is named Brownian motion. The low water diffusion rate in hyperacute ischemic lesions produces high signal in DWI. It is unclear in DWI whether this imaged abnormality represents infarcted brain tissue or areas of ischemic penumbra. DWI or FLAIR visible lesions may be reversible ischemic lesions presenting as TIA. DWI in patients with multiple lacunes can also demonstrate the recent lesion as an area of increased signal. A small cortical infarct may be difficult to identify by CT or routine T1,T2 weighted MRI images but is often clearly seen as an area of increased signal on DWI within few hours post event upto several weeks.

**Perfusion Weighted Image (PWI)**

PWI aims to measure the patency and degree of blood flow through the
cerebral microcirculation. PWI is a hemodynamic imaging and shows reduced cerebral blood flow immediately after vessel occlusion. PWI identifies parts of the brain with reduced blood flow in capillary microcirculation\(^{11,12}\). PWI shows reduced perfusion when \(T_1\) and \(T_2\) images are still normal\(^{11}\). Mismatches between a smaller DWI abnormality and a larger overlapping perfusion defect in PWI identifies a partially ischemic penumbra zone of potentially salvageable tissue. This mismatch area is a target for recanalization therapy with intravenous or intra-arterial tPA beyond the three hours time window\(^{62}\). Knowledge about extent of salvageable brain tissue may be useful to guide the choice of thrombolysis treatment. The presence of matched DWI and PWI abnormalities is predictive of a non-recoverable clinical deficit. In the clinical model DWI lesion represents the irreversibly damaged core of the infarct, however partial reversal of DWI is reported with ultra early reperfusion therapy\(^{62}\). Patients with large DWI-PWI mismatch have poor collaterals which predicts as worse clinical outcome without recanalization therapy\(^{62}\).

**Magnetic Resonance Angiography (MRA)**

MRA is based on velocity-induced phase shifts of moving spins in the presence of a magnetic field gradient. The difference in signal intensity between flowing blood and stationary tissue is proportional to the blood flow velocity and quantitative flow information as well as vessel display\(^{11,12}\). MRA allows non-invasive visualization of intra and extracranial cerebral vessels but provides lower resolution compared with catheter angiography especially in small vessels. Slow or turbulent flow may make loss of flow signal with subsequent overestimation of stenosis or nonvisualization of a vessel abnormality such as aneurysm or atherosclerotic ulcers\(^{11,12}\). MRA is a good diagnostic tool for screening of aneurysm but it could never substitute catheter angiography for neurosurgeon due to its lower sensitivity. MRA is a good neurovascular imaging for detection of intracranial arterial stenosis or occlusion, but addition of TCD is very helpful and complementary in stenosis of both anterior and posterior intracranial circulations. Because the areas that are poorly studied by one of these techniques are usually adequately studied by the other. MRA technology creates an image of flow in blood vessels. The changing angles and curvature of the ICA siphon and rstral cervical VA often makes interpretation of these regions difficult by MRA and performane of TCD could cover this limitation of MRA\(^{12}\). MRA of the VA origin is often suboptimal because of the overlapping of the arteries\(^{6,62}\).
CT Angiography

CT Angiography (CTA) is a noninvasive and reliable neuroimaging for detection of arterial occlusion within 24 hours of symptom onset. CTA using spiral CT is a tool to evaluate circle of Willis. In addition to the assessment of a major vessel occlusion, CTA has the potential to deliver information about the quality of the collateral circulation. In patients with good leptomeningeal collaterals, contrast enhancement in arterial branches beyond the occlusion occurs. A Clot Borden Score (CBS) developed in Calgary for anterior circulation strokes. This CBS allot major arteries 10 points for presence of contrast opacification on CTA. Two points each are substantiated for thrombus preventing contrast opacification in the proximal M1, distal M1 or supraclinoid ICA. One point each is substantiated for M2 branches, A1 and infraclinoid ICA. Quantification of intracranial thrombus extent with the CBS is a reliable method of predicting functional outcome and final infarct size in hyperacute phase of stroke. CTA shows the intracranial aneurysm, AVM and visualizes filling defect in a dural sinus due to CVT. The mismatch between CT perfusion image and infarct volume in spiral CT shows the ischemic penumbra.

Neurovascular Imaging of Cerebral Venous Thrombosis (CVT)

Routine MRI and MRV should be the first neuroimaging in suspected cases of dural sinus thrombosis and venous infarctions. The main direct sign of CVT on a standard MRI protocol is the lack of expected signal flow void on standard spin echo T2 sequences. The most reliable sign of dural sinus thrombosis in MRI is absence of the normal flowing blood signal void in the affected sinus which is best detected by coronal sections of T2 images. Absence of flow signal within a sinus and its nonopacification suggests intraluminal thrombosis. Filling defect of flow enhancement following contrast injection is seen in T1 images of thrombosed dural sinuses. Thrombus can also be seen on routine MRI. Direct visualization of the thrombosed sinus is required to conclusively confirm the diagnosis of CVT. In the acute phase (less than 3 days) the thrombus is isointense on T1 and hypointense on T2 images. At this stage the thrombus signal may mimic normal flow and may be confused with patency. Subsequently the thrombus becomes strongly hyperintense on both T1 and T2 images. Based on the histochemistry, at a very early acute stage (day 1–5), there is an absence of flow void and the thrombi appear isointense on T1 and hypointense on T2 weighted images due to the presence of Oxyhemoglobin in the intact red blood cells. At the subacute stage (day 6–21), the
thrombus becomes hyperintense, initially on $T_1$ (day 6–9) then on $T_2$ weighted images (day 10–15), due to the conversion of Oxyhemoglobin to Methemoglobin\(^6\). FLAIR imaging is the best method for direct observation of fresh thrombus especially in lateral sinuses. MRI and MRV is the method of choice for immediate evaluation of venous infarcts and dural sinus thrombosis\(^{11,12}\). Routine MRI and MRV is replaced catheter angiography for the imaging workup of patients suspected of having CVT. MRV in acute stage shows lack of signal within thrombosed veins and dural sinuses. In chronic stage MRV may document venous recanalization. Catheter angiography is sometimes used showing the sinus fails to fill throughout all or most of its length\(^6\). Catheter angiography also demonstrates dilated tortuous collateral veins extending away from the thrombosed sinus toward alternate outlet for venous drainage\(^{12}\). Corkscrew vessels is the characteristic appearance of CVT in catheter angiography\(^{12}\). The cerebral circulation time is also increased in patients with CVT\(^{12}\). The anterior segment of superior sagital sinus has often absent opacification in healthy individuals. Hypoplasia is an alternative explanation especially in the case of left lateral sinus or anterior third of superior sagital sinus thrombosis\(^{11,12}\). It is necessary to see delayed emptying or dilatation of collateral veins for documentation of sinus thrombosis by catheter angiography. Thrombosis of the cavernous sinus can not be diagnosed with confidence by MRV and catheter angiography because the sinus fills very inconsistently in normal conditions\(^6\). CVT should be considered when the topography of cerebral infarction does not correspond to an arterial branch or arterial boundaryzone territory. Based on the author experience catheter angiography rarely helps in diagnosis of CVT in patients with negative MRI/MRV. When there is high clinical suspicion of CVT, repetition of MRI/ MRV with and without contrast after a few days usually solves the problem.

**Neurovascular Imaging Prior to Carotid End Arterectomy (CEA)**

MRA has shown sensitivity of 90% and specificity of 80% compared to catheter angiography for detection of proximal ICA stenosis\(^{11}\). Catheter angiography is still considered gold standard for detection of proximal ICA stenosis because MRA lacks high sensitivity in the detection of high grade stenosis and tends to overestimate them as vessel occlusion\(^{11,12}\). The combination of MRA and carotid ultrasound helps to diminish potential pitfalls and increases the sensitivity and specificity\(^1\). Many of north American neurovascular surgeons make decision about Carotid EndArterectomy
(CEA) whenever the results of MRA and carotid duplex are congruent without performing catheter angiography, in centers with serially validated neurovascular imaging. In validated centers of Europe, all of the patients with recently symptomatic carotid who fit for and willing to consider CEA first underwent carotid duplex (sonographer is blinded to clinical data to avoid observer bias). If the first duplex shows stenosis above 70%, another sonographer, blinded to the result of first duplex and clinical manifestations, is asked to repeat the duplex. If both sonographers agree that the patient has symptomatic ICA stenosis more than 70%, within about 10% difference of each other, then surgery is requested. If there is interobserver disagreement (50-79% ICA stenosis) between carotid duplex and MRA or repeated carotid duplexes, catheter angiography is requested. Catheter angiography is performed before CEA only for the symptomatic artery to keep any risk to minimum. Some stroke centers still perform catheter angiography for every patient candidated for CEA. The reason of this diagnostic strategy is; of patients who are claimed by ultrasound to have ≥ 70% ICA stenosis, 10% will be shown by angiography to have narrowing that is below this degree. This 10% of patients would receive a procedure (CEA) with a periprocedure risk of upto 6%. While, the convincing evidence that they would benefit when the stenosis is less than 70% is lacking. Catheter angiography or contrast enhanced power/color doppler of ICA should be performed in all patients with suspected pseudo-occlusion. TIAs with an occlusion of the corresponding ICA in duplex studies is highly suspicious for pseudo-occlusion. In these patients CEA should be performed as soon as possible after exclusion of complete ICA occlusion.

**Estimation of proximal ICA stenosis by catheter angiography**

North American Symptomatic Carotid Endarterectomy Trial (NASCET) method calculates the proximal ICA stenosis as: B-A/B × 100 stenosis. European Carotid Surgery Trial (ECST) method calculates proximal ICA stenosis as: C-A/C × 100 stenosis. A is the least luminal diameter at the site of stenosis. B is post stenotic luminal diameter of ICA. C is the assumed normal diameter of ICA at the site of stenosis. The NASCET method tends to underestimate the severity of stenosis at the origin of ICA because the normal carotid bulb is wider than distal post stenotic ICA and also distal to severe stenosis the ICA may collapse. NASCET percent of stenosis equals to ECST percent of stenosis minus 40 and thereafter divided to 0.6.
Angiographic criterion of intraluminal thrombus and atheroma ulcer

Floating intraluminal thrombus is an infrequent angiographic finding. A luminal filling defect separated from the vessel wall by contrast material on two or more projections is considered as the best angiographic criterion for intraluminal thrombus. MRA is not sensitive for detection of floating thrombus and catheter angiography should be performed in this condition. Atheroma ulcers are usually found within the first 2.5 cm of ICA. The best criterion of ulceration is penetrating niche, the crater of contrast material is seen below overhanging edges of atheroma. If ulcer is partly or completely superimposed on the artery, a circumscribed double density may be seen which is another criterion for ulceration. Irregularity of the vessel wall is a less reliable marker of ulcers.

Neurovascular Imaging of Cerebral Vasculitis and Vasculopathies

In vasculitis, brain CT and more sensitive MRI show areas of presumed infarction and sometimes hemorrhage in both grey and white matter unlike multiple sclerosis where only white matter is affected. Diagnosis of cerebral vasculitis is based on clinical and angiographic findings. MRA and catheter angiograms typically reveal long stenotic lesions and fluctuation in the caliber of corticopial arteries. In vasculitis and vasculopathies, i.e. FMD, radiation vasculopathy and drug vasculopathy the angiographic findings are not specific. The most frequent angiographic finding is vessel narrowing which affects long segments. Beading pattern is seen in vasculitis and FMD. String of beads or continuous alternating areas of constriction and dilatation is the hallmark of FMD. The areas of dilatation widens the vessel to more than its normal caliber in contrast to atherosclerosis. Less frequent is the appearance of single or multiple areas of tubular stenosis without intervening dilatation in FMD. It may not be possible to differentiate the arterial beading or tubular stenosis of FMD from changes due to cerebral vasculitis, if the extracranial vessels are unaffected. Involvement of extracranial arteries helps to distinguish FMD, atherosclerosis, polyarteritis nodosa and Takayasu disease from primary cerebral angitis which is purely intracranial. Mid to high cervical portions of the ICA and upper cervical portion of Vertebral Artery (VA) are the usual sites of FMD in the neck, well away from the usual sites of the atheroma. Catheter angiography may be normal even in biopsy proven vasculitis. Although non-invasive neurovascular imaging like transcranial doppler and MRA could reliably assess stenosis of intracranial arteries; however diagnosis of intracranial vasculitis, aneurysm and arteriovenous malformation usually require catheter angiography.
Chronic occlusion of intracranial segments of ICAs makes development of exuberant collaterals through the small perforating branches of the basal arteries described as Moyamoya (puff of smoke in Japanese). The Moyamoya pattern is observed in radiation therapy, FMD, atherosclerosis, neurofibromatosis and Moyamoya disease\textsuperscript{12,62}.

**Dolichoectasia**

Dolichoectasia is a rare vasculopathy which is seen mainly in basilar artery. Dolichoectasia makes a distended basilar artery with >4.5mm diameter\textsuperscript{62}. The dolichoectatic artery is widened, tortuous and elongated with a characteristic flow void in MRA. These vessels can obtain thrombus which embolizes. Obstructive hydrocephalus, cranial nerve and brainstem compression are its other complications\textsuperscript{11,12}. Dolichoectasia if found in an acute stroke patient is not necessarily the cause of stroke. Dolichoectasia very rarely causes intracranial hemorrhage despite its aneurysmal dilatation\textsuperscript{12}.

**Neurovascular Imaging of Dissections**

It is important to ask the patient that in the last few days or weeks have you injured or damaged your neck, have you had a car crash, has anyone manipulated your neck, have you done anything to twist your neck\textsuperscript{16}. In suspected cases of extracranial arterial dissection, i.e. history of neck trauma or special maneuver and cervicofacial pain, MRA or catheter angiography is absolutely indicated\textsuperscript{6}. MRI/MRA is the first choice of neuroimaging and preferable to CT in suspected cases of arterial dissection\textsuperscript{11}. Long irregular stenosis or rat tail sign, double lumen and intimal flaps in places that are not common sites for atherosclerotic stenosis or occlusion (upper cervical part of the ICA and VA) are characteristic of dissections in angiography\textsuperscript{1,11,12}. The string sign could be due to atherosclerosis, dissection, radiation and other causes\textsuperscript{12}. Dissections involving the media with extension through the vessel wall may result in aneurysm formation\textsuperscript{12}. Definite angiographic diagnosis of dissection requires the visualization of the true and false lumina. If the two lumina are en face, then two strips of contrast of different densities may be seen. The presence of intimal flap also makes definite diagnosis of dissection\textsuperscript{62}. The angiographic appearance of tapering artery accompanied by aneurysmal dilatation near the skull base is diagnostic of dissection\textsuperscript{12}. These pseudoaneurysms look extremely ominous but surprisingly heal\textsuperscript{2,3}. Extracranial ICA dissections are often diagnosed by MRI/ MRA investigations and catheter angiography may serve as an adjunct to confirm the diagnosis. Cross-sectional T\textsubscript{1} images could show the
thrombus within the widened arterial wall at the dissection area. The pathognomonic T1 MRI sign of dissection is an eccentrically narrowed lumen with adjacent semilunar-shaped increased signal of thrombus (Crescent sign) representing extravasated blood in the vessel wall. Any imaging modality can show complete arterial occlusion which is nonspecific and does not imply dissection unless there is a typical long tapering or rat tail sign, a double lumen, an intimal flap or a hematoma within the arterial wall. Duplex ultrasound is not a sensitive and reliable test for diagnosis of dissections. The ICA and less often VA dissections are sometimes detected by color/duplex showing double lumen (bidirectional flow). Vascular duplex often shows an intramural thrombus and occlusion which is not diagnostic of dissection. B-mode grey scale imaging shows a tapering stenosis which is not specific for dissection. B-mode image shows infrequently the pathognomonic intimal flap. The sensitivity and specificity of MRA in detection of ICA dissections is higher than VA. ICA dissections diagnosed by T1 MRI may be unrevealed by catheter angiography and MRA, occurring when intramural hematomas failed to narrow the arterial lumen detectably. The most common symptom in extracranial VA dissection is pain in back of the neck with radiation to the occiput. The lateral medulla, pons and cerebellum are common sites of ischemia in VA dissection which may be poorly visualized on CT. A partial or complete lateral medullary syndrome is the most frequent ischemic presentation of these dissections. The extracranial VA is most mobile at C1-C2 level thus dissections are usually found in this area. The most frequent angiographic finding in patients with VA dissection is an irregular tapering stenosis. Double lumen or intimal flap is less frequent in extracranial VA than extracranial ICA dissections. The same is correct in intracranial dissections. The investigations should then be performed within days of symptom onset before the dissection heals spontaneously. Recurrence of dissection in the same or a different artery is about 1% per year. Presence of multifocal regions of dissection in various ages is rare unless there is an underlying vascular disease, i.e. FMD and Marfan syndrome. MRA is superior to MRI in discovering dissections. The sensitivity and specificity of MRA in detection of ICA dissections is higher than VA. Thus catheter angiography is indicated in patients with suspected extracranial VA dissections. Intracranial arterial dissection is infrequent in comparison to extracranial dissection and is mostly spontaneous. Intracranial dissections more often affect VA, BA, MCA stem than intracranial ICA and present with subarachnoid hemorrhage more than cerebral ischemia. The co-appearance of subarachnoid blood, intracranial arterial stenosis and an aneurysm originating at
a non-bifurcation site is highly suggestive of intracranial dissection but is uncommon. Catheter angiography in intracranial dissections reveals stenosis, occlusion, a string of beads; while a double lumen is infrequent in these cases.

**Angiographic investigation of cardioembolic strokes**

The classic appearance of an abrupt arrest of contrast in an artery is strongly suggestive of an embolus. Angiographic or TCD evidence of initial obstruction with later reopening of the basal intracranial arteries (vanishing occlusion) is suggestive of cardioembolic strokes. Demonstration of a patent artery supplying the infarcted territory by catheter angiography, MRA or TCD in the absence of proximal atherosclerosis as a source of arteriogenic emboli favor a diagnosis of cardioembolic stroke. However in clinical practice we do not confirm cardioembolic stroke by these methods.

**Indications for cerebral catheter angiography**

Major indications for cerebral catheter angiography include: 1- Measurement of ICA origin stenosis and assessment of intracranial arteries, i.e. tandem carotid siphon stenosis prior to CEA. In validated centers of neurovascular imaging, catheter angiography is used only in patients in whom carotid duplex and MRA has been shown conflicting estimates of the severity of stenosis. 2- As a prelude to intravascular interventions such as intra-arterial thrombolysis and angioplasty, angiography is performed because the treatment is given directly within the artery. 3- Catheter angiography is done in patients with suspected arterial dissection if MRA is not sufficiently diagnostic, especially in dissections of vertebrobasilar territory. 4- Clinically suspected vasculitis with supporting MRI/MRA findings is another indication of angiography. 5- Catheter angiography is still gold standard neurovascular imaging for detection of intracranial aneurysm. 6- Assessment of arterial feeding of AVM before surgery or interventional therapy is done by catheter angiography. In clinical practice catheter angiography must always be directed to answer a relevant clinical question and any answer must be likely to influence the patient management.

**Indications of Transcranial Doppler (TCD)**

TCD is used in stroke centers with approved protocol for intravenous or intra-arterial thrombolysis in hyperacute stage of the stroke for showing occlusion of a major cerebral artery and the effect of thrombolytic therapy on recanalization of the vessel. Using the fibrinolytic effect of 2 MHz ultrasound beam by TCD with or without intravenous rTPA is an experimental management
in acute MCA stem occlusion\textsuperscript{66}. TCD is covered by health insurance companies when used in patients in accordance with the following indications established by the American Academy of Neurology\textsuperscript{66}; 1- Detecting severe stenosis in the major basal intracranial arteries. 2- Assessing patterns and extent of collateral circulation in patients with known arterial trunk regions of severe stenosis or occlusion in neck. 3- Evaluating and following patients with vasoconstriction of any cause especially after SAH. 4- Detecting AVMs and evaluation of their supply arteries and flow patterns. 5- Assessing patients with suspected brain death. However, TCD has a minor role in routine clinical management of stroke patients\textsuperscript{67}. Evaluation of TCD results in 200 consecutive Persian stroke patients revealed that 27.5\% of TCD results were abnormal in this validation study\textsuperscript{67}. However only 15\% of the TCD results had influence on therapeutic decision of the patients\textsuperscript{67}. Among this later group, 83\% were patients with subarachnoid hemorrhage and 17\% had high risk cardiac source of embolism or severe carotid stenosis with recurrent cerebral ischemic events\textsuperscript{67}. Due to high expense and low percentage of therapeutic influences, performance of TCD is recommended in a restricted group of patients with cerebrovascular disease\textsuperscript{67}. TCD could be useful in noninvasive detection of intracranial arterial stenosis in patients with Moyamoya disease or vasculitis or intracranial atherosclerosis.

![Picture 2: shows detection of severe MCA stenosis by Power M mode TCD in a patient with Moyamoya disease.](image-url)
MicroEmbolic Signal (MES) monitoring

MES monitoring by TCD could have research and diagnostic value in some patients. MES detection criteria include: characteristic chirping sound, unilateral signal, random appearance in cardiac cycle and intensity increase >3 dB above background. For TCD embolus detection, the main stem of MCA is insonated through transtemporal window. Observing microembolic signals in brain vessels by TCD is a very common finding in Persian patients with mechanical heart valve⁶⁸,⁶⁹. No correlations have been found between number of microembolic signals and duration after valve replacement, valve position, cardiac rhythm, intensity of anticoagulation and history of TIA or stroke⁶⁸,⁶⁹. These signals are almost always clinically asymptomatic and their frequency does not indicate the risk of stroke in these patients⁶⁸,⁶⁹. Therefore, microembolic signal monitoring by TCD can not be a clue for severity of anticoagulant therapy in patients with mechanical heart valve⁶⁸,⁶⁹. It seems that microembolic signals in TCD monitoring of our patients are mainly gaseous bubbles caused by blood agitation with mechanical heart valve⁷⁰. Assuming that nitrogen bubbles are underlying embolic material in patients with mechanical heart valve, one would expect an exponential reduction in number of microembolic signals under oxygen inhalation⁷⁰. Oxygen inhalation leads to alveolar denitrogenation and at the same time nitrogen washouts from the blood⁷⁰. TCD with saline contrast could be used for detection of patent foramen ovale and other right to left heart shunts especially in young patients with ischemic cerebrovascular events⁷¹. Among 114 Persian patients with uncertain cause of stroke, 36% had a Patent Foramen Ovale (PFO) detected on TCD monitoring with saline contrast⁷¹. Role of PFO detection without confirmed paradoxical embolism in etiology of stroke is doubtful⁷¹. MES monitoring have been evaluated in 20 Persian patients with acute stroke in MCA territory without mechanical heart valve⁷². MES were detected in 3 patients (15%)⁷². Two of these cases had sever mitral stenosis with atrial fibrillation and one another had a small thrombus at the cardiac apex with mitral stenosis and regurgitation⁷². There seems to be an association between these signals in acute phase of stroke and a definite high risk cardioembolic source⁷².

Research applications of TCD

TCD has been used as a research tool for hemodynamic evaluation of arteriovenous malformations before and after surgery. Among Persian patients with arteriovenous malformation, hemodynamic changes in their
TCD depends on the size but does not show the probability of hemorrhage from the arteriovenous malformation\textsuperscript{73}. Performance of TCD does not have any influence in therapeutic and diagnostic decisions of patients with pulsating tinnitus\textsuperscript{74}. However, normal result of TCD may lead to reassurance of our patients with pulsatile tinnitus\textsuperscript{74}. The influence of race on topography of atherosclerotic stenosis using TCD and neck vascular duplex technology is an interesting subject. A comparative double-center study of north American and Persian stroke patients revealed extracranial ICA stenosis in 23\% of north American and 27\% of Persian patients, \( p=0.3 \). Sever \( \geq 70\% \) extracranial ICA stenosis was found in 7.5\% of north American and 4.6\% of Persian stroke patients, \( p=0.17 \). Significant intracranial stenosis was detected on TCD in 1.6\% of north American and 4.6\% of Persian stroke patients, \( p=0.038 \). Therefore intracranial stenosis is significantly more frequent in oriental races\textsuperscript{75}. Influence of age, gender and other factors on cerebral hemodynamics in Persian population is another usefulness of TCD for research in neuroscience\textsuperscript{76}.

**Detection of vasospasm by TCD in patients with SubArachnoid Hemorrhage (SAH)**

The most important indication of TCD in routine clinical practice is detection of vasospasm in patients with SAH. TCD permits bedside evaluation of intracranial vasospasm and makes possible selection of patients who should be considered for treatment prior to the development of fixed neurological deficit. Mild vasospasm is defined as mean flow velocity values in MCA and ACA more than 120 Cm/s and in intracranial ICA or PCA more than 90Cm/s. The mean flow velocity ratio of MCA or ACA /Extracranial ICA \( \geq 3 \) in anterior circulation and mean flow velocity ratio of PCA or BA/VA \( \geq 3 \) in posterior circulation is another criterion of detecting mild vasospasm by TCD\textsuperscript{77}. Sever MCA vasospasm is defined as mean flow velocity value of more than 200 Cm/s. The mean flow velocity ratio of MCA or ACA /Extracranial ICA \( \geq 6 \) in anterior circulation and mean flow velocity ratio of PCA or BA/VA \( \geq 6 \) in posterior circulation is criterion of detecting sever vasospasm by TCD\textsuperscript{77}. One hundred eighty one Persian SAH patients (54\% females) with mean age 53.7 ±7 years were evaluated by serial TCD and vasospasm in TCD was found in 30.9\% (56 patients)\textsuperscript{78}. Delayed Brain Infarction (DBI) in brain CT was observed in 17 SAH patients (9.4\%). The mean time from SAH onset to development of vasospasm in TCD and mean time from occurrence of vasospasm in TCD to development of DBI on brain CT was 8.51±2 and 9.06±4 days respectively\textsuperscript{78}. 

Difference in distribution of DBI based on the presence and severity of vasospasm in TCD was significant; \( p < 0.001 \). Table 6 represents relationship of DBI and severity of vasospasm on TCD\(^7\)\(^8\).

**Table 6:** Distribution of DBI based on the presence and severity of vasospasm in TCD of our 181 SAH patients

<table>
<thead>
<tr>
<th>Vasospasm/Infarction</th>
<th>Severe vasospasm</th>
<th>Moderate vasospasm</th>
<th>Mild vasospasm</th>
<th>No vasospasm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of infarction</td>
<td>1</td>
<td>6</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Absence of infarction</td>
<td>3</td>
<td>10</td>
<td>26</td>
<td>124</td>
</tr>
</tbody>
</table>

Distribution of DBI was not significantly different between surgical and medical therapeutic groups of our SAH patients, \( p = 0.288 \). Fifty percent of our SAH patients with DBI deceased. Distribution of death in medical and surgical groups of our SAH patients with DBI was not significantly different, \( p = 0.132 \). Moderate and severe vasospasm in TCD had low sensitivity and high specificity for prediction of DBI. While, mild vasospasm in TCD had high sensitivity and moderate specificity for prediction of DBI. Presence of any degree of vasospasm on TCD had low PPV for prediction of DBI in our SAH patients\(^7\)\(^8\). Table 7 demonstrates predictive values of vasospasm detection by TCD for DBI\(^7\)\(^8\).

**Table 7:** Predictive values of mild, moderate and severe vasospasm on TCD for prediction of DBI in our 181 cases.

<table>
<thead>
<tr>
<th>Predictive Values/ Vasospasm in TCD</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>PPV</th>
<th>NPV</th>
<th>Validity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild Vasospasm</td>
<td>94.4%</td>
<td>76.1%</td>
<td>30.3%</td>
<td>99.2%</td>
<td>77.9%</td>
</tr>
<tr>
<td>Moderate Vasospasm</td>
<td>38.9%</td>
<td>92.1%</td>
<td>35%</td>
<td>92.2%</td>
<td>86.7%</td>
</tr>
<tr>
<td>Severe Vasospasm</td>
<td>5.6%</td>
<td>98.2%</td>
<td>25%</td>
<td>90.4%</td>
<td>88.9%</td>
</tr>
</tbody>
</table>

**Duplex Ultrasound of neck arteries**

Detection of atherosclerotic stenosis of extracranial ICA and VA is the main indication of Duplex ultrasound in patients with TIA or stroke. The duplex ultrasound criteria for extracranial ICA stenosis of 50% or more is peak systolic velocity \( >125 \)Cm/s and spectral broadening\(^7\)\(^8\),\(^7\)\(^9\). The duplex ultrasound criteria for extracranial ICA stenosis of 70% or more is peak systolic velocity \( >325 \)Cm/s, end diastolic velocity \( >110 \)Cm/s, and ICA/CCA peak systolic velocity ratio\( >4\)\(^7\)\(^8\),\(^7\)\(^9\). Compared with digital subtraction angiography, carotid duplex sonography has a sensitivity of 88%, specificity of 95%, Positive Predictive Value of 96% and Negative Predictive Value of
87% in detecting extracranial ICA stenosis of 70% and over in our patients\textsuperscript{79}. The yield of MRA as a screening procedure for detection of extracranial ICA stenosis is quite high and addition of carotid duplex is helpful\textsuperscript{1}. The two procedures are complementary. When MRA and ultrasound studies have congruent results with acceptable quality and when sufficient information has been driven to guide treatment, then catheter angiography is not needed for performing CEA or carotid angioplasty\textsuperscript{1}. Duplex ultrasound is a screening tool for detection of extracranial ICA dissection in our patients\textsuperscript{80}. Details of neurosonology is out of the scope of this book.
Chapter V

Etiologic Work up of Ischemic Cerebrovascular Events

How far patients are investigated for the cause of their stroke or TIA depends on how the results of any investigation will influence treatment decisions. Fortunately, most cardiac lesions with a substantial threat can be suspected and even diagnosed by clinical exam and Electrocardiogram (ECG). The extend of cardiac diagnostic investigation must be modified based on the management issues in individual patients, i.e. patients who could not safely receive anticoagulants may not require extensive cardiac evaluation to identify an occult cardioembolic source. Some cardiac lesions are so common in the normal stroke free population (i.e. mitral valve prolaps, patent foramen ovale and mitral annular calcification) that their relevance in an ischemic stroke patient is unassessable without additional evidence of embolism. The criteria to suspect a paradoxical embolism to the heart include; 1- An ischemic event occurring during a valsalva maneuver, i.e. lifting, straining, cauphing. 2- Presence of patent foramen ovale or atrial septal defect identified with contrast echocardiography or TCD with saline contrast. 3- A clinical or ultrasound reason for deep venous thrombosis. Any color doppler must be performed within 48 hours post stroke, because deep venous thrombosis is a common consequence of stroke particularly in a paralysed leg. However these clues are not specific and sensitive for reliable diagnosis of paradoxical embolism. The decision whether an identified potential embolic source in the heart was the definite cause of stroke or TIA can be impossible, i.e. a patient aged 70 years has both atrial fibrillation and sever carotid stenosis corresponding to the infarction. In a patient with sever ICA stenosis, being certain that an ischemic episode is caused either by low flow alone or by acute arterial occlusion seldom really matters. The management is exactly the same, control of vascular risk factors, antithrombotic drugs and CEA.
The first line investigations

The first line investigations for every ischemic stroke and TIA patient include\textsuperscript{1,40}:

1- Complete blood count with platelet count and ESR
2- Blood sugar, Cholesterol, Triglycerid, Urea and electrolytes, (PT, PTT and hepatic function tests are requested in North America and Europe due to approved intravenous rTPA therapy.)
3- ECG, 4-Unenhanced routine brain CT

Note: We request PT, PTT, INR only in young patients with cryptogenic stroke, past or family history of venous thrombosis, and candidate for thrombolytic therapy or anticoagulation.

The second line investigations

A useful diagnostic test is one that leads to a change in therapeutic approach associated with a better outcome. New information that does not improve outcome has no value. The second line investigations are more costly or invasive and are targeted on patients who must gain from a useful change in management. These investigations for selected ischemic stroke and TIA patients include\textsuperscript{1,40}:

1- Chest X Ray

Chest X Ray is indicated in the presence of hypertension, finger clubbing, cardiac murmur, abnormal ECG, ill patient and pulmonary abnormalities. Possible findings include; enlarged heart, aspiration pneumonia, calcified heart valves, aortic dissection.

2- Transthoracic echocardiography (TTE)

Persian (The author) indications of TTE in patients with TIA or stroke include\textsuperscript{81}: Patients with evidence of cardiac disease on history, examination, or ECG\textsuperscript{81}.

1- The history; i.e. rheumatic fever, recent myocardial infarction.
2- Clinical exam; i.e. heart murmur, arrhythmia, Gallop rhythm.
3- ECG; i.e. atrial fibrillation and ST segment elevation.
4- Suspected paradoxical embolism

Braunwald indications of TTE in patients with TIA or stroke include\textsuperscript{82}:
1- Patients aged < 45 years.
2- Patients older than 45 years without other identifiable non-cardiac causes of stroke.
British (Warlow et al) indications of TTE in patients with TIA or stroke include:
1- Patients aged < 50 years.
2- The history; i.e. rheumatic fever, recent myocardial infarction.
3- Clinical exam; i.e. heart murmurs, arrhythmia, Gallop rhythm.
4- ECG; i.e. atrial fibrillation and ST segment elevation.
5- Chest X ray; i.e. enlarged left atrium.

TTE was performed in 302 consecutive Persian stroke patients. High risk cardiac source of embolism influencing management was found in 13.2% (40/302) of the patients.

Thereafter a cost-effective retrospective analysis compared three mentioned methods of TTE indications. Based on the Persian indications, 50 TTE was necessary after complete medical history and examination in 302 patients with takings 302 ECG. According to the Persian method of indications, 87.5% (35/40) of the patients with high risk cardiac source of embolism could be detected. Based on the Braunwald method of indications, Duplex ultrasound of neck arterial trunks and TCD had to be performed for detection of identifiable arterial disease in 282 patients aged more than 45 years. TTE was indicated based on the Braunwald method in 167 of 282 patients who had no identifiable arterial disease in patients aged more than 45 years and in 30 patients due to age less than 45 years.

Thirty eight of 40 patients (95%) with high risk cardiac source of embolism could be detected with using Braunwald method of indications. According to the British (Warlow et al) method of indications, 88 TTE was necessary after taking complete medical history and examination in 302 patients with performing 302 ECG and 302 chest X ray. Thirty seven of these 88 TTE was done due to age less than 50 years. Thirty eight of 40 patients (95%) with high risk cardiac source of embolism could also be detected with using British method of indications. Comparing three methods of TTE indications, two patients with high risk cardiac source of embolism were missed using Braunwald or British methods of indications. Five patients with high risk cardiac source of embolism were missed using Persian method of indications. However due to little expense of Persian method and much more cost-effective benefit, it is recommended for use in developing countries with limited health care budget.

3- Transesophageal echocardiography (TEE)

It is justifiable to examine the heart in considerable detail in young patients aged less than 45 years with no obvious cause of cerebral ischemia.
TEE is indicated in patients aged < 45 years with non-diagnostic TTE, no other clear cause of cerebral ischemia and absence of major risk factors and still suspected on clinical basis for cardioembolism. TEE is not recommended in unselected patients and should always be done after TTE. Most echocardiographers view TTE and TEE as complementary and perform TTE initially in patients with TIA or stroke. Then they proceed with focused TEE study. Possible abnormal findings in TEE include patent foramen ovale, atrial septal aneurysm, aortic arch atheroma and aortic dissection. TEE has superiority over TTE in detecting lesions of the aorta, left atrium and atrial septum. Atrial septal defect and septal aneurysm, patent foramen ovale, atrial appendage thrombi, valvular vegetations and atheroma of the ascending aorta are best detected by TEE. Identification of a condition in TEE requiring anticoagulation such as mechanical heart valve may not lead to a change in patient management. TEE was performed after TTE in 47 consecutive Persian patients with TIA or stroke referring to our echocardiography unit for TEE. The influence of performing TEE on management and preventative strategy of the patients was reviewed by an echocardiographer and a stroke neurologist. Seventy percent of these patients aged less than 45 years. Cardiac and aortic abnormalities were detected in TEE of 35 cases (35/47, 74%) and cardioaortic abnormalities of 17 cases (17/47, 36%) were only detectable by TEE. These 17 cases included 7 patients with PFO, 1 case with atrial septal defect, 7 cases with aortic atheroma and 2 patients with clot in left atrium. While, cardioaortic abnormalities of the remaining 38% could be detected by previous TTE. Comparing the preventive stroke strategies before and after TEE revealed that only in 4.3% of the cases it was changed due to performing TEE. These included one patient with a small-high risk PFO and another case with dehiscence of mechanical mitral valve. Two stroke patients with clot in the left atrium had mitral valve stenosis and had been on warfarin before TEE. However, TEE revealed cardiac or aortic abnormalities in one-third of the patients with cerebral ischemia which has not been detected by TTE previously. The influence of TEE in therapeutic decisions of patients with ischemic cerebrovascular events is very low.

4- 24 hours Holter ECG monitoring

In patients with history of syncope and/or palpitation during a suspected TIA or high suspicion of cardioembolic stroke with non-diagnostic TTE and ECG are selected for continuous ECG monitoring. Possible findings include paroxysmal atrial fibrillation and sick sinus syndrome. Continuous
ECG recording is also performed for ischemic stroke and TIA patients admitted in stroke unit.  

5- MRI  
MRI is indicated in TIA or stroke patients with miscellaneous infrequent etiologies; e.g, in patients with suspected arterial dissection, CVT or cerebral vasculitis. MRI is requested in cerebellar and brainstem infarction with unclear CT. MRI is particularly important in acute stroke patients with unusual presentations or in whom a stroke mimic is suspected but not clarified on CT, e.g, suspected cases of multiple sclerosis. MRI with Diffusion-Weighted Imaging (DWI) has the advantage of higher sensitivity for early ischemic changes than CT and routine MRI. This higher sensitivity is particularly useful in the diagnosis of posterior circulation stroke and lacunar or small cortical infarctions. MRI can also detect small and old hemorrhages for a prolonged period with T2 sequences. If arterial dissection is suspected, MRI of the neck with fat suppressed T1-weighted sequences is required to detect intramural hematoma.  

6- Catheter angiography  
Catheter angiography is indicated: 1- if results of two non-invasive methods; e.g, carotid duplex with MRA and MRA with CT angiography shows discrepancy for detection of a symptomatic severe stenosis and patient fit and willing for CEA. 2- In suspected arterial dissection if results of MRA are inconclusive. 3- In suspected cases of FMD, Moyamoya, vasculitis. 4- Catheter angiography is used for candidates of intra-arterial thrombolysis and angioplasty. 5-Differentiation between subtotal occlusion and complete occlusion of a recently symptomatic ICA is other indication of catheter angiography, if patient fits for CEA. 6-Arteriovenous malformation and aneurysm are also absolute indications of catheter angiography.  

7- Carotid duplex  
Carotid ultrasound is indicated in patients with mild stroke or TIA in carotid circulation if the patient fits and accepts CEA or stenting in approved centers. Carotid ultrasound is requested in asymptomatic subjects with a non-cardiogenic carotid bruit if the patient fits and accepts CEA or stenting in approved centers. Carotid ultrasound is indicated six months after CEA or stenting and every year thereafter for follow up of restenosis. Neck CT-angiography or MRA is recommended in patients with TIA or minor
stroke with corresponding sever extracranial ICA or VA stenosis in ultrasound, if patient fits and accepts CEA or stenting in approved centers.

8- Temporal artery biopsy
Temporal artery biopsy is indicated in patients aged > 60 years with headache, jaw claudication, malaise, polymyalgia and raised ESR.

9- Skin biopsy
Skin biopsy is requested in TIA or stroke patients with periventricular changes on CT/MRI and history of stroke in family.

10- Electroencephalography (EEG)
EEG is indicated if there is doubt about diagnosis of TIA or stroke with focal seizures or Todds paresis. EEG is also indicated in patients with generalized encephalopathies; i.e. herpes encephalitis, CJD and SSPE.

11- Antinuclear, Anticardiolipine and Antiphospholipide antibodies
These tests are requested in patients with venous thrombosis, recurrent miscarriage, thrombocytopenia, cardiac valve vegetations, livedo reticularis, malaise and raised ESR.

12- Arterial blood gas
Arterial blood gas is done if hypoxia is suspected.

13- Antithrombin III, proteins C, S and factor V Leiden
These tests are requested in presence of personal or family history of unexplained deep venous thrombosis, patients with CVT, no obvious cause of stroke in young adults, multiple unexplained strokes and abnormalities in routine screening coagulation tests.

14- Three serial blood cultures
Blood culture is done in patients with fever and heart murmur, valve vegetation and raised ESR.

15- Lipid profile (LDL, HDL, VLDL)
Lipid profile is indicated in hypercholesterolemia or family history of hyperlipidemia. This is a first line investigation in north America.
16- Cardiac enzymes (Troponin, CPK-MB)

These enzymes are requested in the presence of history or ECG evidence of recent myocardial infarction. This is a first line investigation in north America.

17- Genetic analysis

Genetic analysis is done in familial stroke with periventricular changes in CT/MRI.

18- Blood Homocystein

Evaluation of blood homocystein is indicated in all young adult patients with unexplained stroke and young stroke patients with atherosclerosis. Serum homocystein is also indicated in patients with marfanoid habitus, high myopia, dislocated lense, osteoporosis and mental retardation. Even in the absence of low serum folate or B12, plasma homocystein may be lowered by giving dietary supplements of folic acid and B12.

19- Mini-Mental State Exam

MMSE is done for cognitive assessment of stroke patients suspected to have vascular dementia.

20- TCD

TCD is performed based on guidelines illustrated in the previous chapter.

Vasculitic disorders of the CNS

Connective tissue, inflammatory and other vasculopathies may cause not only thrombosis within arteries and veins but also rupture of affected vessels with hemorrhage. Patients with these disorders are more likely to present with a generalized encephalopathy with or without focal features, which does not fit with the typical stroke patient. Cerebral vasculitis should be considered in children and young adults with recurring ischemic or hemorrhagic stroke with encephalopathic manifestations, i.e. fever, headache, cognitive deterioration and multifocal neurologic symptoms. CNS vasculitis most commonly presents as an acute or subacute focal or diffuse encephalopathy or meningoencephalopathy with headache, altered mentation, seizures, cognitive and behavioral abnormality with multifocal neurological signs. Less commonly, patients present with a multiple sclerosis-like picture (relapsing and spontaneously remitting focal neurological
dysfunction) or features of a rapidly progressive space–occupying lesion. Clues to the diagnosis of CNS vasculitis are illustrated below:

1- Preceding systemic features such as weight loss, malaise, fever, skin rash and arthropathy suggests a vasculitic process.
2- The lack of any obvious and more common cause of stroke is in favor of CNS vasculitis.
3- A raised ESR and CRP, antcardiolipine, anti-double strand DNA antibodies suggests a vasculitis involving the CNS. However, in isolated CNS vasculitis ESR is elevated in two-thirds of patients and other serologic and systemic tests are not helpful.
4- CT and MRI may show areas of presumed infarction and hematomas in both grey and white matter in CNS vasculitis, unlike multiple sclerosis where only white matter is affected.
5- In one-half of these patients angiography is abnormal. There are no specific or sensitive angiographic criteria for cerebral vasculitis. Focal narrowing and dilatation or beading of small cerebral arteries sometimes with aneurysm formation are observed in CNS vasculitis. These findings also are seen in tumor emboli, irradiation or drug abuse vasculopathy, intracranial arterial dissection, intravascular lymphoma and periperal angiopathy.
6- Any changes in CSF are non-specific in CNS vasculitis including lymphocytic or occasionally neutrophilic inflammatory reaction, increased protein and oligoclonal bonds (similar to multiple sclerosis).
7- Biopsy of meninges or nondominant temporal cortex should be pursued in patients with multifocal lesions and encephalopathy especially if they have a CSF pleocytosis and a high protein content. The decision to biopsy is made on an individual basis. If an extended period of treatment with potentially hazardous immunosuppressant drugs is being considered, the need to establish an unequivocal tissue diagnosis is of primary importance. False negative biopsy is possible due to patchy distribution of the vasculitic lesions.

**TIA or Stroke due to giant cell arteritis**

This is easily diagnosed by accompanying systemic features such as malaise, polymyalgia, weight loss, low grade fever, nonpulsatile headache, scalp tenderness and ESR over 50 in a patient never under age of 50 years. The superficial temporal arteries may be tender, cord-like and non-pulsatile. A clinical diagnosis is seldom enough to commit elderly patients to risk of using corticosteroids for months. Transcranial color coded duplex abnormalities of external carotid artery branches including stenosis,
occlusion or hypoechoic halo around the perfused lumen, maximize the chance of a positive biopsy. It is best to take biopsy of a tender superficial temporal artery. If negative and the case is still a puzzle the other superficial temporal artery should be biopsied. A negative biopsy does not rule out the diagnosis due to patchy involvement of the artery. The clinical diagnosis is accepted in this circumstances, by the complete resolution of the general polymyalgia and headache symptoms within 1-2 days of starting corticosteroids and a normal ESR within 1 month. In a patient with typical manifestations of giant cell arteritis and oculocerebral ischemic events with raised ESR, high dose of corticosteroids should be started before the results of biopsy are known and sometimes even before the biopsy is performed.

**Antiphospholipid Syndrome**

Among TIA or stroke patients who have raised titer of anticardiolipine antibody, very low percentage have some or all of the features of antiphospholipid syndrome. Antiphospholipid antibodies are circulating polyclonal serum immunoglobulins of IgG, IgM and IgA types. At present, assay for antiphospholipid antibodies only include testing for lupus anticoagulant and anticardiolipine antibodies. These antibodies can be found in up to 5% of healthy people and 10% of persons aged > 70 years. Phospholipids are important constituent of cardiac valve endothelium, vascular endothelium, platelet and coagulation proteins. Antiphospholipid syndrome include all or any combination of recurrent miscarriage, arterial and venous thrombosis, livedo reticularis, valve vegetations, migraine and thrombocytopenia. If a patient has typical syndrome but no antibodies then the test should be repeated after a few weeks because the titers may fall during the acute episode. Raised antibodies in a stroke patient without the antiphospholipid syndrome should probably be ignored because the antiphospholipid syndrome can not be diagnosed on the basis of a single raised titer of anticardiolipine antibody in the serum. The titer must be substantially raised on several occasions and associated not only with cerebral ischemia but also with some combination of the above features.

**Fibromuscular Dysplasia (FMD)**

FMD is an uncommon familial and segmental arteriopathy found at any age and more commonly in females. The renal arteries are most commonly involved causing hypertension. FMD is often diagnosed incidentally in angiograms performed for other purposes. It is unknown how often FMD
causes thromboembolism and whether antithrombotic drugs or angioplasty are sensible treatments. Due to low incidence of stroke and TIA in untreated or medically treated patients with FMD, a conservative approach is recommended in these patients\(^2\). Anticoagulation therapy should be avoided in patients with FMD and associated aneurysm\(^{11,12}\).

**Homocystinuria**

Homocystinuria is an autosomal recessive disease complicated by cerebral arterial and venous thrombosis and thromboembolic events in coronary and peripheral vascular territories of youngs\(^1\). The diagnosis of hyperhomocystinemia should be suspected if there is mental retardation, osteoporosis, dislocated lense, marfanoid habitus and epileptic seizures\(^1\).

**Vascular Dementia**

Vascular dementia was illustrated in the first chapter. Diagnosis of dementia is performed by neuropsychologic tests. Neuroimaging data should provide information on type, number and location of infarcts. Carotid ultrasound, TTE, 24 hours ECG monitoring, blood pressure monitoring, vasculitis screening, skin biopsy and blood homocystein are indicated in selected cases of vascular dementia\(^1\).

**Migraine Induced Stroke (MIS)**

MIS is rare and vastly over diagnosed. MIS occurs in patients with migraine with aura, during an attack of migraine with aura, with symptoms that are those of the aura with a documented infarct in the relevant area and in the absence of other causes at an extensive workup\(^8^7\). It is important to exclude other co-existing conditions before diagnosing MIS. The diagnosis of MIS should be done only in well-known migrainers who suffer a cerebral infarction during a typical attack of migraine\(^1^1\). MIS must meet the following criteria, 1- the neurologic deficit must exactly mimic the migrainous symptoms of previous attacks, 2- the stroke must occur during the course of a typical migraine attack, 3- all other causes of stroke must be excluded although stroke risk factors may be present. There are similar reports of symptomatic migraine occurring in young patients with carotid dissection and it is possible that many MIS in early series were carotid dissection\(^2\). A meta-analysis of 11 case-control studies and 3 cohort studies revealed that the relative risk of migraine with aura for ischemic stroke is 2.27\(^8^8\). A prospective cohort study of 27840 participants in the Women Health Study
determined that, compared with women lacking a migraine history, women who reported active migraine with aura had adjusted hazard ratios of 1.9 for ischemic stroke. The precise mechanism of migraine induced stroke is still a matter of speculation. However inducing cerebral microcirculatory vasoconstriction, cortical spreading depression-related oligemia, intracerebral large vessels spasm and vascular endothelium related hypercoagulability were assumed as its mechanisms. Consecutive patients with MIS admitted in Ghaem hospital, Mashhad during 2006-2009 enrolled a prospective clinical study. All of the patients suspected to MIS had brain MRI with a 0.5 Tesla generation. A complete past medical history and neurologic examination was taken in all of the suspected MIS patients by a neurologist. MIS was detected based on below criteria: 1- The present attack in a patient who has migraine with aura is typical of previous attacks. 2- either A or B is present. A: one or more aura symptoms persists for more than one week. B: one or more aura symptoms persists more than one hour and neuroimaging demonstrates infarction in relevant area. 3- Not attributed to another disorder which can be associated or confused with migraine such as arterial dissection, the antiphospholipid syndrome, CADASIL or even arteriovenous malformation. This criteria is defined based on the first classification of International Headache Society (IHS). Although diagnostic criteria of MIS based on the second edition of IHS classification necessitates that neuroimaging should demonstrate infarction in a relevant area in patients, however we had a 0.5 Tesla generation of MRI in our hospital at that period which could easily lose detection of MIS. MIS may occur in patients who have no ischemic lesion in the neuroimaging. All of the MIS patients underwent a standard battery of diagnostic investigations for detecting etiology of stroke. Disability of MIS patients was detected based on the modified Rankin scale at 90 days post stroke and compared with a similar number of age and gender matched and randomly selected ischemic stroke patients with other etiologies from our stroke registry. 32 Persian MIS patients (18 females, 14 males) with mean age 37.2±3.8 years ranged 15-58 years were evaluated. Recent oral contraceptive consumption was found in 22.2% of females with MIS. Hypodense area of infarction corresponding to clinical manifestations was detected in MRI in 32% of our MIS patients and other patients had normal brain MRI. Sixty two percent of our MIS series had anterior circulation stroke based on the neurologic examination. The mean disability score in our MIS patients and also in other ischemic stroke patients was 1.09±0.32 and 3.12±0.83 at 90 days post event respectively.
Mean disability score of our MIS series was significantly lower than other group of our stroke patients; \( z=2.55, \ p=0.007 \). The reason of better prognosis of MIS is unknown but it could be due to less pathologic damage of MIS in brain parenchyma. Recurrence of MIS has been occurred in 12.5% of our MIS series. Migraine with aura could be an isolated presenting symptom of CVT. This etiology often makes stroke in females, especially in persons who take oral contraceptive\(^1\). Although using IHS classification is a universal method in research articles, however this classification is not routinely used in clinical practice for an obvious case of migraine. The Asian Migraine Criteria (AMC) was developed and validated by the author for diagnosis of migraine with or without aura in routine clinical practice\(^93\). The AMC consists of seven items; 1- Unilateral location, 2- Throbbing quality, 3- Nausea and/or vomiting, 4-Photophobia and/or sonophobia, 5- Osmophobia, 6-Family history of migraine and 7-Aura. Presence of at least 3 items in adults and at least 2 items in children is necessary for detection of definite migraine according to the AMC\(^93\). AMC had sensitivity 99.3%, specificity 84.5%, Positive Predictive Value (PPV) 96.9%, Negative Predictive Value (NPV) 96.1% and validity of 96.8% for diagnosis of adults migraine compared to the IHS criteria as gold standard\(^93\). The AMC had sensitivity 93.5%, specificity 46.8%, PPV 69.9%, NPV 86.6% and validity of 73.4% for detection of childhood migraine against the IHS criteria as gold standard\(^93\).

**Sporadic Hemiplegic Migraine (SHM)**

SHM is defined as migraine attack associated with some degree of motor weakness during the aura phase and where no first degree relative has identical attacks. The degree of motor deficit is highly variable, ranging from mild clumsiness to total hemiplegia. The affected limbs will feel both heavy and dead during the attack. The hemiparesis is often accompanied by hemihyperesthesia. Dysarthria and dysphasia may also be seen in some SHM patients\(^91\). Attacks of hemiparesis may alternatively be right or left sided or always involve the same side. The SHM mimics TIA and ischemic stroke. Among our 200 migrainous patients, 9% had SHM. All of our SHM patients experienced some form of visual aura that occurred at some point in the course of each headache either alone or accompanied by hemiparesis\(^94\). Sensory aura as hemihypoesthesia or hemiparesthesia was present in 61% of SHM cases and dysarthria or aphasia was found in 27% of them\(^94\). The auras in our SHM spreaded with a slow march of symptoms, usually starting with visual, then sensory and finally motor and dysphasic symptoms\(^94\).
According to the relationship between hemiplegic location and headache side, the patients were divided into four groups. In the first group which was made up of 27.7% of our SHM patients, hemiplegia was contralateral to the headache side. In the second group consisting of 50% of SHM patients, hemiplegia was ipsilateral to the headache side. In the third group made up of 5.5% of our SHM cases, hemiplegia presented either contralaterally or ipsilaterally to the headache side. In the fourth group consisting of 16.6% of our SHM cases, hemiplegia was present with bilateral headache. The slow spread of the aura symptoms and their temporal succession in our SHM patients clearly indicates a phenomenon spreading continuously in the cortex. The only known phenomenon that can spread in this fashion is a cortical spreading depression which thought to underlie typical migraine aura. We often observed hemiplegia ipsilateral to the headache side. This data are in opposition to the hypothesis linking the aura to the painful phase of the migraine. Our results are congruent with the cross-over of corticospinal tracts because the headache side is not often the side of cortical dysfunction. Ipsilateral aura and headache is surprisingly common in people referred to headache clinics because they are considered to be unusual by the referring physician. Indeed, both aura and headache reflect a common pathogenic mechanism which produces each symptom on one or other side of the head. Neurologists may be confused by SHM which leads to admission of the patient misdiagnosed as TIA with unnecessary workup and management.

**Stroke in pregnancy and puerperium**

Stroke in these situations should be investigated in the same way as any other stroke. The risk of stroke recurrence in future pregnancies is unknown but presumably is fairly low unless there is a persisting underlying cause such as thrombophilia. MRI/MRA is safe during second and third trimesters of pregnancy. Catheter angiography is safe in second and third trimesters with using abdominal cover but should be cautious in the first trimester. There is curious tendency for migraine auras without headache to occur in pregnancy and these should be differentiated from TIA. There are some causes of stroke which may be particularly associated with pregnancy including; CVT most often in the puerperium, paradoxical embolism from the legs or pelvic veins, cervical arterial dissection during labor, low flow infarction complicating obstetric disasters. In a pregnant woman with hemorrhagic stroke, eclampsia, CVT, pituitary apoplexia, hemorrhagic metastasis of choriocarcinoma, AVM and rupture of aneurysm should be considered.
Oral contraception and stroke

If a woman on any type of oral contraceptives has a stroke do not jump to cause-and-effect conclusion. It is important to investigate for all potential causes of stroke in a young woman. Whether or not a cause is found, it is wise for the woman to avoid oral contraception thereafter.

Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

This is a rare hereditary disorder of small blood vessels caused by mutations of the notch 3 gene on chromosome 19. Migraine with aura develops in patients in their 20s, recurrent mainly lacunar strokes and TIAs in their 30s, progressive subcortical dementia in their 40s and the patients die in their 50s. Depressive symptoms are common in these cases. Family history of above problems without vascular risk factors in the patient guides the diagnosis. Characteristic diffuse and confluent lesions of punctiform or nodular hyposignals on T1 MRI, CT and hypersignals on T2 MRI is found in the periventricular and subcortical white matter and basal ganglia in these patients. These changes may start before the patients are symptomatic and they progress with time. Neuroimaging findings of CADASIL is similar to Binswanger disease. Ultrasound studies and echocardiography are usually normal in CADASIL. No biologic marker of mitochondrial disease have been observed in CADASIL. The changes in the vessel wall are distinctive as a deposite of granular and eosinophilic material (not amyloid) in the leptomeningeal and perforating arteries of the brain. Similar changes can be found in the small vessels of the skin and muscle.

Stroke in Young Adults

Stroke is mainly a disease of middle aged and elderly people. The frequency of stroke death in young adults is lower than in the general stroke population. Stroke is particularly dramatic in younger patients because it involves a previously healthy adult and sometimes leads to serious sequela for the rest of the patients life. The burden is extremely heavy on family and society. Stroke in young adults constitutes a challenge because of its social impact and a large variety of etiologies. The young patient with stroke tends to get more intensively investigated which is not unreasonable because the proportion with unusual and often treatable causes is higher in
Chapter V: Etiologic Work up of Ischemic …

this age group than elderly\textsuperscript{28,96}. Cardioembolism is probably the etiology that clinicians should rule out at first in a young adult with ischemic stroke. In fact, the high rate of recurrence and the possibility of avoiding this by appropriate treatment make cardioembolism the first etiology to determine. Neck arterial dissection, venous infarction due to CVT, MIS and vasculitis are more frequent causes of stroke in young adults\textsuperscript{28,96}. More information about etiology of ischemic stroke in Persian young adults were presented in embolism section at chapter II\textsuperscript{28,96}.

The case with no cause (Cryptogenic stroke)

After taking a complete history and examination and performing numerous investigations, there are still some patients (up to 40%) with no reasonable explanation for their stroke or with marginal causes, i.e. mitral valve prolaps, patent foramen ovale or oral contraceptive with no prothrombotic abnormality\textsuperscript{11}. The intensity of the search for a cause must depend on the previous level of dependency and the age of the patient. Aggressive investigations is reasonable in milder strokes because these patients have more to lose from a disabling recurrence as a consequence of missing the etiologic diagnosis\textsuperscript{3,6}. In TIA/stroke cases with no cause there is little to be done except recommending aspirin as an antithrombotic drug. Fortunately stroke with truly no cause seldom seems to recur\textsuperscript{41}. After performing etiologic investigations based on above indications, stroke etiology is defined according to the criteria of each center. Among Persian stroke patients, uncertain etiology constituted 20.4% of large artery territory and 18.2% of small artery territory infarcts\textsuperscript{40}.

Development and validation of Asian Stroke Criteria (ASC)

All studies describing classification of brain infarction in Asia were sought. The following string of keywords was entered in to MEDLINE (OVID and PUBMED) as well as Google, Proquest, Scopus, Cochrane Library and Science Direct search engines: [Asia] and [Classification] and [Stroke] and [Criteria], with the final search performed October, 1, 2009. Surprisingly, no other Asian classification was found for ischemic stroke. The Asian Stroke Criteria (ASC) has been developed as an academic tool for categorization of brain infarction in Asia. Topographic and etiologic classification of brain infarction based on the ASC is presented in Table 8\textsuperscript{97}.  


Table 8: The Asian Stroke Criteria for Classification of Brain Infarction

<table>
<thead>
<tr>
<th>Topographic Classification</th>
<th>Probable Large Vessel Territory (LVT): either A or B</th>
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<tbody>
<tr>
<td></td>
<td>A. New cortical signs (aphasia, agnosia, apraxia, sensory neglect, visual neglect, seizure, hemianopsia)</td>
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<tr>
<td></td>
<td>B. MRI/CT show a new cortical lesion compatible with stroke manifestations* and/or a new lesion ≥ 2cm* (if negative, repeated MRI/CT ≥ 48h post event is recommended)</td>
</tr>
<tr>
<td></td>
<td>Definite Large Vessel Territory (LVT): both A and B</td>
</tr>
<tr>
<td></td>
<td>Probable Small Vessel Territory (SVT): either A or B</td>
</tr>
<tr>
<td></td>
<td>A. Lacunar syndrome (pure motor hemiparesis, pure sensory stroke, mixed sensorimotor, ataxic hemiparesis, dysarthria clumsy hand) with out new cortical signs</td>
</tr>
<tr>
<td></td>
<td>B. MRI/CT performed ≥ 48h post event show new subcortical lesion &lt;2cm*, no new cortical lesion* and no new lesion ≥2cm*</td>
</tr>
<tr>
<td></td>
<td>Definite Small Vessel Territory (SVT): both A and B</td>
</tr>
<tr>
<td>Note:</td>
<td>If there is new clinical or imaging evidence* of LVT, patient should be classified as LVT regardless new evidence of SVT</td>
</tr>
<tr>
<td>Note:</td>
<td>In brain stem imaging, new lesion* &lt;1.5cm is considered SVT</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Etiologic Classification</th>
<th>Atherosclerosis Grade 1: A and/or B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A: at least two of the following risk factors</td>
</tr>
<tr>
<td></td>
<td>aged ≥ 60 years, hypertension, diabetes mellitus, smoking, hyperlipidemia</td>
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<tr>
<td></td>
<td>B: &lt; 50 % stenosis of the corresponding large intracranial artery, &lt; 70 % stenosis of the corresponding extracranial artery, aortic arch atheroma ≥4 mm without mobile component</td>
</tr>
<tr>
<td></td>
<td>Definite Atherosclerosis Grade 2:</td>
</tr>
<tr>
<td></td>
<td>≥ 50 % stenosis of the corresponding large intracranial artery, ≥ 70 % stenosis of the corresponding extracranial artery, aortic arch atheroma with mobile component</td>
</tr>
<tr>
<td>Cardioembolism Grade 1:</td>
<td>right to left heart shunt with DVT or right heart thrombus, bioprosthetic mitral or aortic valve, mitral valve prolapsed with mitral regurgitation, severe mitral regurgitation, left ventricular aneurysm after acute MI, left ventricular akinetic segment after acute MI</td>
</tr>
<tr>
<td>Cardioembolism Grade 2:</td>
<td>Atrial fibrillation (AF), mechanical mitral or aortic valve, acute MI &lt; 4 weeks, left heart thrombus, bacterial and nonbacterial endocarditis, congestive heart failure, dilative cardiomyopathy, rheumatic mitral stenosis, atrial myxoma</td>
</tr>
<tr>
<td>Miscellaneous Grade 1:</td>
<td>hypercoagulability, migraine induced stroke, fibromuscular dysplasia <em>, aneurysmal sac</em></td>
</tr>
<tr>
<td>Miscellaneous Grade 2:</td>
<td>Arterial dissection*, moyamoya syndrome*, AVM*, vasculitis*, cerebral venous thrombosis*</td>
</tr>
<tr>
<td>Mixed:</td>
<td>any combination of above etiologies</td>
</tr>
<tr>
<td>Undetermined:</td>
<td>none of the above causes could be determined by complete diagnostic investigation</td>
</tr>
<tr>
<td>Incomplete diagnostic investigation:</td>
<td>compatible with stroke manifestations</td>
</tr>
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</table>

The ASC is provided for clinical practice in tertiary care hospitals with and without stroke neurologist and MRI facilities. The ASC was designed by Asian stroke neurologists (K-Gh and M-M) and approved by the University of Alberta, Canada in 2003. Validation of ASC included two steps. In the first validation step, inter-rater reliability of ASC was evaluated. 

* compatible with stroke manifestations
Among 302 stroke patients, 20 patients (11 female, 9 male) were randomly selected. All of the patients underwent a standard battery of diagnostic investigation for stroke etiology and topography. Two stroke neurologists and a general practitioner independently reviewed the data of each randomly selected patient and the patients were classified according to the ASC of stroke topography and etiology. Degrees of inter-rater reliability were measured using simple percentage of agreement and un-weighted k statistics. The three inter-rater agreement for topographic subtyping of the patients was 0.95%, k=0.915(0.662-1), p<0.0001 and for etiology diagnosis was 0.90 %; k=0.9022(0.753-1), p<0.0001. Stroke neurologists were in agreement in topographic diagnosis for all 20 cases (100%; k=1; 95% CI, 1.0 to 1.0; p<0.0001). The general practitioner arrived at the same topographic diagnosis for 19 of the 20 cases (0.95%; k=0.875; 95% CI, 0.638 to 1.0; p<0.0001). Stroke neurologists were in agreement in etiologic diagnosis in 18 of the 20 cases (0.90%; k= 0.855; 95% CI, 0.66 to 1.0; p<0.0001). The general practitioner arrived at the same etiology diagnosis in 18 of the 18 cases that two stroke neurologists agreed (100%; k=0.875; 95% CI, 1.0 to 1.0; p<0.0001). The inter-rater agreement according to the ASC system is much higher than other classifications that have moderate inter-observer reliability. In a retrospective reliability study of 14 randomly selected patients, two neurologists and two internists agreed with subtype diagnosis of only 14% according to Trial ORG 10172 in Acute Stroke Treatment (TOAST) classification. Development of a computerized diagnostic algorithm could increase the inter-rater agreement up to 56%. In the second validation step; the ASC was successfully used for the data bank of multiple stroke registries. The Khorasan Stroke Registry (KSR), Khorasan Posterior Circulation Stroke Registry (KPCSR) and Khorasan Pediatric Stroke Registry (KPSR) are some Asian stroke registries using ASC and illustrated previously. The ASC was also used for etiologic evaluation of patients with TIA.

**Challenging comparison of stroke subtypes classifications**

Various stroke subtype classifications have been used in research and clinical practice. The newest criteria of stroke is phenotypic A-S-C-O classification. The main application of A-S-C-O classification is design and review of case reports, clinical trials and meta-analysis studies by researchers and peer-reviewers of journals respectively. This new classification system recognizes that many patients belong to several categories; some categories may be causally related to the index stroke, whereas others are
simply concurrent\textsuperscript{101}. By introducing the ‘level of diagnostic evidence’, this classification recognizes the completeness and quality of the diagnostic investigations to grade the underlying diseases\textsuperscript{101} and it could be very useful in daily clinical practice. Because it is not possible to be always absolutely sure of a single true mechanism, the clinician must keep in mind that multiple mechanisms might be simultaneously involved. Patients may have two or more competing causes of cerebral ischemia. Despite efforts to arrive an etiologic diagnosis, the cause of infarction may remain undetermined possibly due to inappropriate work up or unwillingness of patient or physician to perform a complete workup. The limitation of Stroke Data Bank criteria is most prominent in patients with multiple coexisting potential causes of ischemic stroke\textsuperscript{102,103}. The TOAST\textsuperscript{99,104} and Lausanne Stroke Registry\textsuperscript{105} defined a mixed etiologic category, however etiologic grading of the A-S-C-O classification\textsuperscript{101} and Asian Stroke Criteria (ASC)\textsuperscript{97} is able to guide physicians in management policy\textsuperscript{106}. This grading of each etiologic subtype for atherosclerosis, cardioembolism and unusual causes in A-S-C-O classification\textsuperscript{101} and ASC\textsuperscript{97} is developed for therapeutic decision-making purpose\textsuperscript{106}. The very restrictive definition for atherothrombotic stroke in the Stroke Data Bank classification\textsuperscript{102,103}, resulting underestimation of the overall burden of atherosclerotic disease and some of patients with atherothrombotic etiology are classified as cryptogenic stroke based on this criterion\textsuperscript{106}. The same limitation is present in TOAST classification\textsuperscript{99,104} in which patients with documented atherosclerotic disease who did not reach the 50\% stenosis limit are not categorized as atherothrombotic stroke\textsuperscript{106}. This limitation is not present in Lausanne stroke registry criteria\textsuperscript{105}, A-S-C-O classification\textsuperscript{101} and ASC\textsuperscript{97} by widening the atherothrombotic group\textsuperscript{106}. Despite TOAST\textsuperscript{99,104} and Lausanne Stroke Registry\textsuperscript{105} classifications of stroke subtyping, the A-S-C-O classification\textsuperscript{101} and ASC\textsuperscript{97} rely on ≥ 70\% stenosis of the corresponding extracranial artery\textsuperscript{106}. Because endarterectomy is usually indicated in symptomatic ≥70\% carotid stenosis and we need a therapeutic classification\textsuperscript{106}. This therapeutic strategy of the A-S-C-O classification\textsuperscript{101} and ASC\textsuperscript{97} is also accepted in Stroke Data Bank classification\textsuperscript{102,103}, however the later did not solve problem of restrictive definition of atherosclerosis and overestimation of cryptogenic stroke\textsuperscript{100,106}. At the other side, categorization of atherosclerotic etiology in the later as atherothrombosis and tandem arterial pathology is a pathophysiologic concept which has no therapeutic usefullness\textsuperscript{100,102,103,106}. Although TOAST classification\textsuperscript{99,104} tried to help therapeutic decision-making process by consideration of high and medium risk cardioembolic causes of stroke.
However there is some limitations in this system, e.g. mitral valve prolapse without mitral regurgitation and patent foramen ovale without deep venous thrombosis or right heart thrombus are accepted as medium cardioembolic mechanisms in TOAST and Stroke Data Bank classifications, while they have a doubtful role in etiology of stroke and are not considered in Lausanne stroke registry and ASC. The main disadvantage of stroke classification systems is necessity of complete diagnostic investigations for detection of stroke etiology. Incomplete etiologic investigation of brain infarction is very common in routine clinical practice. The A-S-C-O classification tried to solve this problem by grading of the diagnostic work up. Mixed etiologies, negative evaluation and incomplete evaluation are all categorized as stroke of undetermined cause in TOAST system while these subtypes are precisely defined in A-S-C-O classification and ASC. Despite A-S-C-O classification and ASC, mixed etiologies and incomplete evaluation are not considered in Stroke Data Bank classification and Lausanne stroke registry did not include incomplete evaluation. Left atrial turbulence (smoke) and mitral annulus calcification are considered as cardiac source of embolism in the TOAST and A-S-C-O classifications and were ignored in Lausanne Stroke Registry and ASC due to their very low emboligenic risk. It is clear that brain infarcts of all sizes and locations can be caused by atheroembolism and cardioembolism. There are clear examples of thrombotic or embolic small deep infarcts presenting as lacunar syndrome, because small emboli can occlude single perforating arteries to cause lacunar infarcts. Evidently, there is no longer a specific vascular occlusive pathology of lacunar stroke and there are no specific clinical risk factors for small artery occlusion. Because various etiologies could lead to brain infarct in small vessel as well as large vessel territories, etiologic classification of the ASC includes all vascular territories. Based on these impressions, we could refuse to define small artery disease as the only subtype of ischemic stroke that characterizes lacunar infarcts. However lacune was assumed as equivalent of small vessel disease in the other stroke classifications. The Stroke Data Bank, TOAST and Lausanne stroke registry assumed small vessel disease as equivalent of lacune. Occasionally stroke patients who present with a cortical stroke syndrome have a recent lacunar infarct corresponding with the manifestations, without any evidence of the expected cortical infarct, on neuroimaging. Equally the patient with a lacunar syndrome may have a recent cortical infarction with no subcortical
lesions in neuroimaging. These discrepancies are considered in the ASC\textsuperscript{97,98}.

Based on the ASC, diagnosis of large or small vessel territory infarct is according to either clinical or imaging results. Any imaging clue of large vessel territory infarction rules out clinical evidence of small vessel territory stroke\textsuperscript{97,98}. This is not a disadvantage of ASC, because diagnostic accuracy of clinical signs of large or small vessel territory strokes is not very high\textsuperscript{13}. However ASC enables clinician for probable clinical differentiation of large or small vessel territory infarction\textsuperscript{97}. New symptoms suggesting cortical involvement are important criteria for definite cardioembolic stroke in SPAF I-III trials\textsuperscript{110}. The ASC includes cortical infarcts that are clinically diagnosed but not detected by CT scan at the acute stage\textsuperscript{97,98}. By using cortical signs or lacunar stroke syndrome concepts the ASC enables the clinician to classify stroke topography even in the absence of imaging studies by a high level of confidence\textsuperscript{97,98}. MRI is unavailable in many tertiary care centers especially in developing countries. The ASC imaging criteria relies on brain CT scan \(\geq 48\) hours of stroke onset\textsuperscript{97,98}. However imaging studies in particular MRI offer further evidence for stroke localization. Because rheumatic valvular disease is still a frequent problem in developing countries\textsuperscript{28,96}, severe mitral regurgitation is considered to be a cardiac source of embolus in the ASC\textsuperscript{97,98}.

**Spinal cord infarction**

Compared with incidence of brain infarcts, spinal ischemic stroke remains rare and their prevalence is not precisely known\textsuperscript{12}. Obviously a major cause of this difference is that the spinal cord is substantially smaller than the brain\textsuperscript{12}. Another reason of rarity of Spinal Cord Infarction (SCI) may be found in the spinal arteries which are rarely affected by atherosclerosis. Besides this, the spinal cord has a rich anastomotic network of arteries\textsuperscript{12}. The various clinical syndromes related to spinal infarcts depend on what part of the vascular system is affected and on whether the pathologic process is acute or progressive in nature. SCI is a diagnostic puzzle with a dismal prognosis. An upsurge of interest to SCI has been replaced the neglect of former years. This has been due in part to the increased accidental production of SCI by cardiovascular surgery and to the advances in MRI which has allowed better visualization of the spinal cord\textsuperscript{11}. SCI in territory of anterior spinal artery appears with abrupt neck or back pain following with a sever flaccid paraplegia or tetraplegia and early sphincter disturbances\textsuperscript{11,12}. Because of spinal shock, the paraplegia may remain flaccid for several days to weeks. The upper limbs may develop
motor neuron signs and spasticity of legs may occur with hyperreflexia and extensor plantar responses. Anesthesia to pain and temperature below the level of infarct without involvement of proprioceptive and vibration sensation is present\textsuperscript{11,12}. SCI in territory of posterior spinal artery is very rare and involves posterior columns of the spinal cord. It presents with paresthesias and abolition of deep sensation below the level of the infarct\textsuperscript{11,12}. Posterior spinal artery syndrome is defined as\textsuperscript{11}: 1- sensory loss for proprioception, vibration and light touch sensation with sensory level. 2- preserved pain and temperature sensation, except at the level of the affected cord segment, where there is global anesthesia. 3-motor function preserved. 4- loss of deep tendon reflexes at the level of affected cord segment. Occlusion of a central sulcal artery rarely produces small lesions in half of the spinal cord. This can present as an incomplete Brown-Sequard syndrome\textsuperscript{11}. Total transverse SCI involves both anterior and posterior spinal artery territories and may be misdiagnosed as transverse myelitis\textsuperscript{11}. In older patients, the sudden onset of neurologic symptoms and signs related to the spinal cord strongly suggests vascular disease. If the neurologic manifestations are attributable to a specific spinal arterial territory, the diagnosis is almost certain\textsuperscript{11}. Vascular event in the spinal cord can be less abrupt in onset, depending mainly on the underlying mechanism and on the presence of collateral circulation\textsuperscript{11,12}. All of the consecutive patients with SCI admitted in Ghaem hospital, Mashhad during 2006-2010 enrolled a prospective clinical study\textsuperscript{111}. We excluded patients whose myelopathies were directly due to spinal cord trauma, tumor, abscess, syringomyelia or in whom there was a history of multiple sclerosis\textsuperscript{1}. Patients with a gradual onset (longer than 24 hours) of transverse myelopathy were also excluded. All of the patients suspected to SCI had MRI of spinal cord at the symptomatic level of cord with a 0.5 Tesla generation. MRI has become the method of choice for diagnosis of SCI, because it reliably excludes compressive lesions, intramedullary neoplasms and cavitations\textsuperscript{11,12}. The infarcted cord can have an increased diameter on MRI. Infarcts can first be seen on T\textsubscript{2} weighted images as high signal lesions during the acute phase\textsuperscript{11,12}. However during the first hours or days after the damage, even T\textsubscript{2} image scan may remain normal\textsuperscript{12}. All of the spinal cord MRI were performed within 24 hours post event. An equal number of patients with brain infarction were randomly selected from our prospective stroke data bank registry. All of the SCI patients and randomly selected group of patients with brain infarction underwent a standard battery of diagnostic investigations for detecting etiology of stroke\textsuperscript{1}. Etiology of SCI and brain infarction was determined
based on the Asian Stroke Criteria. Disability of SCI and brain infarction patients was detected based on the Modified Rankin Scale (MRS) at 2 days post event and at 90 days later. Fourteen Persian patients (9 females, 5 males) with SCI were admitted in Ghaem hospital during 2006-2010. The hospital-based frequency of SCI in our Persian ischemic stroke patients is 0.2%. Female gender was significantly more preponderant to SCI than brain infarction, df=1, p=0.034. Mean age of Persian patients with brain infarction and SCI was 64.36 ±SD: 7.53 and 38.86±SD: 19.95 years respectively which is significantly different, t=4.475, df=26, p<0.001. Miscellaneous causes consisted 50% of etiologies in Persian patients with SCI and 21.4% of SCI patients had iatrogenic causes. These iatrogenic causes were also included within miscellaneous etiologies. Uncertain etiologies, atherosclerosis and cardioembolisms consisted 35.7%, 7.1% and 7.1% of SCI causes respectively. None of our SCI or brain infarction groups of patients had mixed or multiple causes of stroke. Atherosclerosis, cardioembolism, uncertain and miscellaneous etiologies constituted 57.1%, 21.4%, 14.3% and 0% of causes in 14 randomly selected patients with brain infarction. Distribution of etiologies was significantly different between SCI and brain infarction patients, X²=12.94, df=3, p=0.003. The mean disability score of SCI and randomly selected patients with brain infarction based on the MRS is 4.36±SD: 0.1 and 3±SD: 0.6 respectively in acute phase of stroke. Difference in mean disability score at acute phase of stroke was not significant between two studied groups, z=1.54, p=0.057. The mean changes of MRS for SCI and brain infarction group at 90 days later is 0.57±SD: 0.1 and 1.28±SD: 0.3 respectively. Difference in mean changes of disability was significant in two groups of patients, z=2.65, p=0.019. Table 9 demonstrates clinical characteristics of our SCI patients.

Mean age of Persian patients with SCI is significantly lower than patients with brain infarction. The main reason of this age difference could be distribution of etiologies in patients with SCI. Miscellaneous causes constituted half of SCI etiologies in our SCI patients. It is well known that Persian stroke patients with miscellaneous etiologies have lower mean age than other stroke cases. Due to the increased frequency of cardiovascular surgery and invasive interventional procedures, iatrogenic SCI is encountered more than it used to be. Spinal cord perfusion may be compromised by the aortic cross-clamping syndrome. Aortic surgery was the etiology of SCI in 7% of our cases (number 3 in table 9). A profound fall in perfusion pressure may lead to an ischemic myelopathy involving primarily the watershed area of midthoracic cord. Hypoperfusion was the
mechanism of SCI in one of our cases (number 8 in the table 9) who underwent cardiac surgery\textsuperscript{111}. SCI is a well known complication of epidural anesthesia in other case reports\textsuperscript{112} and we had one patient (number 1 in table 9) with this complication. SCI was observed in MRI of 48% of our SCI patients. The main reason of low rate of visible SCI in MRI of our cases is using lower generation 0.5 Tesla MRI equipment. However 1.5 Tesla or higher generation MRI technologies also may not show SCI especially in the a few hours post event\textsuperscript{113}. Anterior spinal artery syndrome constituted 85\% of SCI presentations in our study group, which may be due to large territory of anterior spinal artery in the cord\textsuperscript{11,12}. SCI patients had more disability and less improvement at 90 days comparing to our brain infarction patients. Similar results has been reported elsewhere\textsuperscript{11,12}. The spectrum of etiologies for SCI is diverse and includes its own set of susceptibilities according to the anatomic relationship of spinal cord vascularity to the spine and the aorta. The degree of recovery is generally poor in comparison with cerebral stroke where there is more likely to be adjacent neural tissue capable of assuming some of the lost function.

Table 9: Clinical characteristics of our 14 SCI patients

<table>
<thead>
<tr>
<th>Patient number</th>
<th>Age</th>
<th>Gender</th>
<th>Spinal cord syndrome</th>
<th>MRI†</th>
<th>Etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>68</td>
<td>F</td>
<td>ASAS</td>
<td>-</td>
<td>Epidural anesthesia*(^\wedge)</td>
</tr>
<tr>
<td>2</td>
<td>26</td>
<td>F</td>
<td>ASAS</td>
<td>+</td>
<td>Uncertain</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>M</td>
<td>ASAS</td>
<td>-</td>
<td>Aortic Surgery*(^\wedge)</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>F</td>
<td>ASAS</td>
<td>-</td>
<td>Cardiogenesis</td>
</tr>
<tr>
<td>5</td>
<td>60</td>
<td>F</td>
<td>ASAS</td>
<td>-</td>
<td>Uncertain</td>
</tr>
<tr>
<td>6</td>
<td>35</td>
<td>M</td>
<td>ASAS</td>
<td>-</td>
<td>IV drug abuser*</td>
</tr>
<tr>
<td>7</td>
<td>56</td>
<td>M</td>
<td>ASAS</td>
<td>-</td>
<td>Cardiac surgery*(^\wedge)</td>
</tr>
<tr>
<td>8</td>
<td>55</td>
<td>F</td>
<td>ASAS</td>
<td>-</td>
<td>Aortic dissection*</td>
</tr>
<tr>
<td>9</td>
<td>18</td>
<td>M</td>
<td>TSCS</td>
<td>+</td>
<td>Arteriovenous Malformation*</td>
</tr>
<tr>
<td>10</td>
<td>30</td>
<td>F</td>
<td>ASAS</td>
<td>+</td>
<td>Uncertain</td>
</tr>
<tr>
<td>11</td>
<td>28</td>
<td>F</td>
<td>ASAS</td>
<td>+</td>
<td>Uncertain</td>
</tr>
<tr>
<td>12</td>
<td>20</td>
<td>F</td>
<td>ASAS</td>
<td>-</td>
<td>Systemic Lupus*</td>
</tr>
<tr>
<td>13</td>
<td>22</td>
<td>F</td>
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<tr>
<td>14</td>
<td>58</td>
<td>M</td>
<td>Brown-Sequard</td>
<td>+</td>
<td>Atherosclerosis</td>
</tr>
</tbody>
</table>

ASAS: Anterior Spinal Artery Syndrome
TSCS: Transverse Spinal Cord Syndrome
* : Miscellaneous etiologies
\(^\wedge\) : Iatrogenic causes
†: + and – means presence or absence of spinal cord infarction visible in MRI
Chapter VI

Prevention of Ischemic Cerebrovascular Events

Control of Risk Factors

In order to decrease stroke incidence and mortality, promotion of correct life styles at the whole population are recommended. Cessation of cigarette smoking is recommended for all smokers independent of age and amount of smoking. Moderate physical activity, i.e. 45 minutes walking per day is recommended because it is associated with 45% reduction of stroke incidence, especially in men. The reduction of dietary salt especially in hypertensive elderly people is necessary because it can reduce hypertension. The treatment of hypertension either systolic or diastolic is recommended independent of age and severity of hypertension. According to WHO guidelines the optimal systolic and diastolic arterial pressures, for young adults and for diabetics of any age, are <130 mmHg and <85 mmHg and for elderly people are <140 mmHg and <90 mmHg respectively. Individuals with recent ischemic events have a much higher risk of stroke than general population. Because of this, TIA or stroke patients with relatively normal blood pressure may benefit substantially from blood pressure reduction after stroke. Angiotensin Converting Enzyme Inhibitors reduce the rate of recurrent stroke, MI and vascular death by one-quarter, even in normotensive patients. The reduction in vascular events is larger than might be expected from just lowering the blood pressure. Statins are used for patients with TIA and stroke with hypercholesterolemia if diet correction is not effective in reducing blood cholesterol. Statins not only reduce cholesterol levels but also are effective in reducing coronary artery events and ischemic stroke even in patients with normal levels of cholesterol. Using statins slows progression of carotid artery atherosclerotic plaques. The beneficial effects
of statins on nearly all aspects of atherosclerotic disease are not entirely explained by reduction in serum lipid levels. Basic researches indicates some other important salutary effects of statins including; normalization of the vascular endothelium, improvement of endothelial cell function, anti-inflammatory effects, depletion and stabilization of the lipid core content of the plaques, strengthening fibrous cap of plaque, decrease in formation of platelet-fibrin thrombi, decreased deposition of white clot on endothelial surfaces and reduction in the thrombogenicity of plaque elements\textsuperscript{11,12}. Statins have antiplatelet and antioxidant effect. Daily statin intake appears to be associated with a better functional outcome following an acute stroke\textsuperscript{62}. The use of statins significantly reduces stroke risk in patients with ischemic heart disease or hypertension or diabetes\textsuperscript{62}. Some studies have demonstrated that low cholesterol is a risk factor for ICH\textsuperscript{22}. Diagnosis and management of diabetes mellitus is recommended for its contribution in reducing stroke risk. Young women who have an ischemic stroke when taking oral contraceptives should stop it and use an alternative form of contraception\textsuperscript{1}.

\textbf{Antiplatelet drugs}

In patients with TIAs and non-cardioembolic brain infarctions antiplatelet therapy with aspirin (80-500mg/day) and control of risk factors is indicated. Aspirin therapy reduces risk of further TIA or stroke about 20%. There is no significant difference between aspirin doses of 80 mg/day and 1000 mg/day in secondary prevention of cerebral ischemic events. The gastrointestinal and hemorrhagic side effects of ultralow doses (<100 mg/day) is much lower than regular doses. Aspirin can be given in ultralow doses as infrequently as every other day. If aspirin is not tolerated or patient is allergic to it (in 5% of cases), clopidogrel one 75 mg tablet/day is recommended. Clopidogrel is slightly more effective than aspirin in preventing vascular events\textsuperscript{114}. Despite higher cost of clopidogrel, it is recommended in high-risk stroke patient; i.e. those with previous stroke on another arterial territory, peripheral artery disease, symptomatic coronary disease, or diabetes\textsuperscript{83}. Clopidogrel has less gastrointestinal and hemorrhagic side effects than aspirin and in patients with peptic ulcer is the antiplatelet drug of choice. The frequency of neutropenia and thrombocytopenia in patients using clopidogrel is rare and not higher than aspirin\textsuperscript{11}. In fibrillating patients with contraindication to aspirin and warfarin clopidogrel is prescribed. Compared with clopidogrel alone, the combination of aspirin and clopidogrel did not
reduce the risk of ischemic stroke, myocardial infarction, vascular death, or re-hospitalization. While, life-threatening or major bleeding were increased with the combination. However, in patients who have had an acute coronary event within 12 months, unstable angina, non-Q wave MI, carotid or coronary stenting, the combination of clopidogrel and aspirin is recommended for upto 9 months. Clopidogrel is an expensive drug. If the low or regular doses of aspirin is not able to prevent further ischemic events and the cause still thought to be atherothromboembolism, you could try either clopidogrel 75 mg/day or aspirin 80-100 mg/day plus dipyridamole 400 mg/day. Each capsule of aggrenox contains 25 mg aspirin plus 200 mg slow release dipyridamole. Aggrenox is prescribed twice per day. Dipyridamole in mono or polytherapy has vasodilatory effect and should be used with caution in patients with unstable angina or recent MI. Headache and gastrointestinal side effects, i.e. nausea and diarrhea are main reasons that patients receiving dipyridamole and aggrenox discontinue treatment prematurely. Addition of dipyridamole to aspirin does not appear to exaggerate the excess risk of hemorrhage associated with aspirin. Dipyrdamole alone is not an effective antiplatelet therapy. Conventional dipyridamole is as effective as extended release dipyridamole but conventional dipyridamole is less tolerated in higher doses. Conventional dipyridamole with dose of 225 miligram per day appears arbitrary and will decrease discontinuation due to headache in Persian stroke patients. Aspirin failure is detected in 10% of stroke patients. The preventive effect of 400 mg slow release dipyridamole per day is less than 50 mg aspirin per day, however the combined formula have a synergistic effect due to different mechanisms of action. Currently, aggrenox is the most powerful antiplatelet drug in the market. Aggrenox reduces stroke risk 17% more than aspirin and the two drugs in aggrenox are more effective than either alone. If the patient is considered to be at high risk of another stroke and likely to benefit from another 10% relative risk reduction that more costly treatments such as clopidogrel and aggrenox can offer, then these should be considered before trying aspirin initially. Ticlopidine (Ticlid) is another antiplatelet drug prescribed in 250 mg tablets twice per day. Antiplatelet effects of ticlopidine is higher than aspirin and similar to clopidogrel. Ticlopidine has been rarely used in stroke clinics due to higher rate of skin rash, diarrhea and most importantly neutropenia in recent decade. Ticlopidine had been a substitute or an addition for aspirin, however it is
expensive and agranulocytosis is a complication in 2% of the persons. Blood counts must be performed every two weeks for 4-6 months and medication stopped if leukopenia develops. Warfarin is used in recurrent ischemic events uncontrolled with above antiplatelet regimens. Comparison of warfarin therapy (target INR range 2-3) versus aspirin (30-325 mg) alone or aspirin plus dipyridamole 400 mg daily has shown that warfarin is not more effective than other methods in secondary prevention of ischemic cerebrovascular events with arterial origin. It is recommended that stroke patients not requiring anticoagulation should receive antiplatelet therapy. Combined aspirin and dipyridamole, or clopidogrel alone should be given. Alternatively, aspirin alone may be used. It is recommended that anticoagulation should not be used after non-cardioembolic stroke except in some specific situations; e.g., dolichoectasia of the basilar artery, cervical artery dissection, or patent foramen ovale in the presence of proven deep vein thrombosis. Oral anticoagulation after non-cardioembolic stroke is not superior to aspirin and causes more bleeding. The treatment of patients who have a recurrent vascular event on antiplatelet therapy remains unclear. Alternative causes of stroke should be sought and consistent risk-factor management is mandatory especially in these patients. Alternative treatment strategies may be considered in this situation including; leave unchanged, change to another antiplatelet agent, add another antiplatelet agent, or use oral anticoagulation. Recurrence of repeated TIs and ischemic strokes despite control of vascular risk factors and optimal antiplatelet drug therapy is infrequent. The first step is to verify again that the attacks are truly ischemic in nature and do not represent focal epileptic seizures, migraine or psychogenic disorders. Three months of warfarin therapy (INR 2-3) may reduce the ischemic events. Thereafter, it is often possible to withdraw warfarin gradually and replace it with aspirin. In such cases, the unstable atheromatous plaque that was causing the frequent attacks has perhaps healed and become covered with endothelium. It is recommended that low-dose aspirin may be considered in men for the primary prevention of myocardial infarction. However, it does not reduce the risk of ischemic stroke. Antiplatelet agents other than aspirin also are not recommended for primary stroke prevention. Cilostazol, an antiplatelet drug prescribed 100 mg twice daily showed a 42.3% relative risk reduction of recurrent brain infarction without clinically significant adverse drug reactions. In the Cilostazol Stroke Prevention Study (CSPS) in Japan, 1034 patients with ischemic stroke
were randomly assigned to either cilostazol 100 mg twice daily or placebo. The annual incidence of recurrent stroke was 3.4% in the cilostazol group compared to 5.8% in the placebo group, p=0.02. In the second CSPS, 2700 ischemic stroke patients were randomly assigned to receive either 100 mg of cilostazol twice daily or 81 mg aspirin one daily. The annual incidence of ischemic and hemorrhagic stroke was 2.76% in the cilostazol group compared with 3.71% in the aspirin group, p=0.04\textsuperscript{117}.

**Prevention of cardioembolic strokes in developed countries**

In patients with embolic cardiopathies, valvulopathies, non-valvular atrial fibrillation and cerebral embolism, long term warfarin therapy is recommended, maintaining the INR between 2-3\textsuperscript{111}. The INR should be maintained between 3-4 in patients with mechanical heart valves. Oral anticoagulation (INR 2–3) is recommended after ischemic stroke associated with AF. Oral anticoagulation is not recommended in patients with co-morbid conditions such as falls, poor compliance, uncontrolled epilepsy, or gastrointestinal bleeding\textsuperscript{83}. Increasing age alone is not a contraindication to oral anticoagulation. In case of stroke recurrence in patients with mechanical heart valve who are on proper warfain therapy, addition of aspirin 80-100 mg/day is recommended\textsuperscript{83}. Less frequently dipyridamole 400 mg/day or clopidogrel 75 mg/day may be added to warfarin in above circumstances\textsuperscript{114,115}. Although adding antiplatelet drugs to warfarin could further reduce the risk of embolic events but this is often offset by an increased risk of hemorrhagic complications. There are three types of fibrillating patients. High risk fibrillating patients with 6-12% per year risk of stroke, has one of these risk factors\textsuperscript{83,115}; 1- age >75 years and hypertension or diabetes, 2- previous TIA or stroke, 3- valvular heart disease, 4- clinical heart failure or impaired left ventricular function on TTE, 5- recent myocardial infarction, and 6- left atrial thrombus. Warfarin (target INR 2-3) should be given for high risk group unless a contraindication exists\textsuperscript{115}. Moderate risk group of fibrillating patients (3-5% per year risk of stroke) includes; 1- aged <75 years with hypertension or diabetes, 2- aged >75 years and not in high risk group. Preventive management of this group is warfarin (target INR 2-3) or aspirin 325 mg/day\textsuperscript{83,115}. Low risk group of fibrillating patients (<1% per year risk of stroke) includes; aged <65 years without hypertension, diabetes, TIA, stroke or other clinical risk factor\textsuperscript{83,115}. Preventive management of low risk fibrillating patients is aspirin 325 mg/day\textsuperscript{115}. The risk of hemorrhagic complications in fibrillating patients receiving standard warfarin therapy is
4% per year and if receiving aspirin 100 mg/day plus standard warfarin therapy, the risk raises up to 15% per year. In patients with non-valvular atrial fibrillation and cerebral ischemic events who have a contraindication for warfarin therapy, aspirin with regular dose of 325 mg/day is recommended\textsuperscript{83}. Aspirin reduces the risk of stroke by about 20-25% in these fibrillating patients (aspirin prevents about 20-25 strokes per 1000 patients per year of treatment) with no significant excess risk of bleeding\textsuperscript{12}. The management strategies in patients with paroxysmal atrial fibrillation is similar to chronic atrial fibrillation. In outpatients, warfarin with a starting dose of 5 mg per day will achieve an INR of 2 in 4-5 days\textsuperscript{12}. The INR is measured daily during the first week of treatment with the dose of warfarin taken in the evening titrated against the mornings INR\textsuperscript{1}. It is then measured at increasing intervals depending on the response. Many patients, once the dose is stable, can be well controlled with 4 weekly testing and dose adjustment but others need more frequent assessment\textsuperscript{12}. In patients with mechanical heart valves, warfarin therapy is recommended keeping INR 2.5-3.5. Oral anticoagulation is more effective in patients with AF who have one or more risk factors, such as previous systemic embolism, age over 75 years, high blood pressure or poor left ventricular function\textsuperscript{83}. Aspirin 325 mg/day is recommended for patients with non-valvular AF who are younger than 65 years and free of vascular risk factors. Unless contraindicated, either aspirin or an oral anticoagulant (INR 2.0-3.0) is recommended for patients with non-valvular AF who are aged 65-75 years and free of vascular risk factors\textsuperscript{83}. Unless contraindicated, an oral anticoagulant (INR 2.0–3.0) is recommended for patients with non-valvular AF who are aged >75, or who are younger but have risk factors such as high blood pressure, left ventricular dysfunction, or diabetes mellitus. It is recommended that patients with AF who are unable to receive oral anticoagulants should be offered aspirin\textsuperscript{115}. It is recommended that patients with AF who have mechanical prosthetic heart valves should receive long-term anticoagulation with a target INR based on the prosthesis type, but not less than INR 2–3 (bioprosthetic valve)\textsuperscript{83}. CHA\textsubscript{2}DS\textsubscript{2}-VASc risk scoring system for atrial fibrillation was designed for assessing the risk of thromboembolism in non-valvular atrial fibrillation\textsuperscript{118}. Major risk factors (previous stroke, TIA or systemic embolism and age 75 years or more) are given a score of two points while other clinically relevant non-major risk factors (congestive heart failure or moderate to severe left ventricular systolic dysfunction, left ventricular ejection fraction of 40% or less, hypertension, diabetes mellitus, age between 65-74 years, female sex and vascular disease are given one point each\textsuperscript{118}. Table 10 explains the CHA\textsubscript{2}DS\textsubscript{2}-VASc risk scoring system for patients with atrial fibrillation.
Table 10: The atrial fibrillation CHA2DS2-VASc risk scoring system

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Congestive heart failure/LV dysfunction</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1</td>
</tr>
<tr>
<td>Age &gt;75</td>
<td>2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>1</td>
</tr>
<tr>
<td>Stroke/TIA/thromboembolism</td>
<td>2</td>
</tr>
<tr>
<td>Vascular disease*</td>
<td>1</td>
</tr>
<tr>
<td>Age 65-74</td>
<td>1</td>
</tr>
<tr>
<td>Sex category (female)</td>
<td>1</td>
</tr>
<tr>
<td>Maximum score</td>
<td>9</td>
</tr>
</tbody>
</table>

*prior myocardial infarction, peripheral artery disease or aortic plaque

The CHA2DS2-VASc score is a predictive risk assessment scoring system. The risk increases as the score increases from 0 to 9. In a study involving over 7300 patients stroke rate was 0 when the score was 0, though there was only one patient in that category. There were fourteen patients with a score of nine and they had stroke rate of 15.2%. Maximum number of patients scored 3 and 4 with 1730 and 1718 patients in these categories respectively. Score 3 had a stroke rate of 3.2% and score 4 had a stroke rate of 4%. In fibrillating patients with one major risk factor or 2 or more clinically relevant non-major risk factors (CHA2DS2-VASc risk score 2 or more), oral anticoagulation therapy (INR2-3) is recommended\(^\text{118}\). In fibrillation patients with one clinically relevant non-major risk factor (CHA2DS2-VASc risk score 1), either oral anticoagulation (INR2-3) or aspirin 75-325 mg daily is recommended\(^\text{118}\). Apart from stroke risk assessment, an assessment of bleeding risk during anticoagulation therapy should be considered and bleeding risk score, HAS-BLED is recommended for this purpose\(^\text{119}\). Table 11 illustrates clinical characteristics comprising the HAS-BLED bleeding risk score in anticoagulated patients with atrial fibrillation.

Table 11: The HAS-BLED bleeding risk score

<table>
<thead>
<tr>
<th>Letter</th>
<th>Clinical characteristics</th>
<th>Points awarded</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>Hypertension (uncontrolled)</td>
<td>1</td>
</tr>
<tr>
<td>A</td>
<td>Abnormal renal or liver function</td>
<td>1 point each</td>
</tr>
<tr>
<td>S</td>
<td>Stroke history</td>
<td>1</td>
</tr>
<tr>
<td>B</td>
<td>Bleeding (prior major bleeding)</td>
<td>1</td>
</tr>
<tr>
<td>L</td>
<td>Labile INRs (unstable, high INR)</td>
<td>1</td>
</tr>
<tr>
<td>E</td>
<td>Elderly, age &gt;65 years</td>
<td>1</td>
</tr>
<tr>
<td>D</td>
<td>Drugs (antiplatelet,NSAID)or alcohol</td>
<td>1 point each</td>
</tr>
</tbody>
</table>
Assessment of both stroke and bleeding risk using the \( \text{CHA}_2\text{DS}_2\text{-VAS} \) and HAS-BLED schemas, respectively, in the EuroHeart Survey on atrial fibrillating population would have resulted in withholding oral anticoagulation therapy in 12% of the patients who suffered a major bleeding within one year and the initiation of oral anticoagulation therapy in 95% of the patients at high risk for stroke who were discharged without oral anticoagulation and had suffered a stroke within one year\(^{119}\). Dabigatran is an oral direct thrombin inhibitor. Eighteen thousands patients with atrial fibrillation randomly assigned to receive dabigatran 110 mg or 150 mg twice daily or adjusted does of warfarin\(^{120}\). People whose HAS-BLED scores show they’re at higher bleeding risk could be prescribed the lower dose (110 mg twice a day) of dabigatran, which demonstrated a significant reduction in major bleeding compared to warfarin, with a similar stroke risk. For people whose bleeding risk is lower, dabigatran could be prescribed at 150 mg, which offers superior efficacy but with a similar major bleeding risk to warfarin\(^{119,120}\). Rheumatic mitral stenosis is the most important native valvular lesion that predisposes to cardioembolism. Warfarin therapy is recommended for patients with mitral stenosis and enlarged left atrium, prior embolism and atrial fibrillation keeping INR 2-3\(^{62}\). First three months following bioprosthetic valve replacement is another indication of oral anticoagulation with INR 2-3. Warfarin therapy is recommended maintaining INR between 2-3 in patients with dilative cardiomyopathy or left ventricular ejection fraction <35% or intraventricular thrombus. In stroke patients with paradoxical embolism short- term anticoagulation (INR 2-3) is recommended\(^{11}\). Any patient with acute myocardial infarction admitted in the hospital except during fibrinolytic therapy should receive short-term anticoagulation with INR 2-3\(^{12}\). Post-myocardial infarction left ventricular akinetic segment and left ventricular aneurysm, if are associated with intramural thrombus, are indications for warfarin therapy (INR 2-3)\(^{11}\). Indeed a mobile or protruding left ventricular thrombus is a clear indication for anticoagulation (INR 2-3)\(^{11}\). An INR<2 is an inadequate preventive management of stroke\(^{115}\). Dolichoectasia is another indication for long-term warfarin therapy (INR 2-3), if it makes TIA or ischemic stroke uncontrolled with antiplatelet drugs\(^{11}\). In very old patients, hemorrhagic complications of warfarin therapy is higher. At the other side comorbidity frequently contraindicates use of warfarin therapy in the geriatric patients. We prefer to not use warfarin in very old patients\(^{83}\). It is recommended that combined low dose aspirin and dipyridamole should be given if oral anticoagulation is contraindicated in this age group\(^{115}\).
Surgical preventive treatment of TIA/stroke in developed countries

Carotid Endarterectomy (CEA) is indicated for cases of symptomatic (within recent 6 months) and >70% extracranial ICA stenosis (measured with NASCET method). Symptomatic means stenosis associated with corresponding TIA or minor non-disabling stroke. These patients should be referred to a center and a surgeon with a complication rate of less than 6% for perioperative death or stroke. If this rate approaches to 10%, the benefits of CEA is negated. The risk of surgery in each center in not related to the degree of ICA stenosis and the risk of ischemic stroke ipsilateral to symptomatic carotid stenosis without performing CEA increases as the stenosis becomes more severe. Thus patients with more stenosis take more benefit from surgery. The risk of ipsilateral ischemic stroke is highest within the first weeks or months of the most recent ischemic event in symptomatic sever carotid stenosis. Therefore the benefit of surgery is maximized if it is done as soon as possible. CEA could also be performed with loco-regional anesthesia. Some vascular surgeons have done CEA with regional anesthesia on patients with high risk of general anesthesia. The perioperative complication risk of some vascular or neurovascular surgeons for CEA is less than one percent and they would think about performing CEA on symptomatic 50-69% carotid stenosis or asymptomatic >70% carotid stenosis. The surgeons make a 10 cm long incision, opening up the artery, cleaning it out and then sewing it up again. If the combined angiographic and surgical risk of stroke is about 10% in routine clinical practice and if the unoperated risk of stroke of >70% carotid stenosis is 20% during next two years. Assuming that successful surgery reduces stroke risk to zero, then doing 10 operations would cause one stroke and avoid two. The net gain would be one stroke avoided. Based on the NASCET results in symptomatic patients with more than 70% ipsilateral carotid stenosis, 6 CEA need to be performed to prevent one stroke in a 2 years period, if perioperative risk is less than 6%. In surgical centers with this perioperative risk incidence, for every 100 symptomatic >70% carotid stenosis treated surgically 17 patients will be spared an ipsilateral stroke. Thus CEA decreases risk of ischemic events by 17% in these surgical centers. CEA is not recommended for recently symptomatic <50% carotid stenosis. Because the unoperated risk of stroke in these patients is very low, the risk of surgery is not often worth-while for them. In patients with symptomatic carotid stenosis between 50-70%, CEA could be recommended only in cases of non-ocular symptoms, ulcerated plaque, absence of diabetes, male sex and not very old age if the major perioperative complication rates is less than 3%. In
surgical centers with <3% perioperative risk about 50 asymptomatic patients with >70% carotid stenosis have to underwent surgery to prevent one having a stroke in the next 3 years. The greatest benefit of CEA for asymptomatic patients is for those with the tightest stenosis (>90%)\textsuperscript{12}. Clearly, we need to know who is at highest risk of surgical stroke and who will be at highest risk of ipsilateral ischemic stroke if surgery is not done. This strategy reduces the number of patients that have to be operated on to prevent one having a stroke and maximizes cost-effectiveness. It is therefore essential that surgery is offered to those patients who have most to gain and who are most likely to survive for years to enjoy that gain\textsuperscript{1}. The benefit of surgery over medical therapy alone holds true only if the risk of stroke and death from the procedure is kept below 3% in asymptomatic and below 6% in symptomatic patients with >70% carotid stenosis\textsuperscript{11}. For most patients with moderate 50-69% symptomatic carotid stenosis or sever >70% asymptomatic carotid stenosis, medical therapy alone is probably the best strategy\textsuperscript{12}. The highest risk of future stroke is in symptomatic patients with more than 90% ICA stenosis and ulcerated plaque who are on medical therapy alone\textsuperscript{12}. There is only a minimal increase in the risk of CEA in these patients. Therefore the highest benefit of CEA is achieved in patients with symptomatic >90% ICA stenosis\textsuperscript{11}. Only four of such patients need to be submitted to the procedure to prevent 1 stroke in the next 2 years. Even with >90% carotid stenosis, seven out of 10 patients will not have a stroke in 3 years without performing CEA\textsuperscript{12}. The estimate of incidence of CEA perioperative complications (death and stroke) conducted by every surgical center is recommended for its weight on surgery indications\textsuperscript{12}. The perioperative stroke risk depends not only on the skill of the surgeon and anesthetist but also on various patient related risk factors such as increasing age, female gender, hypertension, diabetes, coronary artery disease, contralateral ICA occlusion, ipsilateral ICA siphon or ECA stenosis and ischemia of the brain rather than the eye\textsuperscript{12}. The risk of stroke is three times higher in medically treated patients with hemispheric symptoms related to carotid stenosis than similar patients with only retinal ischemic symptoms and patients in both groups benefit from CEA\textsuperscript{1}. Patients who are candidated for CEA should have strict control of hypertension and diabetes. CEA in the diabetics, regardless of regulation, carries a higher risk of perioperative stroke than in non-diabetic patients (7.8% versus 3.7%)\textsuperscript{12}. There is doubling risk of the perioperative complications for patients in whom the opposite (usually asymptomatic) carotid artery is occluded\textsuperscript{5}. If an intraluminal thrombus at the site of stenosis is seen on angiogram, anticoagulation for
1 month and performing CEA after disappearance of the thrombus in repeated angiogram is recommended. Uncontrolled hypertension at the time of CEA raises the risk of postoperative ICH and increases disability of perioperative ischemic stroke. Patients receiving CEA should not discontinue platelet inhibitors and relying on CEA alone for stroke prevention. Decisions regarding the management of patients with concurrent intracranial vascular lesions, i.e. aneurysm, AVM must be made on an individual basis and symptomatic lesions should be treated first. Accordingly, a symptomatic carotid stenosis takes priority over unruptured intracranial aneurysm and following recovery from CEA, the aneurysm should be treated if it represents high risk for future SAH. In the absence of corresponding symptoms, the lesion with highest risk should be treated first. For patients with stenosis of both carotids the best approach is to repair only the symptomatic artery. Tandem lesions are usually found in the siphon. Whether to repair proximal ICA in patients with tandem stenosis depends in the condition of inaccessible lesion. If the intracranial stenosis exceeds the proximal stenosis, reconstruction of the cervical lesion is not justifiable because flow through the distal stenotic segment would not be increased by CEA. The perioperative complication rate is the same in the presence of tandem siphon stenosis.

The American Stroke Association indications for CEA (if the rate of perioperative complications is <6%) include:

1- One or more TIAs or mild ischemic stroke within the last 6 months and carotid stenosis ≥70% (proven benefit).

2- One or more TIAs or mild ischemic stroke within the last 6 months and carotid stenosis 50-69% and if operation performed in institution with perioperative complication rate <3% (acceptable but not proven benefit).

3- Asymptomatic low risk male patients with carotid stenosis ≥70% and if operation performed in institution with perioperative complication rate <3% (acceptable but not proven benefit).

The European Stroke Association guidelines for CEA include:

1- Carotid surgery is not recommended for asymptomatic individuals with significant carotid stenosis (NASCET 60-99%), except in those at high risk of stroke.

2- It is recommended that patients should take aspirin before and after surgery.

3- CEA is recommended for patients with symptomatic 70–99% carotid stenosis.

4- CEA should only be performed in centres with a perioperative complication rate (all strokes and death) of less than 6%.

5- It is recommended that CEA be performed as soon as possible after the last ischemic event, ideally within 2 weeks.
6- CEA for stenosis of 50–69% should only be performed in centres with a perioperative complication rate (all stroke and death) of less than 3%.
7- Older patients (>75 years) without organ failure or serious cardiac dysfunction benefit from CEA.
8- Women with severe (>70%) symptomatic stenosis should be treated medically.
9- Patients with amaurosis fugax, severe stenosis and a high risk profile should be considered for CEA; those with amaurosis fugax and few risk factors do better with medical treatment.
10- Patients with mild-to-moderate intracranial stenosis and severe extracranial stenosis should be considered for CEA.
11- Occlusion of the contralateral ICA is not a contraindication to CEA but carries a higher perioperative risk. The benefit from CEA is less in patients with lacunar stroke. Patients with leukoaraiosis carry an increased perioperative risk. The benefit from CEA is marginal in patients with carotid near-occlusion. The urgent CEA is indicated in patients with multiple low flow TIAs related to severe extracranial ICA stenosis. Elective CEA is recommended following heparinization of crescendo TIAs in carotid circulation with atherothromboembolic mechanism.

Assessment of Carotid Endarterectomy (CEA) in Iran

A multicenter retrospective observational study was performed in Persian patients who underwent CEA by vascular surgeons during 2001-2008. Three hundreds eighty eight CEA in 345 Persian patients (65% males) with mean age 66.8 years ranged 46-84 years were evaluated. Detection of carotid stenosis was made by one carotid duplex ultrasound in 90% of Persian CEA candidates. Because Iranian vascular surgeons trust to the skill of their sonographers in detection of ICA stenosis, however validation study of their sonographers is not published. At the other hand, Iranian vascular surgeons prefer to refuse the risk and complications of catheter angiography in candidates of CEA. In Emam Reza and Razavi hospitals, detection of symptomatic and asymptomatic ICA stenosis was made only by one carotid duplex in 95% of candidates. MRA have been requested for confirmation of ICA occlusion reported by carotid duplex. Catheter angiography was performed in 5% of patients with symptomatic and asymptomatic ICA stenosis. In Tajrish hospital, detection of symptomatic ICA stenosis was made only by one carotid duplex in 94% !, while catheter angiography was performed in 90% of asymptomatic candidates of CEA. MRA is not requested for CEA candidates in Tajrish hospital because their vascular surgeons do not have trust to results of MRA even as an adjunctive neurovascular imaging. In Taleghani and Iranmehr hospitals, symptomatic
ICA stenosis was detected only by one carotid duplex in 95% and their vascular surgeons do not use MRA for detection of carotid stenosis or occlusion\cite{121,122}. Method of detection of carotid stenosis in Iranian vascular surgery centers should be corrected. Catheter angiography is still gold standard for detection of ICA stenosis and is indicated when two noninvasive vascular imagings such as carotid duplex, MRA, CT angiography show disparate results. None of the Iranian vascular surgeons paid attention to presence of tandem stenosis in ipsilateral siphon or MCA by TCD, MRA or conventional angiography\cite{121,122}. Although presence of tandem stenosis reduces the probability of hyperperfusion syndrome after CEA, however it has negative influence in usefullness of CEA in restoring cerebral blood flow\cite{12}. Thus vascular surgeons should pay attention to tandem stenosis in candidates of CEA. Various methods of patients selection for CEA were detected in Iranian vascular surgery centers\cite{121,122}. Patients with symptomatic $\geq 60\%$ ICA stenosis or asymptomatic $\geq 75\%$ ICA stenosis were candidates for CEA in Emam Reza and Razavi hospitals. Patients with symptomatic $\geq 70\%$ ICA stenosis were candidates for CEA in Tajrish hospital, however 24\% of CEA operations in Tajrish hospital were performed in patients with asymptomatic $\geq 70\%$ ICA stenosis. Ninety eight percent of CEA in Taleghani and Iranmehr hospitays were carried out in patients with symptomatic $\geq 70\%$ ICA stenosis. Results of reported clinical trials of CEA have shown that groups of patients with symptomatic $\geq 70\%$, $\geq 90\%$ and $\geq 50$-$69\%$ ICA stenosis require 6, 4, 24 CEA operations for prevention of one stroke in the next two years respectively\cite{123,124}. The risk of medical therapy alone increases with increasing degree of stenosis\cite{11,12}. Based on the ACAS trial, 67 patients with asymptomatic $\geq 60\%$ ICA stenosis should be operated for prevention of 1 stroke in the next two years\cite{125}. There is no difference in adverse outcome events of CEA among those with different degrees of stenosis\cite{126}. All of the CEA operations were done with general anesthesia in Tajrish, Taleghani, Razavi and Iranmehr hospitals. Cervical sympathetic ganglionic block served for all of the CEA operations until 2007 in Emam Reza hospital and thereafter general anesthesia has been used for 90\% of CEA in this center\cite{121,122}. Intraoperative arterial shunting was used in all of CEA operations in Tajrish, Taleghani, Iranmehr and Razavi hospitals\cite{121,122}. In Emam Reza hospital, all of the CEA operations were done without intraoperating shunting upto 2007 and thereafter intraoperative shunting served for CEA\cite{121,122}. Despite Razavi and Emam Reza hospitals, arterial patch in site of CEA was used in other Iranian vascular surgery centers\cite{121,122}. The whole perioperative stroke and death rate in reported
Iranian vascular surgery centers is 6.4%. Perioperative stroke and death rate in Emam Reza, Razavi, Tajrish, Taleghani and Iranmehr hospitals was 2.4%, 0%, 4.8%, 10.2% and 8.1% respectively121. Table 12 represents perioperative complications of CEA in multiple Iranian vascular surgery center121.

Table 12: Frequency of perioperative complications of CEA in Iran

<table>
<thead>
<tr>
<th>Perioperative complication</th>
<th>Emam Reza 86 CEA</th>
<th>Razavi 14 CEA</th>
<th>Tajrish 42 CEA</th>
<th>Taleghani 49 CEA</th>
<th>Iranmehr 197 CEA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke</td>
<td>1(1.2%)</td>
<td>-</td>
<td>1(2.4%)</td>
<td>2(4.1%)</td>
<td>12(6.1%)</td>
</tr>
<tr>
<td>Death</td>
<td>1**(1.2%)</td>
<td>-</td>
<td>1*(2.4%)</td>
<td>3(6.1%)</td>
<td>4(2%)</td>
</tr>
<tr>
<td>Hyperperfusion cerebral edema</td>
<td>-</td>
<td>1(7.1%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Wound hematoma</td>
<td>7(8.1%)</td>
<td>-</td>
<td>3(7.1%)</td>
<td>-</td>
<td>3(1.5%)</td>
</tr>
<tr>
<td>Lower cranial nerve paresis</td>
<td>1(1.2%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1(0.5%)</td>
</tr>
<tr>
<td>Total</td>
<td>10(11.6%)</td>
<td>1(7.1%)</td>
<td>5(11.9%)</td>
<td>5(10.2%)</td>
<td>20(10.2%)</td>
</tr>
</tbody>
</table>

* Death due to intracerebral hemorrhage secondary to hyperperfusion syndrome
** Death due to extensive brain infarction

The first published Iranian CEA data belong to Fazel et al who work in both Taleghani and Iranmehr hospitals127,128. They had a perioperative stroke and death rate of CEA of 10.2%127,128. They have been the pioneer of CEA in Iran. This complication rate belongs to their learning curve period and probably after 2001 they have had lower perioperative stroke and death rate. However general perioperative stroke and death rate of CEA in Iran is more than 3%121,122. In Iran, CEA is recommended only in patients with symptomatic ≥70% ICA stenosis and preferably in patients with symptomatic ≥90% ICA stenosis121,122. Performance of CEA in asymptomatic patients with carotid stenosis is not recommended in Iranian hospitals due to superiority of its hazards than its benefits in asymptomatic candidates. Each country or in more details each vascular surgery center should determine its guidelines of selection of CEA patients based on its complications rate.

Extracranial-Intracranial arterial bypass

Bypass of branches of superficial temporal artery to MCA stem has been performed in patients with ICA occlusion, M1 occlusion or Moyamoya disease. Recanalization occurred in one-third of these bypassed patients129.
A surgical bypass can be created connecting one vessel to another beyond the obstruction, i.e. common carotid artery to VA connection in cases of proximal VA occlusion. One patient with extracranial ICA occlusion underwent successful superficial temporal artery branch to MCA bypass operation in our center.

**Interventional Preventive Therapy**

Ongoing stenting technology assessment of neck and brain arteries has resulted in a desire to accurately benchmark expected and reasonable stent performance and risk rates in order to understand what complication rates are acceptable for each group of patients. There should be concern when endovascularly manipulating a vessel which has diffuse atherosclerosis within it, runs the risk of dislodging and embolizing plaque. There are numerous cardiovascular, neurologic and systemic complications that can be seen with cervicocerebral angioplasty and stenting. It is important to understand the scenarios in which additional efforts may be beneficial to the patient, and when heroic or misdirected efforts may acutely expose the patient to greater danger. One set of complications deal with the intra and periprocedural embolic neurologic complications. These may arise from the stent lattice if there has been inadequate anticoagulation and antiplatelet administration. During instrumentation of an artery, a dissection flap may be made which leads to embolic creation and seeding. There are reported case series of embolic complications arising at the time of stent placement, which were technically and clinically benefitted by directed intracranial thrombolytic therapy and by pursuing the clot intracranially for directed and aggressive microcatheter-based treatment. Many of the embolic complications are in fact atherosclerotic emboli rather than thrombotic emboli. In addition to embolic complications, procedural complications also include reperfusion injury. Chronic response to hypoperfusion could make maximal vasodilatation through autoregulation in the hypoperfused circulation bed. This may be dangerous if the protective vasoconstrictive reflex is blunted or temporarily lost. With the absence of the counteracting reflex, once the stenosis in the artery is opened, this increases the pressure in the downstream circulation, permitting leakage in the arterial and capillary bed. This could cause brain edema and intracerebral hemorrhage. This technique is to put a needle in to the femoral artery, a catheter is passed through the needle and guided up in to the neck arteries and a little balloon on the end of the catheter is then inflated. This procedure opens up the artery. Balloon inflation denutes the endothelium, splits and cracks the
atheromatous plaque so that it is dehisced from the underlying media, and stretches the media and adventitia. However in order to keep the artery open, a tiny cylinder of wire mesh, called a stent, is then placed over the balloon. The balloon is deflated and the catheter is withdrawn. The stent remains imbeded in the inner lining of the artery and helps to keep the artery open. Stent replacement eliminates the risk of immediate embolism, dissection and reduces the chance of delayed restenosis. The remodeling process that occurs after Percutaneous Transluminal Angioplasty (PTA) is a new endothelium lining the atheromatous plaque. Full restoration of the normal arterial diameter may not be necessary to prevent stroke. PTA is performed under local anesthesia, avoiding the major complications of general anesthesia and local complications of an incision in the neck. The patient needs to stay in the hospital for the duration of intravenous heparin therapy (usually 48 hours) and can resume normal activities immediately.

The most important requirement for safe PTA is that a guide wire will pass easily through the stenosis. A very tortuous lumen or an acutely angled approach to the stenosis is not suitable because of the risk of the guide wire penetrating the arterial wall. Vessel stenosis greater than 3-4 cm in length requires balloon longer than those now generally available. The presence of ulceration visible on ultrasound or angiography is not by itself a contraindication to PTA and such lesions can be successfully treated without complications. The presence of visible thrombus is regarded as a contraindication, although it might be feasible to use local infusions of thrombolytic agents to dissolve the clot prior to PTA.

**Percutaneous Transluminal Angioplasty and Stenting of neck arteries**

The risks of PTA in the proximal ICA and VA are not greater than those of PTA at other sites and are similar to the risks of CEA. Carotid angioplasty with stenting may be a good and safe alternative for CEA (it has similar major risks and effectiveness in preventing stroke comparing to CEA). The indications for PTA in proximal ICA are similar to those of CEA. If danger of emboli or arterial dissection is about 6% for symptomatic and 3% for asymptomatic cases of extracranial ICA stenosis then PTA and stenting is recommended in that neurointerventional center. PTA should be considered mainly for patients with severe symptomatic carotid stenosis measuring more than 70% linear diameter reduction using the NASCET method. PTA and stenting could be considered in the following circumstances for neck arteries:

1. Patients whose stenotic lesions are relatively inaccessible for surgery,
i.e. proximal intrathoracic segment of common carotid artery and distal cervical ICA.

2- Patients with non-atherosclerotic pathologies, i.e. dissection, postradiation stenosis, FMD and restenosis after CEA.

3- Patients with higher than average risk of CEA, i.e. contralateral carotid occlusion and poor medical condition.

4- PTA and stent insertion is used for reconstruction and reopening of the occluded carotid dissections.

The European Stroke Association guidelines of extracranial carotid percutaneous transluminal angioplasty and/or stenting:

1- Carotid percutaneous transluminal angioplasty and/or stenting is only recommended in selected patients. 2- It should be restricted to the following subgroups of patients with severe symptomatic carotid artery stenosis: those with contra-indications to CEA, stenosis at a surgically inaccessible site, re-stenosis after earlier CEA, and post-radiation stenosis. 3- Patients should receive a combination of clopidogrel and aspirin immediately before and for at least 1 month after stenting. 4- The incidence of complications after either angioplasty or stenting may be up to 6%.

Percutaneous Transluminal Angioplasty and Stenting of intracranial arteries

Intracranial angioplasty and stenting for symptomatic intracranial atherosclerosis remains an investigational procedure. Petrous and cavernous segments of ICA are accessible to stent insertion. Stents could be put in the ICA, VA, BA and sometimes M₁ (MCA), however it depends on patients vascular anatomy, atherosclerotic changes of the vessel and the catheter. Coronary stents are often used for intracranial arteries. PTA of distal VA, BA, carotid siphon, MCA, ACA and PCA is more hazardous than extracranial segments of ICA and VA. Probably because the intracranial arteries has a thin adventitia more prone to dissection and the small penetrating arteries are easily occluded. The incidence of dissection of the petrous ICA after angioplasty is so high that it always should be done with putting stent. Intracranial VA and BA are accessible and safe for putting stent. The intracranial ICA, VA, BA, stem of MCA, ACA, and PCA are accessible for angioplasty in the atherosclerotic disease. Angioplasty and stenting is not an approved treatment and is rarely used for intracranial symptomatic atherosclerotic stenosis. The risk of dissection and hemorrhage and infrequency of intracranial atherosclerotic disease are among the contributing factors. If a patient with intracranial segmental
Arteriosclerotic stenosis develops several corresponding TIAs or minor strokes which does not respond to antiplatelet drugs and warfarin therapy, stroke neurologists may consider PTA. PTA is an approved treatment for vasospasm of SAH patients if it is resistant to vasodilator and hypervolemic therapy. Some part of M2 (MCA) and A2 (ACA) are also accessible for angioplasty of vasospasm in the SAH patients.

Angioplasty and Stenting in Cervicocerebral arteries by Iranian Neurointerventionists Concertium

Retrospective assessment of neurointerventional archives of 9 Iranian neurointerventionists working in 5 university hospitals and 7 private hospitals during June 2003-June 2009 and review of their published articles is the basis of this national survey of cervicocerebral arterial angioplasty stenting.

Angioplasty and Stentig of Extracranial Internal Carotid Artery (ASEICA)

Four neurointerventionists only performed ASEICA in symptomatic >70% carotid stenosis and 4 of them enrolled symptomatic patients with >50% carotid stenosis or patients with asymptomatic >70% carotid stenosis for ASEICA. Allergy to aspirin, clopidogrel and angiographic contrast, angiographic appearance of fresh thrombus at the lesion site and arterial total occlusion or long preocclusive lesion (string sign lesion) considered as exclusion criteria. Percutaneous access was gained through the femoral artery guiding catheters (7-8 French, MP7F). All patients underwent an angiographic examination of cervicocerebral arteries in the anteroposterior and lateral projections before and after the procedure. All of the patients had distal protection device; FilterWire EZ embolic protection device (Boston Scientific Natick, MA, USA), Spider X embolic protection device (ev3, Plymouth, MN, USA), Angiogaurd Cordis and Acculink Guidant. The choice of the protection device and stent was at the discretion of the operator and the availability of the devices. After deployment of the protection device, self expandable mesh stent; Wallstent (Boston Scientific, Natick, MA, USA), Protégé (ev3, Plymouth, MN, USA) and Acculink (Guidant, Indianapolis, IN, USA) were implanted. Balloon predilation was performed with coronary balloons in tight or subocclusive arterial stenosis. The predilation balloons were routinely undersized to reduce vessel dissection and/or distal embolization. Stent placement was optimized with postdilation, by using suitably-sized balloons (Via Trace) based on the quantitative analysis of the vessel.
Technical success was defined as the ability of access to the carotid artery and stenting the lesion with <30% residual stenosis. Arterial sheets were usually removed the same day. After the procedure, patients had ECG monitoring and blood pressure measurements every 3-4 hours for at least 12 hours. Plasma Troponin 1 levels was checked daily during hospitalization period. Aspirin 325 mg/day and clopidogrel 75 mg/day were started 5 days before the procedure. Heparin 70-100 IU/kg was given just before the procedure to achieve an activated clotting time >250 seconds. Patients were discharged on a regimen of aspirin indefinitely and clopidogrel for 1 month. Neurologic examination including the National Institute of Health stroke scale was performed before and after the procedure. All of the patients underwent another neurologic examinations at 1 and 30 days after the ASEICA. A postprocedure brain CT scan was performed in patients with documented neurologic complications. Procedure related complications from the beginning of the procedure through 30 days follow-up were recorded. Fatal stroke was defined as death attributed to an ischemic stroke or Intra-Cerebral Hemorrhage (ICH). Mild hyperperfusion syndrome was defined as headache, nausea, hallucination, dysorientation occurring within 24 hours postprocedure. The rate of single complications and of
cumulative complications was calculated as the number of complications divided by the total number of successful procedures.

**Angioplasty and Stenting of Extracranial Vertebral Artery (ASEVA)**

Patients were administered aspirin 325 mg/day and clopidogrel 75 mg/day orally starting 3 days before the procedure. Patients underwent laboratory tests for platelet, hematocrit and coagulation profile before the procedure. Administration of warfarin was discontinued 3 days before the procedure in patients who were taking it in a long term basis, and a repeated coagulation profile was performed for these patients on the morning of the procedure. A complete neurologic examination was documented before the procedure. After arterial access through the femoral artery, a 70 IU/kg bolus of heparin was administered intravenously to achieve an activated coagulation time above 250 seconds. A 6F guide catheter (Cordis, Miami Lakes, Fla) was placed in the ipsilateral subclavian artery. If necessary, the guide catheter was stabilized by coaxial placement of a control microwire (Boston Scientific, Natick, Mass) into the distal subclavian artery. The distal protection device FilterWire (EZ Boston Scientific, Natick, MA, USA) or (Spider X embolic protection device, Med Corporation) was introduced through the lesion and deployed into the distal cervical segment of the vertebral artery. Drug eluting coronary stents (Cordis Precise, Cordis Corporation or Boston Scientific or Guidant Multilink Vision, Guidant corp) were used. Angioplasty was performed before and after stent placement in selected situations to provide the most optimal results. After treatment of the stenosis, the distal protection device was retrieved. No further heparin was infused after the procedure. A complete neurologic examination was performed immediately after and at 1 and 30 days after the endovascular intervention. Aspirin 325 mg/day and clopidogrel 75 mg/day were prescribed at discharge. Clopidogrel was discontinued after 1 month and aspirin was continued indefinitely. The primary technical end point for the study was the ability to traverse, deploy and retrieve the distal protection device and deployment of the stent with a residual stenosis of less than 30%. The primary clinical endpoint was 30 days composite occurrence of stroke and death.

**Angioplasty and Stenting of Intracranial Arteries (ASIA)**

Preprocedural and postprocedural management and endpoint assessment for intracranial angioplasty and stenting was similar to extracranial vertebral artery endovascular intervention. Predilatation of selected intracranial
arterial stenosis was performed, then drug eluting coronary stents; (Liberte coronary stent, Boston Scientific), (Magic stent, Eurocor, Gmbh, Germany), (Vision Medlike, International) was advanced over the guide wire to cover the stenosed segment and deployed following with postdilatation by balloon inflation (Liberte Balloon)\textsuperscript{134,135}. Protection filter is not used for intracranial angioplasty and stenting. The Wingspen stent has not been commercially available for Iranian neurointerventionists till now. Five hundreds eighty one patients (73\% males) with mean age 63.4 ±7 years underwent 592 ASEICA. Procedure success was present in 95\% of our ASEICA. TIA, stroke, ICH, and death occurred in 1.7\%, 1.7\%, 0.34\% and 1.52\% of ASEICA respectively\textsuperscript{134,135}. Mild hyperperfusion syndrome, seizure, bradycardia and acute tubular necrosis (due to sensitivity to contrast media) developed in 3.55\%, 1.86\%, 4.39\% and 0.17\% of ASEICA respectively\textsuperscript{134,135}. Whole stroke and death rate of Iranian neurointerventionists concertium for ASEICA is 3.2\% (19/592). Table 13 illustrates details of complications in 592 ASEICA performed by Iranian neurointerventionists\textsuperscript{134,135}.

<table>
<thead>
<tr>
<th>Death</th>
<th>ICH</th>
<th>ATN</th>
<th>Bradycardia</th>
<th>Seizure</th>
<th>MHS</th>
<th>Stroke</th>
<th>TIA</th>
<th>Procedure access</th>
<th>SS</th>
<th>Number of ASEICA</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>1</td>
<td>17</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>96%</td>
<td>63%</td>
<td>81</td>
<td>Karimi</td>
</tr>
<tr>
<td>1*</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>94%</td>
<td>92%</td>
<td>80</td>
<td>Ghorbani</td>
</tr>
<tr>
<td>3**</td>
<td>-</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>5</td>
<td>95%</td>
<td>100%</td>
<td>300</td>
<td>Edraki</td>
<td></td>
</tr>
<tr>
<td>1***</td>
<td>-</td>
<td>8</td>
<td>12</td>
<td>1</td>
<td>2</td>
<td>96%</td>
<td>100%</td>
<td>41</td>
<td>Kojuri-Ostovan</td>
<td></td>
</tr>
<tr>
<td>4****</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>-</td>
<td>95%</td>
<td>20%</td>
<td>38</td>
<td>Haji-Zeinali, Kazemi-Saleh</td>
<td></td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>1</td>
<td>96%</td>
<td>100%</td>
<td>52</td>
<td>Shabestrai</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>2</td>
<td>1</td>
<td>26</td>
<td>11</td>
<td>21</td>
<td>10</td>
<td>10</td>
<td>95%</td>
<td>389</td>
<td>Total</td>
</tr>
</tbody>
</table>

ASEICA: Angioplasty and Stenting of Extracranial Internal Carotid Artery Stenosis
SS: Symptomatic Stenosis MHS: Mild Hyperperfusion Syndrome ATN: Acute Tubular Necrosis
*Death due to ICH and hyperperfusion syndrome ICH: Intra-Cerebral Hemorrhage
**One death due to stroke and two deaths due to acute MI
***Death due to ICH and hyperperfusion syndrome
****Four deaths due to acute MI

Haj-Zaeniali et al and Kojuri et al have been pioneers of ASEICA procedure in Iran\textsuperscript{136,137}. Cumulative stroke and death rate of Iranian neurointerventionists concertium for ASEICA is 3.2\% which is better than other studies\textsuperscript{134,135}. Assessment of Carotid EndArterectomy (CEA) in Iranian neurovascular centers has shown whole stroke and death rate of 6.4\% for CEA performed by Iranian vascular surgeons\textsuperscript{121,122}. Therefore ASEICA is a good alternative to CEA in Iran. Meta-analysis of ten clinical trials on 3580 patients comparing the primary outcome of 30 days stroke or death of ASEICA versus CEA \textsuperscript{181}, has shown that patients who underwent
ASEICA has a higher risk of stroke and death relative to patients who underwent CEA; risk ratio=1.30. Subgroup analysis of trials enrolling only symptomatic patients showed higher relative risk of 30 days stroke and death for ASEICA; risk ratio=1.63. 114 ASEVA was performed in 110 patients (68% males) with mean age 65.3 ±6 years. Procedure success was present in 99% of our ASEVA. TIA and stroke each developed in one patient (0.92%) and mild hyperperfusion syndrome was seen in 3 patients (2.7%) during procedure. ICH and death did not occur in these patients. Table 14 represents details of complications in 114 ASEVA procedures performed by Iranian neurointerventionists concertium.

<table>
<thead>
<tr>
<th>MHS</th>
<th>Stroke</th>
<th>TIA</th>
<th>Symptomatic Stenosis</th>
<th>Procedure success</th>
<th>Number of EVAAS</th>
<th>Interventionist</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>1</td>
<td>100%</td>
<td>99%</td>
<td>70</td>
<td>Edraki</td>
</tr>
<tr>
<td>-</td>
<td>1</td>
<td>-</td>
<td>55%</td>
<td>100%</td>
<td>17</td>
<td>Ghorbani</td>
</tr>
<tr>
<td>3</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>100%</td>
<td>18</td>
<td>Kojuri-Ostovan</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>100%</td>
<td>7</td>
<td>Shabestrai</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>50%</td>
<td>100%</td>
<td>2</td>
<td>Karimi</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>92%</td>
<td>99%</td>
<td>114</td>
<td>Total</td>
</tr>
</tbody>
</table>

ASEVA: Angioplasty Stenting of Extracranial Vertebral Artery MHS: Mild Hyperperfusion Syndrome

The whole stroke and death rate of ASEVA by Iranian neurointerventionists concertium is less than one percent which is similar to German results. Seventy ASIA was delivered in 67 patients (males 76%) with mean age 68.5±8 years. TIA and stroke was observed in 1.4% and 8.6% of ASIA respectively. ICH due to hyperperfusion syndrome, death and mild hyperperfusion syndrome developed in 1.4%, 2.8% and 11.4% of ASIA procedures respectively.

Table 15 demonstrates localization of 70 ASIA performed by Iranian neurointerventionists concertium. Complications of these 70 ASIA is represented in Table 16.

Review of six multicenter prospective studies of ASIA in 1011 patients with intracranial atherosclerosis revealed 30 days any stroke and death rate of 4.5% to 6.6% respectively. Perioperative complications of ASIA remain a prime concern as they may offset the potential benefit of the procedure. Hyperperfusion and vessel perforation are the two major causes of ICH after intracranial stenting. Currently, aggressive control of systemic blood pressure is the best available way to prevent and treat hyperperfusion syndrome. Based on the clinical trials; sufficient evidence now exists to recommend that intracranial angioplasty with or without stenting should be offered to
symptomatic patients with intracranial stenosis who have failed medical therapy\textsuperscript{132,145}. Careful patient selection, meticulous peri-procedural care and skillful neurointerventionists are all essential for performing ASIA with an acceptable risk\textsuperscript{143,144}. Studies have suggested that intracranial stenosis $\geq 50\%$ with the following characteristics may be considered for ASIA: 1- recurrent transient ischemic attacks or ischemic stroke within 180 days; 2-refractoriness to antithrombotic therapy and; 3- relevant cerebral hypoperfusion or borderzone infarct in the corresponding territory\textsuperscript{143}. Contraindications of ASIA include vasculitis, moyamoya disease, intracranial hemorrhage within 6 weeks, platelet count $<100000$, international normalized ratio $>1.5$, bleeding diathesis or patient contraindication for antithrombotic therapy or contrast medium\textsuperscript{143,144}. Patients with recent cerebral ischemic symptoms attributed to an intracranial stenosis $\geq 70\%$ and associated with perfusion failure may benefit most from this procedure\textsuperscript{143,144}. Overall stroke and death rate of ASIA performed by Iranian neurointerventionists concertium is $10\%$ which is similar to best results of western neurointerventionists\textsuperscript{134,135}.

### Table 15: Localization of 70 ASIA performed by Iranian neurointerventionists

<table>
<thead>
<tr>
<th>BA</th>
<th>Intracranial VA</th>
<th>PCA</th>
<th>ACA</th>
<th>MCA</th>
<th>Intracranial ICA</th>
<th>Number of ASIA</th>
<th>Interventionist</th>
</tr>
</thead>
<tbody>
<tr>
<td>6</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>4</td>
<td>1</td>
<td>16</td>
<td>Ghorbani</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>Karimi</td>
</tr>
<tr>
<td>4</td>
<td>6</td>
<td>-</td>
<td>1</td>
<td>3</td>
<td>15</td>
<td>29</td>
<td>Edraki</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>1</td>
<td>-</td>
<td>8</td>
<td>21</td>
<td></td>
<td>Kojuri-Ostovam</td>
</tr>
<tr>
<td>2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>2</td>
<td>Sanatgar-Ghasemi$^2$</td>
</tr>
<tr>
<td>20</td>
<td>15</td>
<td>2</td>
<td>8</td>
<td>25</td>
<td>70</td>
<td></td>
<td>Total</td>
</tr>
</tbody>
</table>

ASIA: Angioplasty Stenting of Intracranial Arteries ICA: Internal Carotid Artery MCA: Middle Cerebral Artery ACA: Anterior Cerebral Artery PCA: Posterior Cerebral Artery VA: Vertebral Artery BA: Basilar Artery

### Table 16: Complications of 70 ASIA performed in Iran

<table>
<thead>
<tr>
<th>Death</th>
<th>ICH</th>
<th>MHS</th>
<th>Stroke</th>
<th>TIA</th>
<th>Symptomatic stenosis</th>
<th>Procedure success</th>
<th>Interventionist</th>
</tr>
</thead>
<tbody>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>1</td>
<td>100%</td>
<td>100%</td>
<td>Ghorbani</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>3</td>
<td>-</td>
<td>100%</td>
<td>100%</td>
<td>Karimi</td>
</tr>
<tr>
<td>1*</td>
<td>-</td>
<td>-</td>
<td>3**</td>
<td>-</td>
<td>100%</td>
<td>96%</td>
<td>Edraki</td>
</tr>
<tr>
<td>1***</td>
<td>1</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>95%</td>
<td>Kojury-Ostovan</td>
</tr>
<tr>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>100%</td>
<td>100%</td>
<td>Sanatgar-Ghasemi$^2$</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>1</td>
<td>100%</td>
<td>97%</td>
<td>Total</td>
</tr>
</tbody>
</table>

MHS: Mild Hyperperfusion Syndrome ICH: Intracerebral Hemorrhage

*: Death due to stent thrombosis in BA and stroke

**: 2 MCA and 1 BA intervention

***: Death due to ICH and hyperperfusion syndrome
Mechanical & Interventional Clot Removal

The MERCI device is approved for removal of blood clot in ischemic stroke patients, when the location of a clot has been identified by angiography. The MERCI balloon guide catheter is inserted through the femoral artery in the groin. The catheter is maneuvered up to the clot. Once the clot is captured, it is pulled into the MERCI balloon guide catheter and is removed\textsuperscript{115}. This technique is used in patients who have failed with intraarterial rtPA or patients with contraindication to thrombolysis. Although the MERCI device is a reasonable intervention for extraction of intra-arterial thrombi in carefully selected patients, the panel also recognizes that the utility of the device in improving outcomes after stroke is unclear. Interventional mechanical thrombectomy grasping jaws is another device which has shown efficacy up to 8 hours post stroke\textsuperscript{83}. At present, mechanical interventions to restore perfusion cannot be recommended outside the setting of clinical trials\textsuperscript{83}.

Prevention of Ischemic Stroke in the Developing Countries

In developing countries, there is no doubt about usefulness of controlling vascular risk factors and prescribing antiplatelet drugs. Unfortunately most of the patients with a cardiac source of emboli who are potential candidates for warfarin therapy do not have permanent access to the laboratory for checking INR and PT in developing countries\textsuperscript{145}. Inadequacy in logistics and poor socioeconomic status of the patients and low concern of some of the physicians about optimal warfarin therapy (frequent INR tests and visits) are among the contributing factors\textsuperscript{145}. These make unwise warfarin therapy in most of the potential candidates in the developing countries\textsuperscript{145}. Only 46% of Persian stroke patients due to rheumatic valvular disease had been underwent anticoagulation therapy as primary prevention of stroke and only 21% of them had an INR within therapeutic range\textsuperscript{86}. Half of Persian stroke patients with non-rheumatic cardiac source of embolism who had indication of oral anticoagulation were treated with warfarin and only 16.6% of these candidates had an INR within therapeutic range\textsuperscript{86}. The reasons for this inadequate management of cardiac source of embolism in Iran and other developing countries are unknown. Thought inadequacies in logistics and infrastructure may be among the contributing factors\textsuperscript{86}. In Iran, only patients with mechanical heart valve are usually receiving optimal anticoagulation and in other potential candidates, hemorrhagic complications of warfarin therapy outweights its preventive benefits. Therefore, physicians in developing countries should not prescribe warfarin unless the patient has optimal
facilities and knowledge about frequent laboratory tests and visits by the responsible doctor\textsuperscript{145}. Although aspirin with regular dose of 325 mg/day is less effective in preventing cardioembolic strokes, it is safe and better in this situations\textsuperscript{145}. There is no difference in management strategies about anticoagulant therapy between developed and developing countries in hospitalized patients who have access to frequent INR tests, blood products, CT scan and visits by the doctors. If the perioperative complication rate in a surgical center is $>10\%$, the benefit of CEA for $\geq70\%$ symptomatic carotid stenosis is negated\textsuperscript{12}. The CEA perioperative major complication rate (stroke and death) is often $>6\%$ in surgical centers of the developing countries\textsuperscript{121,122}. Thus CEA is not recommended in every patient with symptomatic $\geq70\%$ ICA stenosis. However CEA could be considered in some carefully selected patients of this group. Any neurovascular imaging is considered only in patients who have access to CEA facilities and who are willing to consider the risk of surgery. The overall reported perioperative stroke and death rate of CEA in Iranian centers is more than 3\%. Based on the NASCET, ESCT and ACAS trials and our Iranian CEA data, CEA is recommended in Iranian vascular surgery centers only in patients with symptomatic $\geq70\%$ ICA stenosis and preferably in patients with symptomatic $\geq90\%$ ICA stenosis\textsuperscript{121,122,123,124,125}. At the other words performance of CEA in asymptomatic patients with carotid stenosis is contraindicated in Iranian hospitals, due to superiority of its hazards than its benefits in asymptomatic candidates\textsuperscript{121}. Stroke and death rate of extracranial carotid PTA and stenting in Iran is more than 3\%, so this procedure is recommended only for selected patients with symptomatic $\geq70\%$ ICA stenosis\textsuperscript{146}. 
General Supportive Care and Treatment of Acute Ischemic Stroke

General management in acute stroke patients

In practice, more intensive monitoring is often provided for subgroups of patients, such as those with reduced consciousness, progressive neurological deficits, or a history of cardiorespiratory disease. Close monitoring is also required for the first 24 hours after thrombolysis. Glucose containing solutions should be avoided in stroke patients. Normal saline serum 2 liters/day is the preferred fluid in ischemic stroke patients. Serum K should be tested serially, and if necessary, KCL solution be added to the serum. Normal saline (0.9%) is recommended for fluid replacement during the first 24 hours after stroke. There is general agreement about control of hypoglycemia and hyperglycemia in acute phase of stroke. By consensus a reasonable goal would be lowering elevated glucose levels to <200 mg/dL by insulin and correction of hypoglycemia <50 mg/dL. Pressure sores are more common in stroke patients who are bedridden, malnourished, infected and incontinent. Bed sore causes pain, increasing spasticity and slowing the recovery. Immobile patients should be examined regularly to identify early signs of pressure damage (skin redness). The most important measure in preventing pressure sores is to relieve the pressure on the tissues by regular turning of the patients. Space-occupying brain edema is a main cause of early deterioration and death in patients with large supratentorial infarcts. Life-threatening brain edema usually develops between the 2nd and 5th day after stroke onset, but up to a third of patients can have neurological deterioration within 24 hours after symptom onset. Elderly indiviuals with pre-existing cortical atrophy tolerate brain edema quite well. Younger patients with extended early infarct signs in CT, are at higher risk of deterioration from brain edema. Medical therapy in patients with large space-occupying
infarctions threatened to transtentorial herniation includes head positioning at an elevation of up to 30°, fluid restriction to 1-1.5 liter per day and a bolus of 1 g/kg manitol with a maintaining dose of 0.25-0.5 g/kg every 4-6 hours. Manitol should be used for few days with restricted water intake. Corticosteroids do not appear to improve outcome in survivors of acute cerebral infarction even with massive cerebral edema. We do not use dexamethasone for patients with ischemic stroke unless in patients with suspected inflammatory vascular disorders, i.e. giant cell arteritis, systemic lupus erythematosus, polyarteritis nodosa and primary cerebral angitis. Studies of corticosteroids in ischemic and hemorrhagic stroke patients have shown a significant excess of infections and hyperglycemia in corticosteroid treated patients. When seizures occur in the acute phase of stroke, diazepam (10-20 mg, 5 mg/min) followed by rapid loading phenytoin (10-15 mg/kg) is the treatment of choice following by maintenance dose of phenytoin 5 mg/kg/day.

**Management of hypoxia**

Identification and treatment of hypoxia is believed to be important in individuals with extensive brain stem or hemispheric stroke, seizure activity, or complications such as pneumonia, cardiac failure, pulmonary embolism. Airway support and ventilatory assistance are recommended for the treatment of patients with acute stroke who have decreased consciousness or who have bulbar dysfunction causing compromise of the airway. Maintaining adequate tissue oxygenation is of great importance during periods of acute cerebral ischemia in order to prevent hypoxia and potential worsening of the neurological injury. The most common causes of impaired oxygenation are partial airway obstruction, hypoventilation, aspiration pneumonia and atelectasis. Patients with decreased level of consciousness or brainstem stroke have an increased risk of airway compromise due to impaired oropharyngeal mobility and loss of protective reflexes. In general, the prognosis of patients who need endotracheal intubation is very poor. There is general agreement for airway support and ventilatory assistance in the treatment of stroke patients who have depressed level of consciousness or airway compromise and supplement of oxygen to hypoxic patients. Indications for endotracheal intubation in stroke patients include; PO$_2$<50-60 mmHg, PCO$_2$>50-60 mmHg, vital capacity<500-800cc, tachypnea >30/min, recruitment of accessory muscles, respiratory acidosis, high risk of aspiration and loss of maintaining stable airways. When consciousness is reduced, patients may be hypoventilated, thus raising the
arterial PCO$_2$, which is a potential vasodilator. The potential importance of vascular congestion in these patients can be shown by the use of mechanical hyperventilation in rapidly reducing ICP. Hyperventilation causes an almost immediate decrease in ICP but the peak decrement occurs 30 minutes after the arterial PCO$_2$ is reduced. The initial acute reduction in arterial PCO$_2$ of 5-10 mmHg often reduces ICP by 25-30%. The PCO$_2$ should be kept between 25-35 mmHg$^{147}$. Blood gases should be monitored in patients with reduced consciousness. The ICP-reducing effect of hyperventilation is temporary and lasts only 1-2 days. A rebound phenomenon may be seen if normoventilation is resumed too rapidly. Mechanical hyperventilation is not a routine therapeutic procedure for decreasing ICP. Pneumonia occurs in up to one-third of stroke patients and is associated with increasing morbidity and mortality. Major contributing factors for pneumonia include dysphagia, impaired gag or cough reflexes, impaired cognitive function, immobility, expiratory muscle weakness, and decreased level of consciousness$^{147}$. Pulmonary embolism is the cause of death in up to 20% of stroke patients. Sudden onset of chest pain and dyspnea occurs in 70-80% of these cases. Tachypnea is a sensitive sign. Hemoptysis, hypotension and agitation, cyanosis and decreased consciousness are other manifestations of pulmonary embolism. Arterial blood gases, chest X ray, chest perfusion CT, ECG and color doppler of leg veins are indicated in these patients. Arterial gasometry shows decreased O$_2$ saturation as low as 60%, PO$_2$ as low as 25-30 mmHg, PCO$_2$ up to 80 mmHg. Although these findings are not specific for pulmonary embolism, but in a stroke patient with sudden onset of chest pain and dyspnea are a clear indication for heparin therapy, even in the absence of confirmation in perfusion chest scan. In an ischemic stroke patient with signs of Deep Venous Thrombosis (DVT) and sudden onset of chest pain and dyspnea, intravenous heparinization should be started 24000 U/day, even without gasometry and followed with warfarin for 3 months. Most symptomatic pulmonary embolism arise from previously subclinical DVT.

**Management of feeding and defecation disturbances**

Patients should be sitted during swallowing$^{12}$. In general, enteral feeding should be started as soon as possible. Bedside swallowing assessment is routinely done for every stroke patient by a clinician. The gag reflex should not be used to assess swallowing function because it is not a reliable sign. Frequent oral suction is needed in patients with swallowing disturbance, i.e. patients with wallenberg syndrome$^{148}$. After the bedside swallowing
assessment, patients are classified as either safe to swallow or not, and this must be communicated clearly to the patient, relatives and staff. NG tube should be placed in patients with depressed level of consciousness or impaired swallowing test. Liquid feeding via NG tube is started at 10 mL per hour and increases every 4 hours up to 70 mL/hour. Patients with wallenberg syndrome have severe and often permanent dysphagia. In these cases endoscopic gastrostomy may be required. Avoidance of constipation by ensuring adequate intake of fluid and fiber is the best approach, but laxative, suppositories and occasionally enemas are required in constipated patients. A low-residue diet reduces bulk and patients on these diets do not need bowel movements so often. Diarrhea may occur with various tube feedings because of their hypertonicity or content of poorly digestible substances such as lactulose and long chain fatty acids. Often a change in feeding formula is all that is required.

**Management of fever**

Increased body temperature in the setting of acute ischemic stroke has been associated with poor neurological outcome. Fever is quite common after stroke and its treatment depends on the cause. The usual causes of fever in these patients are stroke complications, i.e. aspiration pneumonia, urinary tract infection, DVT, pressure sores, infected intravenous access site. The effect of stroke itself (central fever), preceding infections (infective endocarditis, encephalitis, arteritis) and drug allergy are other causes of fever in these patients. Treating sources of fever, usually aspiration pneumonia and urinary tract infection, by appropriate antibiotics and also use of antipyretics are indicated in febrile stroke patients. There are insufficient data about the usefulness of induced hypothermia in stroke patients to recommend this treatment.

**Management of urinary incontinence**

Pulpation of the patients pelvic on admission and later is important to exclude a distended bladder. The most common causes of bladder dysfunction after stroke is detrusor hyperreflexia and impaired sphincter control as a direct result of the stroke, inability to communicate, immobility and impaired consciousness, urinary tract infection and prestroke bladder outflow obstruction. In stroke patients with urinary retention intermittent catheterization (every 6-8 hours) is necessary. Permanent catheterization of incontinent patients should be limited to the first days of hospitalization. Condom drains for males and napkins for females has less chance of urinary
tract infection than permanent catheterization. Treatment of urinary tract infections with antibiotics should be reserved for patients with symptomatic infections. Because incontinence of urine frequently resolves spontaneously during the first week or two after stroke, it is important to remove the catheter for a trial of voiding and re-assessment of bladder function as soon as the patients condition begins to improve.

**Management of depression**

About one-third of the stroke victims show signs of depression. Depression is often early onset and temporary. Post-stroke depression is associated with poor rehabilitation results and ultimately poor outcome. Degree of disability and location of the vascular lesion are effective in making depressed patients. Predictors of post-stroke depression in the rehabilitation setting include increasing physical disability and cognitive impairment. Nortriptyline is a good choice for managing depression of these patients. Antidepressant drugs such as selective serotonin reuptake inhibitors and heterocyclics can also improve mood after stroke.

**Antithrombotic therapy in acute stroke**

Aspirin may act in several ways to reduce the volume of brain tissue damage by ischemia. It may prevent distal and proximal propagation of arterial thrombus, prevent re-embolization, prevent platelet aggregation in the microvasculature and reduces the release of thromboxane and other neurotoxic eicosanoids. Platelets are probably involved in the process of atherogenesis in arterial wall. Aspirin therapy in acute stroke patients reduces recurrent ischemic events during treatment period by 30%, avoiding 7 events per 1000 treated patients. Aspirin appeared to be of net benefit among the 9000 stroke patients randomized without a prior CT brain scan without unusual excess of hemorrhagic stroke. Moreover among 800 patients who inadvertently been randomized after a hemorrhagic stroke, there was no evidence of net hazard (further stroke or death, 63 Aspirin vs 67 control). All patients with suspected ischemic stroke should receive early aspirin therapy unless there is a clear contraindication and this should be continued for 2 weeks before changing the patient to a maintenance dose of 80-100 mg/day. Early aspirin therapy does not lead to excess of hemorrhagic infarction. If CT scanning is not immediately available and the clinician feels on clinical grounds that the patient is unlikely to have a hemorrhagic stroke then aspirin can be started. The use of clopidogrel, dipyridamole, or combinations of oral antiplatelet agents in
acute ischemic stroke has not been evaluated. In patients with suspected acute cardioembolic or atherothrombotic stroke, there is no evidence to support the routine use of immediate anticoagulation because the risk of hemorrhagic complications cancel out the benefits of fewer recurrent ischemic strokes, DVT and pulmonary embolism. Subcutaneous unfractionated heparin at low or moderate doses, e.g. enoxaparin have failed to show an overall benefit of anticoagulation when initiated within 24 to 48 hours from stroke onset. Improvements in outcome or reductions in stroke recurrence rates were mostly counterbalanced by an increased number of haemorrhagic complications. Aspirin therapy is a safe and effective alternative to anticoagulation which reduces the risk of early recurrent stroke even in patients with acute ischemic stroke and atrial fibrillation.

Aspirin is likely to be adequate thromboprophylaxis for patients at low and moderate risk of DVT and pulmonary embolism. For patients at high risk of DVT (i.e. severe hemiplegia and bedridden, depressed consciousness, previous history of DVT and other venous thrombosis, presence of thrombophilia) graded compression stockings and low dose subcutaneous heparin (5000 units twice per day) are recommended. We encourage the patients to flex and extend the knees and ankles throughout the day.

Management of hypertension in acute stroke

Half of the stroke patients are hypertensive before onset of stroke. These patients will tend to have higher blood pressure than those without previous hypertension. Elevated blood pressure can result from stress of the stroke, a full bladder, pain, pre-existing hypertension, or increased intracranial pressure. Aggressive treatment of hypertension could be detrimental because of secondary reduction of perfusion in the area of ischemic penumbra which could expand the size of the infarction. Decrease in blood pressure may promote irreparable injury of the tissue at risk. On the other hand, untreated elevated blood pressure may precipitate hemorrhagic transformation of brain infarction, worsen edema and lead to hypertensive encephalopathy. Current policy is not to initiate new antihypertensive therapy for the first 7 days after stroke. Situations that require urgent antihypertensive therapy include hypertensive encephalopathy (seizures and depressed consciousness), acute renal failure (with microscopic hematuria and proteinuria), acute pulmonary edema, acute myocardial infarction, severe hypertensive retinopathy (papilledema, retinal hemorrhage and exudates), left ventricular failure (clinical and TTE evidence) and aortic dissection. The consensus based on the guidelines of American and European stroke associations is that
antihypertensive agents should not be used in acute stroke patients unless the diastolic blood pressure is >120mmHg or the systolic blood pressure is>220mmHg. When treatment is indicated, lowering the blood pressure should be done cautiously. Parenteral agents such as labetolol that are easily titrated and have minimal vasodilatory effects on cerebral vasculature are prefered. In some cases, an intravenous infusion of sodium nitroprusside may be necessary for adequate blood pressure control. Patients can be treated with oral agents such as captopril, enalapril and triamteren H. Oral or sublingual nifedipine had been the most widely used antihypertensive medication for acute stroke patients. Although it is effective, rapid absorption, difficulty in estimating its therapeutic effects and frequent secondary precipitous decline in blood pressure due to its overshout makes unwise its general using. Excessively high blood pressure is associated with parenchymal hemorrhage among patients who are candidates for treatment with thrombolytic agents. Careful management of blood pressure is critical before and during the administration of rTPA and during the next 24 hours. Thrombolytic therapy is not given to patients who have a systolic blood pressure >185 mmHg or a diastolic blood pressure >110 mmHg at the time of treatment. It is recommended that blood pressures of 185/110 mmHg or higher is lowered before thrombolysis. The titrable and rapid acting labetolol, nitroprusside and diazoxide are not routinely available in neurologic emergency divisions of Iran and other deveping countries. Blood pressure of acute stroke patients is not well monitored in most of these patients in developing countries and may reach above 220/120 mmHg cutoff points leading to organ damage. Therefore, cutoff levels of 180/100 mmHg for management of hypertension seems to be appropriate in Iran and other deveping countries. However, the approach to elevated blood pressure according to the American and European stroke associations guidelines is presented below.

Patients are categorized as below groups.

1. Patient is not eligible for thrombolytic therapy
   A. If Systolic Pressure (SP) is <220mmHg or Diastolic Pressure (DP) is <120mmHg, then observe the patient unless end-organ damage occurs.
   B. If SP >220 or DP >120<140mmHg, then prescribe Labetolol 10-20 mg intravenous over 1-2 min, may repeat or double every 10-20 min (maximum dose is 300mg/day).
   C. If DP is >140mmHg, then prescribe Nitroprusside 0.5 microgram/kg/min IV infusion as initial dose with blood pressure monitoring, aimed for 10-15% reduction of blood pressure.
2- Patient is eligible for thrombolytic therapy
Pretreatment with rTPA;
A. If SP is >185mmHg or DP is >110mmHg, then prescribe
Labetolol 10-20 mg intravenously over 1-2 min, may repeat one time. If
blood pressure is not reduced or maintained at desired levels (SP <185 and
DP <110mmHg) do not administer rTPA.
B. If SP is <185 and DP is <110mmHg, do nothing and give rTPA
During and after thrombolytic treatment;
A. If SP is >180 or DP is >105mmHg, then prescribe
Labetolol 10-20 mg intravenous over 1-2 min, may repeat or double
every 10 min (maximum dose is 300mg/day).
B. If DP is >140mmHg, prescribe nitropruside 0.5 microgram/kg/min IV
infusion as initial dose with blood pressure monitoring, aimed for 10-15%
reduction of blood pressure.

Very low blood pressure in stroke patients may be the consequence of
co-morbidity, i.e. heart failure, dehydration and hypovolemia. The later is
the most frequent problem and patients usually improve with intravenous
fluids. Obviously, it is important to exclude cardiac failure and acute
myocardial infarction, before giving fluids in this way.

**Worsening after Ischemic Stroke**

Causes of worsening after ischemic stroke include3,6,11,12:
1- progression of stroke, 2- early recurrence of stroke, 3- development of
the huge edema around the infarct, 4- obstructive hydrocephalus or brain
stem compression in patients with cerebellar infarctions, 5- incorrect diagnosis
(tumor, abscess, encephalitis), 6- epileptic seizures, 7- infections (respiratory,
urinary, septicemia), 8- metabolic disorders (hypo or hyperglycemia,
electrolyte disturbances), and 9-drugs (sedatives, opiums). Prognosis in a
patient with sever stroke is worse than a patient with mild to moderate
stroke complicated with infection, seizure and metabolic problem. Sever
concurrent illness or stroke complications may make a stroke appear much
worse than it really is, i.e. a patient with a pure motor stroke (lacunar
syndrome) and a sever chest or urinary tract infection may be drowsy or
confused1. Of course, an infection is more easily treated than a large volume
of necrotic brain, so with appropriate therapy the prognosis of the two
patients may be quite different. A through general examination will identify
signs such as fever, confusion, increased respiratory rate, crackle, purulent
urine and usually indicate any relevant co-existing disorder1. Simple
investigations such as WBC, ESR, urea, electrolytes, urine microscopy and
culture, chest X ray, ECG, blood culture are useful not only to identify the cause of stroke but also to alert one to serious co-existing disease. Seizures occurring in acute phase of stroke make the assessment of stroke severity difficult and should be treated. Decreased conscious level may be due to metabolic disorders, using sedative drugs and opioids. Very old patients with pre-existing brain atrophy tolerate ischemic brain edema or intracerebral hemorrhage better than younger patients without brain atrophy.

**Anticoagulation in patients with acute cardioembolic stroke**

A meta-analysis restricted to patients with acute cardioembolic stroke showed that anticoagulation given within 48 hours of clinical onset was associated with a non-significant reduction in recurrence of ischemic stroke, but no substantial reduction in death or disability. Despite this lack of evidence, some experts recommend full-dose heparin in selected patients, such as those with a high risk cardiac sources of re-embolism, arterial dissection or high-grade arterial stenosis prior to surgery. Contraindications for heparin treatment include large infarcts, e.g. more than half of MCA territory and uncontrollable arterial hypertension. Patients with cardioembolic stroke are at high risk of cerebral hemorrhage on early anticoagulation if there is infective endocarditis, large cerebral infarct with midline shift, major hemorrhagic transformation on brain CT and severe uncontrolled hypertension. We are not usually worried about early recurrent ischemic stroke because the risk is low, 3.5% within 30 days and 0.5% per day in first 3 days post stroke. Even in fibrillating patients the risk of recurrence is not much higher. It is prudent to withhold warfarin in patients with large brain infarcts or uncontrolled hypertension until about 10-14 days after the stroke. For patients at high risk for recurrent embolization, i.e. patients with mechanical heart valve, intracardiac thrombus, atrial fibrillation with mitral stenosis, congestive heart failure, and acute anterior myocardial infarction early anticoagulation is indicated when a large or hemorrhagic arterial infarction is ruled out 2 days after stroke onset by performing CT. Ten to 14 days after stroke is a suitable time of beginning anticoagulation therapy in stroke patients with a large or hemorrhagic infarction. Therapeutic decision for anticoagulation of acute stroke patients with a very high risk cardiac source of embolism, e.g. pediculated mobile intracardiac thrombus is challenging in patients with large or hemorrhagic infarction. The author recommends enoxaparin 1mg/Kg/day subcutaneously in these challenging cases. Management with low dose 15000Units/day subcutaneous heparin is
also sufficient to activate antithrombin III and prevention of clot formation. However its to low to prolong PTT or clinically produce apparent bleeding. This type of anticoagulation does not accentuate petechial hemorrhagic transformation which is usually a silent clinical event. In cases of neurologic worsening, heparin should be stopped completely if CT shows hemorrhagic transformation of brain infarct resposible for clinical worsening. Therapeutic approach for anticoagulation of cardioembolic acute stroke patients who have been on warfarin therapy is similar to other patients who have not been receiving warfarin as explained above. Ultimately, the decision is determined by a balance between the risk of hemorrhagic transformation of the infarct and the risk of re-embolization from the heart. Therapy with intravenous heparin should not be prescribed before exclusion of hemorrhagic transformation or intracerebral hemorrhage. The presence of unruptured aneurysm is not considered as contraindication for anticoagulant therapy in patients who have the indication.

**Anticoagulation in patients with progressive stroke and crescendo TIAs**

Neurological deficits of ischemic stroke are frequently unstable during early phase of stroke. Patients may show progressive deterioration with stepwise or nonstepwise fashions or fluctuations with periods of improvement. In progressive stroke (PS), the focal ischemia worsens over several hours, or a day or two. Thus, stepwise deterioration is continued for several hours up to 2 days in PS. Stroke in evolution is a non-specific term and is not synonymous with thrombosis in evolution. Almost 30% of stroke patients worsen after entry to the hospital. Intravenous heparin followed by warfarin is frequently prescribed in patients with PS. This practice has been based on incomplete and largely anecdotal data. Progression of stroke in a stepwise fashion is easier to regard as stroke due to repeated episodes of thromboembolism than is an indolent PS. Patients exhibiting stepwise progression may speculatively be considered as likely to benefit from anticoagulation. Conversely, patients who are adding to their neurologic deficit in a nonstepwise progressing fashion probably are not exhibiting progressive thrombus formation and will not be expected to respond to anticoagulation. Brain edema accounts for most of the progression in the later situation. Accumulation of excitatory neurotoxins and edema probably accounts for most of the progression in this common situation. PS patients exhibiting stepwise progression may be considered to benefit from short term (3-5 days) intravenous 24000 U/day heparinization. Basilar artery thrombosis with stepwise progression has
better response to heparin therapy. Immediate intravenous heparinization in patients with BA thrombosis and without hemorrhagic transformation may be effective. Multiple or Crescendo Transient Ischemic Attacks (CTIA) are frequent in clinical practice. The term CTIA is defined as occurrence of multiple episodes over a few hours or days, often with increasing duration or severity. Some studies suggest that CTIA may represent a condition of impending brain infarction. Common practice of medicine recommends short term anticoagulation in patients with CTIA without proven efficacy. In patients with CTIAs secondary to atherothromboembolism or cardiogenic embolism short term (3-5 days) treatment with intravenous 24000 U/day heparin is advisable. CTIA and major TIA require urgent evaluation and admission of the patient. In patients with CTIA or progressive stroke, an urgent CT scan should be performed to identify the presence of intracerebral hemorrhage or severe edema. Consecutive patients with PS and CTIA admitted in Ghaem hospital, Mashhad during 2007-2008 enrolled in a prospective observational study. PS was defined as stepwise or fluctuated worsening of focal neurologic deficits over several hours, or a day or two. These deficits could increase in severity, extent or number. CTIA was defined as two TIAs within 24 hours, three TIAs within 3 days or 4 TIAs within 2 weeks. These crescendo attacks often are increasing in duration and in severity of deficit. Patients with CTIA were evaluated for presence of motor, sensory, aphasic and amaurotic disturbances. Consecutive patients with PS and CTIA underwent intravenous heparin therapy 1000 units per hour for 3 days without an initial bolus dose. PS Patients with coma, dense hemiplegia or extensive signs of ischemia in the initial CT (more than one-third of a hemisphere) were excluded. PS and CTIA patients with a contraindication of anticoagulation therapy were excluded. Antiplatelet drugs and warfarin were not administered during intravenous heparinization in this 3 days. A brain CT was done for exclusion of intracranial hemorrhage before initiation of heparin therapy in all of these patients. Prothrombin Time, Partial Thromboplastin Time and International Normalized Ratio were evaluated before anticoagulation therapy and thereafter one time per day during heparin therapy. PS and CTIA patients who had an initially abnormal coagulation tests were excluded. Short term intravenous heparin therapy in these patients is a routine therapeutic strategy in our institution. PS and CTIA patients with a contraindication of intravenous heparin therapy administered aspirin 80 mg per day during hospitalization period. The National Institute of Health Stroke Scale (NIHSS) was detected in all of
patients with PS and CTIA before heparinization and 3 days later\textsuperscript{12}. The clinical course of these patients was categorized as improvement, stabilization and deterioration\textsuperscript{12,44}. Improvement was defined as \( \geq 3 \) points decrease and deterioration as \( \geq 3 \) points increase in the second NIHSS\textsuperscript{11,12,44}. Other patients were assumed as stabilization group\textsuperscript{11,12,44}. The same NIHSS assessment was performed in PS and CTIA patients who have taken aspirin therapy\textsuperscript{11,12,44}. Presence of stroke at 3 days after anticoagulation therapy was evaluated in all of our patients with PS and CTIA. All of these patients had a repeated CT after anticoagulation therapy for investigation of a visible infarct. A residual stroke was defined as presence of ischemic focal neurological deficit lasting more than 24 hours or observation of a hypodense lesion in the CT corresponding to the manifestations\textsuperscript{12}. 170 patients (103 males, 67 females) with mean age 60.4\( \pm \)12.3 years developed PS. 141 PS patients (84 males, 57 female) underwent short term intravenous heparin therapy and and 29 PS patients(19 males, 10 females) received aspirin 80 mg per day\textsuperscript{151}. Assessment of early stroke course in two therapeutic groups of our PS patients is presented in Figure 1.

![Figure 1: Comparison of early PS course in two therapeutic groups](image-url)

Frequency rate of subtypes of early stroke course was significantly different in our two therapeutic groups of PS patients; \( X^2=10.487, \, df=2, \, p=0.005 \). the influence of gender on early course of PS was not significant in the heparin and aspirin therapeutic groups; \( X^2=0.063, \, df=2, \, p=0.969 \) and \( X^2=0.021, \, df=2, \, p=0.990 \) respectively\textsuperscript{151,152}. 119 PS patients including 68.1\% of heparin and 79.3\% of aspirin groups developed a residual stroke. Distribution of residual stroke was not significantly different in our two therapeutic groups of PS patients; \( X^2=1.443, \, df=1, \, p=0.23, \, OR=0.557 \) (0.212-1.462). Distribution of residual stroke based on the gender was not
significantly different in PS patients who received short term intravenous heparinization; $X^2=0.089$, df=1, p=0.766, OR=1.11 (0.543-2.29)\textsuperscript{151,152}. Difference in frequency of residual stroke based on the gender was not significant in PS patients who underwent aspirin therapy; $X^2=df=1$, p=0.947, OR=0.938 (0.140-6.28)\textsuperscript{151,152}. A residual stroke developed in 30% of improvement, 100% of stabilization and 100% of deterioration courses among 170 PS patients. 88 patients (50 males, 38 females) with mean age 60.1±6.8 years had CTIA. 64 patients (36 males, 28 females) with CTIA underwent short term intravenous heparinization and 24 CTIA patients (14 males, 10 females) received aspirin 80 mg per day\textsuperscript{151,152}. Difference in distribution of residual stroke in two therapeutic groups of CTIA patients was not significant; $X^2=1.01$, df=1, p=0.315, OR=0.612 (0.24-1.587). The effect of gender on frequency of residual stroke in CTIA patients who received short term intravenous heparinization was not significant; $X^2=0.367$, df=1, p=0.545, OR, 0.734 (0.27-1.997)\textsuperscript{151,152}. Distribution of residual stroke was not significantly different based on the gender in CTIA patients who received aspirin therapy; $X^2=0.12$, df=1 , p=0.729, OR=1.33 (0.261-6.801). Frequency of early clinical course in two therapeutic groups of CTIA patients was significantly different; $X^2=6.72$, df=2, p=0.035. Distribution of early clinical course was not significantly different based on the gender in CTIA patients who received short period intravenous heparinization and aspirin therapy ($X^2=0.12$, df=2 , p=0.941) and ($X^2=0.171$, df=2 , p=0.918) respectively\textsuperscript{151,152}.

Figure 2 illustrates early clinical course of 88 CTIA patients in our two therapeutic groups.
Motor, sensory, aphasic and amaurotic manifestations were found in 48%, 19%, 15% and 2% of our CTIA cases respectively. Two PS and one CTIA cases had minor hemorrhagic complications of intravenous anticoagulation including ecchymosis and hematuria \(^{151,152}\).

Controlled clinical trials performed more than 30 years ago suggested a beneficial effect of anticoagulation therapy in PS patients \(^{11,148,149}\). Based on the results of these trials, the indication for heparin therapy in this condition became widely accepted \(^{148,149}\). Other randomized and observational studies have not been conclusive in regard to the indication of anticoagulation in PS \(^{154}\). The data in aggregate suggested that heparin reduces the risk of PS \(^{11,149,154}\). The lack of precise criteria for entry and outcome, non-blinded observation and small number of patients makes these studies inadequate by current methodological standards \(^{11,12,154,155}\). Use of heparin in PS patients is still a matter of controversy in recent years \(^{156}\). The main reason that 72 hours was selected as cut off point in assessment of our patients is that progression period in usually completed in 72 hours \(^{149}\). At the other side, some of these patients are practically discharged in 3-4 days after anticoagulation therapy and extension of hospitalization time only for research is not possible ethically. Although short term intravenous heparinization demonstrated non significant influence on development of residual stroke in our PS patients, however it has confirmed a significant influence on early stroke course in PS patients \(^{151,152}\). PS patients who have been on short period intravenous heparinization had significantly more probability for improvement and less probability for deterioration \(^{151,152}\). Heparin is widely used for clustering or CTIA \(^{11,12}\). This therapeutic strategy for CTIA has been largely for theoretical reasons and by extrapolation from the results of studies of anticoagulation for PS \(^{11,12,148,149}\). Although heparin appears to be the preferred treatment for CTIA, the data supporting its efficacy are meager and come from old and limited studies \(^{156}\). However, intravenous heparinization has been shown to be a safe therapy in these cases \(^{156}\). Despite reports of safety in administration of bolus of intravenous heparin while initiating heparin therapy \(^{157}\), bolus dose of heparin was not administered in our PS and CTIA patients and none of them developed major hemorrhagic complications \(^{151,152}\). There remains relatively evidence-free practice of using heparin in patients with CTIA \(^{156}\). Although short period intravenous heparinization was associated with a non significant effect on development of residual stroke in our CTIA patients, however our CTIA patients who have been on this therapy had significantly more probability of improvement and less probability of deterioration in their early clinical
course evaluation. Common practice of neurologists in regard to using heparin in patients with PS and CTIA is different. United States neurologists are significantly more likely than Canadian neurologists to use intravenous heparin in PS and CTIA patients (51% versus 33%) and (47% versus 9%) respectively. The main reason of this difference is the effect of medicolegal factors on the neurologists. Up to date therapeutic guidelines of American and European stroke associations do not recommend short term intravenous anticoagulation in PS and CTIA patients. This management is recommended in textbooks of cerebrovascular disease and is the routine therapeutic strategy in our department. It is not ethically possible to compare heparin with placebo in the PS and CTIA patients. Thus we compared heparin therapy with ultra low dose of aspirin. Although our clinical study suggests using intravenous heparinization in PS and CTIA patients, however randomized and double blind clinical trials is recommended in this concept. If repetition of TIAs persists despite optimal management, underlying causes such as arteritis that responds to steroids or vasospasm appearing with transient monocular blindness, that responds to calcium channel blockers should be considered. Other possible causes of recurrent focal neurological disturbances, i.e. migraine aura, epilepsy, tumor attacks, AVM and episodes of hypoglycemia should be excluded in this circumstances. The empirical treatment for patients in whom a thrombus is radiologically visible in an extracranial artery is 4-6 weeks anticoagulant therapy. Patients with intra-arterial mural thrombus confirmed by MRI/MRA or catheter angiography should be managed like extracranial arterial dissection.

**Anticoagulation in patients with extracranial arterial dissection**

Intravenous 1000Units/hour heparin therapy following with warfarin keeping INR 2-3 is a standard treatment in patients with extracranial dissection. Anticoagulation may prevent occlusion of the stenotic vessels and distal embolization. Anticoagulation does not increase the extent of dissection in these patients. There is no difference between dissection of the anterior and posterior circulation in management with anticoagulants. The usual time for anticoagulation therapy is 12 weeks and follow up ultrasound, MRA or CT angiography in 6 and 12 weeks will guide physicians in this regard. Oral anticoagulation is continued in patients with dissected patent arteries until luminal stenosis improves to the point that flow is not significantly obstructed, thereafter antiplatelet drugs is substituted. If dissection has resolved with smooth
lumen, warfarin is discontinued. If there is persisting severe luminal stenosis and irregularity, warfarin therapy is continued. If there is persisting complete occlusion with a smooth lumen at its origin and terminus antiplatelets are substituted. Anticoagulants could be stopped after 6 weeks in patients with dissected arteries that remain occluded. Antiplatelet drugs may be used if oral anticoagulation is not feasible after heparinization.

**Anticoagulation in patients with CVT**

Patients with CVT with or without venous infarctions who are treated with heparin have a lower mortality rate and disability than those not treated with heparin. Patients with hemorrhagic venous infarction do not seem to be worsen or developing new hemorrhagic changes after institution of anticoagulants. Seventy percent of CVT patients with hemorrhagic venous infarction or focal venous subarachnoid hemorrhage have an improvement course and 25% of them have stabilization course during anticoagulation despite presence of intracranial hemorrhage. Therefore, presence of a hemorrhagic venous infarction or focal venous subarachnoid hemorrhage in patients with CVT is not a contraindication for anticoagulation therapy. In admitted patients with CVT, early anticoagulation with intravenous heparin 1000 Units/hour following with warfarin (INR 2-3) before thrombus spreads to cortical veins is recommended. Oral anticoagulation is recommended for 3-6 months in CVT patients with a transient risk factor such as OCP consumption or periperal period. Longer duration of anticoagulation is recommended for other CVT patients. Enoxaparin 1 mg/Kg /every 12 hours SC is a good alternative and is as effective as intravenous heparinization in CVT patients. Enoxaparin 1 mg/Kg/every 12 hours SC is especially recommended in patients with venous hemorrhagic infarction and focal subarachnoid hemorrhage. Follow up MRI/MRV after 3 months and 6 months for observing recanalization of the dural sinus is a useful guide for determining duration of anticoagulation. If the affected sinus is opened anticoagulation is discontinued. If there is still stenosis or occlusion with hypercoagulable state, anticoagulation is continued. If there is stenosis or occlusion without hypercoagulable state, warfarin could be replaced with aspirin. Interventional thrombolysis have been used experimentally in some deteriorating patients with CVT who do not response to anticoagulation. Antibiotics and surgical drainage of paranasal sinus, middle ear or mastoid infections remains the most important treatment in patients with septic dural sinus thrombosis. Anticonvulsants are used in
venous infarctions with seizure. Diuretics, acetazolamide and dexamethasone are used in CVT patients with raised ICP. CVT patients with pseudotumor cerebri syndrome can usually be managed using therapeutic lumbar puncture.

**Anticoagulation therapy of hemorrhagic Cerebral Venous Thrombosis (CVT)**

Some physicians may fear of clinical deterioration and legal complications of anticoagulation therapy in CVT patients who have hemorrhagic venous infarctions or focal venous Subarachnoid Hemorrhage (SAH). CVT is sometimes a diagnostic and therapeutic challenge. There are several rationales for anticoagulation therapy in CVT: To prevent thrombus growth, to facilitate recanalization, and to prevent deep vein thrombosis. Controversy has ensued because cerebral venous infarction with hemorrhagic transformation or intracerebral hemorrhage is commonly present at the time of diagnosis of CVT and it may complicate treatment. One-third of patients with CVT present with intracerebral hemorrhage or hemorrhagic venous infarcts. Hemorrhage on CT is among predictors of bad outcome of CVT patients. Isolated SAH may also occur rarely due to CVT. In the special situation of CVT with cerebral hemorrhage on presentation, the clinician must balance the risks and benefits of anticoagulation. This subgroup of CVT patients can be target for new therapeutic strategies. Consecutive CVT patients with hemorrhagic venous infarction or SAH admitted in Ghaem hospital, Mashhad enrolled a prospective observational study during 2006-2011. The diagnosis of CVT in suspected cases was confirmed by MRI/MRV, CT angiography and catheter angiography following established diagnostic criteria. Venous thrombus frequently appears as isointense in T1 and hypointense in T2 weighted images in the first week. By the second week it appears as hyperintense in both T1 and T2 weighted images. Absence of flow void with alternation of signal intensity in the dural sinus is the principal early sign of CVT in MRI. MRV was done in all of the cases to define the extent of CVT in MRI positive cases and rule out of CVT in MRI negative cases. Cerebral angiography and CT angiography was done in selected situations in which MRI/MRV results are inconclusive. Patients with high clinical suspicion of CVT and negative MRI/MRV results underwent serial MRI/MRV. Demographic data, clinical manifestations from onset to end of observation period, location of thrombus, location and size of infarction and hemorrhage, imaging method used and clinical course during treatment were recorded. Early hemorrhage was defined as any
hemorrhagic transformation of venous infarction present on CT or MRI at time of diagnosis. Delayed hemorrhage was defined as any hemorrhagic transformation of venous infarction or SAH that was not present on CT or MRI scan at time of diagnosis but occurred later or new hemorrhage located elsewhere later. The choice of the treatment was left to the opinion of the treating physician. CVT patients in our institution were routinely administered adjusted dose heparin with continuous intravenous infusion to achieve an activated partial thromboplastin time twice the pretreatment value. Clinical course during 1 week of treatment was assessed based on the modified NIHSS score (see chapter VIII). Three or more points decrease or increase of modified NIHSS after 1 week of treatment was considered as improvement or deterioration courses respectively. Other clinical courses were categorized as stabilization. Clinical course of hemorrhagic CVT patients who received other methods of anticoagulation treatment was also recorded. Outline of the venous infarction was carefully determined in the brain MRI by using a point grid. Subsequently, the surface area of infarct was manually calculated, based on square millimeter. Size of venous infarctions was categorized as \( \geq \frac{1}{3} \) and \( \geq \frac{2}{3} \) of cerebral hemisphere. The extension of hemorrhagic transformation within venous infarction was also categorized as \( \geq \frac{1}{3} \) and \( \geq \frac{2}{3} \) of infarct area. All of the CVT patients underwent a standard battery of diagnostic investigations for determination of the cause of their CVT. Fifty two hemorrhagic CVT patients (40 females, 12 males) with mean age 38.6±8 years were prospectively investigated. Fourty seven patients had hemorrhagic venous infarction, 5 cases had isolated focal venous SAH and 16 had both hemorrhagic venous infarction and SAH. Improvement, stabilization and deterioration constituted 65.4%, 23.1% and 11.5% of clinical courses in these 52 cases respectively. Brain CT, MRI and MRV were done in all of the CVT cases. CT angiography and catheter angiography were requested in 3.8% and 3.8% of the patients respectively. The diagnosis of CVT was established by MRI/MRV in 92.3%, by CT angiography in 1.9% and by serial MRI/MRV in 5.8%. Among 84 hemorrhagic CVT patients in the acute phase; 52 patients (61.9%) were anticoagulated with adjusted dose intravenous heparin infusion, 13 patients (15.5%) received weight adjusted subcutaneous enoxaparin in therapeutic dose, 15 cases (17.9%) received either subcutaneous heparin or enoxaparin in prophylactic dose and 4 cases (4.8%) did not receive anticoagulation at all. Additional treatments included antiepileptic drugs (48.1%), acetazolamid (90.4%), steroid (76.9%), diuretics (90.4%) and decompressive craniotomy (3.8%). Decreased
consciousness, headache, seizure, weakness and aphasia were found in 55.8%, 96.2%, 48.1%, 32.7% and 7.7% of the hemorrhagic CVT patients respectively. Decreased consciousness had a significant effect in clinical course of the patients; $X^2=9.493$, df=2, p=0.009. The influence of headache, seizure, weakness and aphasia in clinical course of the patients were not significant; $(X^2=5.581, df=2, p=0.053)$, $(X^2=0.041, df=2, p=1)$, $(X^2=0.985, df=2, p=0.614)$ and $(X^2=0.844, df=2, p=1)$ respectively. The effect of gender on clinical course of our patients was not significant; $X^2=2.020$, df=2, p=0.347. Early hemorrhage constituted 92.3% of hemorrhagic CVT in our series. Patients with early pretreatment hemorrhage had a significantly better clinical course than patients with late hemorrhage; $X^2=7.604$, df=2, p=0.036. Presence of SAH had a nonsignificant effect on clinical course of our hemorrhagic CVT cases who underwent treatment with intravenous heparin; $X^2=0.304$, df=2, p=0.914. Table 17 represents statistical relation of imaging characteristics with clinical course of hemorrhagic CVT cases who received adjusted dose intravenous infusion of heparin.

Table 17: Relation of imaging characteristics with clinical course of hemorrhagic CVT cases who received adjusted dose intravenous infusion of heparin.

<table>
<thead>
<tr>
<th>Imaging Characteristic/Clinical course</th>
<th>$X^2$</th>
<th>df</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infarction $\geq 1/3$ hemisphere*</td>
<td>4.628</td>
<td>2</td>
<td>0.090</td>
</tr>
<tr>
<td>Infarction $\geq 2/3$ hemisphere*</td>
<td>5.867</td>
<td>2</td>
<td>0.044</td>
</tr>
<tr>
<td>Hemorrhagic transformation $\geq 1/3$ of infarct area*</td>
<td>4.616</td>
<td>2</td>
<td>0.137</td>
</tr>
<tr>
<td>Hemorrhagic transformation $\geq 2/3$ of infarct area*</td>
<td>3.445</td>
<td>2</td>
<td>0.143</td>
</tr>
<tr>
<td>Superior Sagital Sinus thrombus**</td>
<td>0.020</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Left Transverse Sinus thrombus**</td>
<td>1.362</td>
<td>2</td>
<td>0.628</td>
</tr>
<tr>
<td>Right Transverse Sinus thrombus**</td>
<td>1.797</td>
<td>2</td>
<td>0.479</td>
</tr>
<tr>
<td>Straight Sinus thrombus**</td>
<td>2.322</td>
<td>2</td>
<td>0.295</td>
</tr>
<tr>
<td>Multiple Sinus thrombus**</td>
<td>0.637</td>
<td>2</td>
<td>0.815</td>
</tr>
</tbody>
</table>

*: Within 47 patients with hemorrhagic venous infarction
**: Within 52 patients with hemorrhagic venous infarction or venous SAH

Among 47 patients with hemorrhagic venous infarction 91.4% had infarct in the anterior circulation, 4.3% had infarct in posterior circulation and 2.1% had mixed infarct localizations. Comparison of clinical course with four therapeutic groups revealed significant difference; $X^2=18.662$, df=6, p=0.007. Table 18 illustrates distribution of clinical course categories in different therapeutic groups of our hemorrhagic CVT patients.
Table 18: Distribution of clinical course categories in different therapeutic groups of our 84 hemorrhagic CVT patients.

<table>
<thead>
<tr>
<th>Therapeutic group/clinical course</th>
<th>Improvement</th>
<th>Stabilization</th>
<th>Deterioration</th>
</tr>
</thead>
<tbody>
<tr>
<td>adjusted dose intravenous infusion of heparin</td>
<td>36</td>
<td>10</td>
<td>6</td>
</tr>
<tr>
<td>weight adjusted subcutaneous enoxaparin</td>
<td>11</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>subcutaneous prophylactic heparin or enoxaparin</td>
<td>4</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>No anticoagulation therapy</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

Due to low number of hemorrhagic CVT patients who received other categories of anticoagulation strategy, the statistical analysis regarding relation of clinical and imaging characteristics with clinical course was only performed in patients who received routine adjusted dose intravenous infusion of heparin. Observational studies reported range of risks for ICH after anticoagulation for CVT from zero to 5.4%\(^1\). The outcome of CVT remains largely unpredictable. It is not unusual to see deeply comatose or severely hemiplegic patients recover dramatically, without any sequelae\(^12\). Conversely, a patient with headache as the only presenting symptom can suddenly worsen, with a dense hemiplegia if thrombus spreads from a sinus to a cerebral vein\(^12\). Interestingly, it is well established that clinical recovery starts much more rapidly than vessel recanalization and can occur even in the absence of recanalization\(^11\). Heparin has been widely used in hemorrhagic CVT as evidence has accumulated that it is both effective and safe\(^1,11\). Our study population is not representative of all CVT, but consists a subgroup of patients who have a higher risk for poor outcome when compared with CVT patients without hemorrhage. This selective evaluation of hemorrhagic CVT patients is an advantage of our study. Decreased consciousness and extension of infarction in more than two-thirds of a hemisphere had a significant effect in clinical course of the patients in our study. Our anticoagulated CVT patients with early pretreatment hemorrhage had a significantly better clinical course than patients with late hemorrhage. In general, limited data from randomized controlled clinical trials in combination with observational data on outcomes and bleeding complications of anticoagulation support a role for anticoagulation in treatment of CVT, regardless of the presence of pretreatment ICH and anticoagulation appears safe and effective\(^1,2,3,11,12\). Our observational therapeutic study showed safety of anticoagulation therapy and favorable clinical course in patients with hemorrhagic venous infarction or venous
SAH. Low dose anticoagulation therapy or no anticoagulation have shown worse outcome in our hemorrhagic CVT patients. One reason of this effect may be the bias created by items that prohibited treatment by standard dose of anticoagulation, e.g. extreme hemorrhage and mass effect of the infarction. Therefore, patients with hemorrhagic CVT without other contraindication for anticoagulation should be treated either with dose-adjusted intravenous heparin or body-weight-adjusted subcutaneous low molecular weight heparin (e.g. enoxaparin). In conclusion; acute intravenous anticoagulation therapy is safe in CVT patients with hemorrhagic brain infarction or focal SAH secondary to CVT. However, In CVT cases with massive hemorrhagic infarction or large SAH, the author recommends enoxaparin 1mg/kg/ every 12h SC. A more conservative method of treatment in these later high risk group could be enoxaparin 0.5mg/kg/ day SC or 10000-15000 SC heparin per day.

**Surgical therapy in acute ischemic stroke**

Surgical decompressive therapy within 48 hours after symptom onset is recommended in patients up to 60 years of age with evolving malignant MCA infarcts.

It is recommended that osmotherapy can be used to treat elevated intracranial pressure prior to surgery. Decompressive craniotomy could be life saving in patients with massive hemispheric and cerebellar infarctions. Surgery should not be delayed until development of irreversible brain stem damage as expected with bilateral fixed and dilated pupils and coma. Early craniotomy should be considered in patients with rapid clinical deterioration and CT signs of hemispheric infarction with midline shift despite receiving manitol. Patients with cerebellar infarction who have hydrocephalus secondary to compression of fourth ventricle or show compression of posterior fossa cisterns on CT, should underwent immediate surgical decompression. Ventriculostomy or surgical decompression is recommended for treatment of large cerebellar infarctions that compress the brainstem. Patients with malignant MCA infarction or large cerebellar infarction should be transferred to hospitals with neurosurgery facilities. In hemispheric infarctions, the author prefers decompressive craniotomy for young previously healthy individuals with right sided massive infarcts. Because survivors of left massive infarcts would remain hopelessly disabled by global aphasia and right hemiplegia involving dominant side of the body. The neurosurgeon should be a friend because the procedure takes 3-4 hours and good results are only seen in carefully selected patients. Decompressive
craniotomy was performed in 6 patients with huge MCA infarction, 3 cases with large arterial cerebellar infarction and 2 patients with extensive hemorrhagic venous infarction in our hospital\(^{160}\). Unfortunately two of these cases died some days after operation due to delayed surgery after making indication of decompression\(^{160}\). This is a common problem in developing countries. Urgent thromboendarterectomy of an hyperacute occluded proximal ICA may be considered in a patient with minimal neurologic deficit and no ICH\(^{129}\). If there is an acute major infarction in patients who are candidated for CEA, it is better to wait 3-6 weeks before CEA for possibility of hyperperfusion syndrome following surgery\(^{129}\). If there is an acute minor stroke, CEA could be performed within 2 weeks.

**Neuroprotective therapy in acute stroke**

The pharmacological industry has been able to identify a very large number of compounds for clinical testing on pathophysiological cascade between vessel occlusion and irreversible cell death. The occurrence of a cerebral infarction depends on two essential variables; the severity of decrease in cerebral blood flow and the ischemic tissue\(^3\). Neural death depends on multiple factors including\(^3\)

1- Level of activity, the more work that goes on the more fuel is needed.
2- Presence of neurotoxic local metabolites such as lactic acid and \(O_2\) free radicals at the ischemic cells.
3- Temperature of the system, at low temperature there is less metabolism and less need for fuel.
4- Preservation or damage in integrity of the ischemic neural cell membranes.
5- Influx of calcium ions into cells and intra-to-extracellular gradient for neurotransmitters, especially glutamate that over-exits ischemic neurons causing further toxic damage.

Voltage-dependent calcium channel antagonists (nimodipine, flunarizine, izaridine) did not improve neurological outcome in clinical trials\(^{115}\). Inhibitors of presynaptic glutamate release (lubeluzole, propentophyline, lifaricine, fosphenytoin) did not show any benefit in clinical use\(^{161}\). N-Methyl-D-Aspartate antagonists (NMDA), polyamine locus antagonists and glycine locus antagonist has not shown significant neuroprotective effect. Antioxidants or free radical antagonist (trilazad) is not recommended either\(^{161}\). Exogenous gangliosides and GABA agonists (clomethiazole) and basic fibroblast growth factor have not significant therapeutic effect\(^{161}\). In experimental stroke research it appears appropriate to associate thrombolysis
therapy with a neuroprotective treatment, in an attempt to increase the therapeutic time window for thrombolysis in the ischemic penumbra\textsuperscript{161}. This method also makes more penetration for the neural protective agent. Given the complex mechanisms involved in the ischemic cascade, it seems unlikely that any single neuroprotective agent is able to cover the whole cascade and apoptosis\textsuperscript{161}. In experimental stroke research\textsuperscript{s}, two or more neuroprotective agents with different mechanisms have been shown to be more effective than any single agent alone\textsuperscript{11}. Currently, there is no recommendation to treat ischaemic stroke patients with neuroprotective substances by the American and European stroke associations guidelines. Despite general nonsignificant effects of neuroprotective drugs in acute stroke patients these have been widely used in recent five decades. Based on the author experience no neuroprotective drug has magic influence on recovery of stroke patients and their effects are often biased by rehabilitation and spontaneous recovery of stroke patients due to brain plasticity.

**Citicoline (citidin-5-diphosphocholine)**

Citicoline increases the synthesis of phosphatidylcholine, an essential cell membrane component, stimulates acetylcholine synthesis, decreases the accumulation of free fatty acids in ischemic tissue and has an antioxidant effect\textsuperscript{162}. Citicoline (or CDP-choline) is normally present in all cells in the body. Citicoline causes activation of neuronal metabolism, stabilization of neuronal membranes and their function and normalization of neurotransmission\textsuperscript{162}. It has been shown that patients with acute brain infarction may benefit from intravenous citicoline (750-1000mg/day, for 2 weeks) and that it is safe and well tolerated\textsuperscript{162}. Lower doses of intravenous citicoline has not shown therapeutic effects in acute stroke and hypoxic ischemic encephalopathy. Using 2000 mg oral citicoline for 6 weeks has shown therapeutic effects in recovery of patients with major to moderate acute stroke in clinical trials and insignificant effects in other studies\textsuperscript{162,163}. Lower dose of oral citicoline (500 mg/day for 6 weeks) has shown therapeutic effects in some clinical trials\textsuperscript{162}. Oral citicoline (250-500 mg capsules) is not available in many countries.

**Cerebrolysin**

Cerebrolysin is a neuropeptide mimicking the action of neurotrophic factors. It is produced by enzymatic breakdown of purified brain proteins and consists of low molecular weight peptides and aminoacids\textsuperscript{164}. Cerebrolysin has been shown to affect several pathophysiological mechanisms in the
cascade leading to ischemic cell damage and supports neuroplasticity and neurogenesis\textsuperscript{165}. Because of its composition, it requires parenteral administration for full bioavailability over a short time period\textsuperscript{164,165,166}. The drug is administered as a single daily does of 30ml diluted with physiological saline to a total volume of 100 ml as an intravenous infusion over a time period of 30 min for 10-20 days\textsuperscript{164,165}. Cerebrolysin significantly improved cognitive function of stroke patients. However it has not shown significant improvement on other neurological functions\textsuperscript{164,165,166}. Twenty patients with vertebrovasilar territory infarction and top of basilar syndrome received cerebrolysin in our stroke unit. Consciousness and cognitive function improved in 6 cases but other neurological items were not changed.

**Piracetam (Nootropil)**

Piracetam is among the list of the major agents which are considered to have neuroprotective effects in man. Piracetam is a nootropic drug which increases regional cerebral blood flow and has neuroprotective effects acting at cell membrane level. Each piracetam (800 mg) film-coated tablet contains colloidal anhydrous silica, magnesium stearate, macrogol 6000, croscarmellose sodium, hydroxypropylmethylcellulose, macrogol 400, titanium dioxide\textsuperscript{167}. Stroke patients are given 2 tablets 3 times a day for 3 months\textsuperscript{167}. Piracetam is started within 7 hours of stroke onset (4.8 gram/day) and continuing for next 3 months, it may make better neurologic recovery in some of the ischemic stroke patients\textsuperscript{167}. Piracetam Acute Stroke Study (PASS) was a double-blind, randomized, controlled trial in the acute treatment of ischemic stroke\textsuperscript{168}. More patients recovered completely in the piracetam group (18.8%) than on placebo (13.6%) and in contrast level of function requiring constant care was more frequent on placebo (25%) than on piracetam (19.6%) group\textsuperscript{168}. The outcomes of impairment and disability were not significantly different between placebo and piracetam patients, but there were significantly less residual aphasia after 3 months of treatment\textsuperscript{168}. Oral forms of piracetam as film coated tablets 800 mg and 200ml bottle of 20% solution (1mL=200 mg piracetam) was widely used as the routine nootropic drug for stroke recovery in Iran since two decades ago. However, trials on piracetam have shown a nonsignificant beneficial effect in acute ischemic stroke\textsuperscript{167,168,169}. Piracetam is not used in the north America due to marketing issues but it has been used for 3 decades in Iran.

**Neuroaid (MLC601)**

Dangi Piantag Jiaonang (Neuroaid) is a traditional chinese medicine product which is available as a neuroprotective drug. Neuroaid effectiveness
in improving stroke recovery may be related to its role in neuronal protection and plasticity to build and grow new neuronal pathways. Neuroaid (MLC 601) combines nine herbal components (radix astragali, radix salviae miltorrhizae, radix paeoniae rubra, rhizoma chuanxiong, radix anglicae sinensis, carthamus tinctorius, prunus persica, radix polygalae and rhizoma acori tatarinowii) and five animal (hirudo, eupolyphaga seu steleophaga, calculus bovis artifactus, buthus martensii and cornu saigae tataricae) components. Stroke patient in neuroaid is given 4 capsules 3 times a day for 3 months and each capsule of neuroaid weights 0.4 gram. Previous clinical studies performed in china have shown that neuroaid enhances recovery of stroke patients from their neurological disability and improves functional outcome. A large-scale randomized controlled trial is currently recruiting in south east of Asia to evaluate the impact of 3-month treatment with neuroaid and is assessing patients on neurological disability scores. Another double-blind, placebo-controlled, randomized phase II pilot study to investigate the potential efficacy of neuroaid (MLC601) in enhancing recovery after stroke was performed in Singapore. This study detected an insignificant difference in the effect of neuroaid on the motor recovery when starting treatment within a month of stroke onset. Subgroup analysis of this study has shown that neuroaid group performed better than the placebo group when the severity of the stroke was high. Additionally, this study revealed a strong tendency of a better recovery in posterior circulation infarction. However it was difficult to draw any conclusion given the small number of patients involved (n=7) and the imbalance of score at the baseline.

Comparison of neuroprotective drugs in stroke patients: an example

A prospective observational study was conducted on consecutive stroke patients with posterior cerebral artery territory infarction admitted in Ghaem hospital, Mashhad, Iran during 2009-2010. The patient was eligible for inclusion in the comparative study only if all the following criteria are fulfilled at baseline: 1- Age 18 years old and above, 2- Time window is less than one week after onset of ischemic symptoms, 3- Clinical presentation of ischemic symptoms as isolated pure homonymous hemianopsia without neglect and macular sparing confirmed by routine perimetry, 4- Posterior cerebral artery territory infarction with isolated occipital lobe involvement confirmed with brain CT or MRI, 5- Females are eligible to participate in the study if they are of non-child-bearing potential; e.g postmenopausal period, hysterectomy, and taking oral contraceptive pills, 6- Patient or his/her legally acceptable relative signed informed consent.

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consent. A subject was not eligible for inclusion in the study if any of the following criteria apply at baseline\textsuperscript{169,170,171,172}: 1- Received recently thrombolysis, 2- Evidence of intracerebral hemorrhage on brain CT or MRI, 3- Rapidly improving neurological deficit, 4- Stupor or coma as defined as a score of <5 on the Glasgow Coma Scale which makes impossible to perform perimetry, 5- Other significant nonischemic brain lesions that could affect functional disability; e.g intracranial tumor and demyelinating lesions, 6- Coexisting ophthalmologic disease that could affect evaluation of homonymous hemianopsia; e.g cataract, optic neuritis and retinal abnormalities, 7- Coexisting systemic diseases; e.g terminal cancer, renal failure, liver failure and psychosis, 8- Patients with lacunar infarction in the posterior cerebral artery territory, 9- Aphasia or any other cognitive disabilities which prevent cooperation with study instructors, 10- History of craniotomy or seizure, 11- Previous stroke which presented with visual field defect. 12- Recurrence of stroke during 3 months follow up period presenting with visual field defect. All of the studied patients had brain CT or MRI, complete blood count, blood urea, serum creatinine, blood glucose, liver enzymes, serum bilirubin, serum electrolytes, urine albumin and glucose, and electrocardiogram. All patients received standard stroke care including appropriate antiplatelet therapy or anticoagulation therapy (aspirin with or without dipyridamole, clopidogrel, warfarin) and control of vascular risk factors. Neuroaid (MLC601) or piracetam was given as an add-on to other medications which were used as the patients condition dictated\textsuperscript{173}. Subjects randomized to receiving a 3-month course of either neuroaid or piracetam. The degree of homonymous hemianopsia recovery or change comparing baseline and 3 months perimetries was calculated based on square milimeter\textsuperscript{173}. The outline of the visual field defect was carefully determined in perimetry sheet, then using a point grid, the surface area of each visual field defect was manually calculated. All of the perimetries were performed by one ophthalmologist who was blind to drug group of each patient with a single perimetry facility\textsuperscript{173}. A total of fifty three patients were screened and 40 subjects (20 females, 20 males) with mean age 60.0±13.6 completed this study. Neuroaid and piracetam groups constituted of 20 patients (10 females and 10 males) with mean age 62±12.9 and 59.2 ±14.4 respectively\textsuperscript{173}. Right sided homonymous hemianopsia constituted 11 patients in neuroaid and 10 patients in piracetam group. In neuroaid group, difference in quantitation of visual field defects before and after treatment was significant in right and left visual fields (t=5.49, df=19, p=0.000) and (t=6.04, df=19, p=0.000) respectively\textsuperscript{173}. At the other hand in piracetam group, difference in quantitation
of visual field defects before and after treatment was also significant in right and left visual fields \((t=5.08, df=19, p=0.000)\) and \((t=5.38, df=19, p=0.000)\) respectively. Difference in quantitation of mean right visual field defects between two therapeutic groups of homonymous hemianopsia at first and follow up perimetrries was not significant, \((t=-0.0418, df=38, p=0.678)\) and \((t=-1.429, df=38, p=0.161)\) respectively. Difference in quantitation of mean left visual field defects between two therapeutic groups of homonymous hemianopsia at first and follow up perimetrries was also not significant, \((t=0.035, df=38, p=0.972)\) and \((t=-1.799, df=38, p=0.080)\) respectively. Relative reduction of right and left visual field defects after treatment with neuroaid was 45% and 45.7% respectively. While, relative reduction of right and left visual field defects after treatment with piracetam was 32.7% and 30.3% respectively. Therefore, neuroaid has about half more therapeutic effect than piracetam in improvement of visual fields. The influence of age groups and gender on recovery of right and left visual field defects was not significant in neuroaid and piracetam groups.

Another analysis of homonymous hemianopsia recovery as ≤25%, 26-50%, 51-75% and >75% categories revealed that distribution of homonymous hemianopsia recovery patterns was not significantly different between neuroaid and piracetam groups; \(X^2=0.376, df=3, p=0.329\). Side effects including abdominal discomfort were found in 10% of neuroaid group. However side effects were mild and excluded no patient in neuroaid group. Side effects including headache, drowsiness and dizziness were observed in 10% of piracetam group. One patient using piracetam was excluded from study due to severe headache. Despite administration of appropriate antiplatelet or anticoagulation therapy in two therapeutic arms, hemorrhagic complications was not seen in any patient in neuroaid and piracetam groups. Because neuroaid is usually used in a higher socioeconomic group of Iranian stroke patients who usually receive better rehabilitation therapy, we only studied homonymous hemianopsia in the stroke patients who do not need rehabilitation and speech therapy. This research strategy resolves therapeutic bias of our study in comparing neurotropic effects of neuroaid and piracetam. Despite huge difference in cost of neuroaid versus piracetam, due to importance of vision and visual field in quality of life and working disabilities it seems wisely to pay the cost of neuroaid in these subgroups of stroke patients.

**Rehabilitation**

A meta-analysis showed that continued rehabilitation after discharge during the first year after stroke reduces the risk of deterioration in function and improves activities of daily living. The interventions included occupational
therapy and physiotherapy\textsuperscript{174}. Many of the immediate complications of stroke (DVT, skin breakdown, contracture formation, constipation, and hypostatic pneumonia) are related to immobility, and hence mobilization is a fundamental component of early rehabilitation\textsuperscript{174}. No controlled trial data described the effectiveness of rehabilitation therapy beyond 1 year after stroke\textsuperscript{115}. A systematic review of speech therapy for dysarthria in non-progressive brain damage (stroke and head injury) found no good-quality evidence for benefit. Similarly, a systematic review of speech therapy for aphasia reported insufficient good-quality evidence to recommend formal interventions\textsuperscript{115}. The effectiveness of speech therapy in promoting actual improvement in speech and language function is controversial, although speech therapy is useful in some individuals\textsuperscript{12}. The most dynamic period of recovery lies beyond the hyperacute phase of stroke up to 48 hours after onset. The patients reach at least half of their individual maximum best scores within 2 weeks post stroke. Ninety percent of the stroke patients having reached their best outcome within 3 months after onset of stroke\textsuperscript{115,174}. Alert patients should be mobilized as soon as possible when they are medically stable\textsuperscript{16}. Standing practice begins when patient is able to sit with good balance. Active and passive range of motion movements should be initiated in bed, since the stroke day\textsuperscript{1}. Patients must be taught to move their own paralysed limbs with intact ones\textsuperscript{11}. Until then nurses and family members must move them passively through their full range of motion\textsuperscript{1}. Shoulder joint dislocation could be prevented by using sling and frequent full range of motion exercise. A pillow should be put under the affected shoulder and the flaccid and plegic arm may be hanged from the neck by a neck lace connected to the affected wrist\textsuperscript{1}. Passive movement of a paretic limb may be preventive for post stroke shoulder pain. Gabapentin may be considered for neuropathic pain. It is well tolerated, but has cognitive side effects\textsuperscript{115,174}. Swallowing assessment is routinely done for every stroke patient. Turning the head toward the affected plegic side decreases the flexor tone. Muscles should not be allowed to remain in a relaxed and shortened position for long periods\textsuperscript{1}. For example if the arm is left in a flexed posture at the elbow or the foot in plantar flexion, this can lead to permanent shortening and contracture\textsuperscript{1}. To prevent shortening of the Achilles tendon, a brace may be used or the soles placed on a foot board. Baclofen and benzodiazepines are used when spasticity is not adequately controlled by physical techniques or the patient is suffering from painful muscle spasm\textsuperscript{1}. Driving a car requires good vision (absence of visual field defect and inattention), intact reflex responses and rapid decision making. Stroke patients without these capabilities should be prohibited of driving.
Predictors of recovery by rehabilitation

Survival is significantly better after cerebral infarction when compared with a similar sized intracerebral hemorrhage, but disability is greater with infarction because hemorrhage often leaves tissue intact, whereas infarction destroys affected neurons. Patients with pure hemiparesis have a better recovery than patients with sensorimotor deficit. If impairment is unchanged after 6-12 months, it can be assumed with some confidence that little will occur thereafter. The rate and degree of recovery is relatively unpredictable, continues for months and varies from patient to patient. In general, reduced conscious level, urinary incontinence in the first few days of stroke and large stroke lesions on CT are associated with poor functional outcome. Pre-stroke disability is clearly also a strong determinant of outcome. Of course, functional recovery depends not only on the severity of stroke but also on other factors such as premorbid disability. Other factors, such as sex, stroke etiology, age and topography of lesion, have all been studied as potential predictors of rehabilitation outcome; however, there is no evidence that these non-modifiable factors could influence decisions on rehabilitation. Stroke patients with homonymous hemianopsia and ipsilateral hemiplegia have poor recovery of hemiplegia because they do not effort to use the paretic limbs in the hemianopic side. The same is correct for hemiplegia and ipsilateral hemineglect. Three hundreds twenty nine Persian stroke patients were investigated in an observational study. Hemihyposthesia, hemianesthesia, hemineglect and homonymous hemianopsia were found in 37.4%, 13.8%, 7.9% and 7.3% of them respectively. Modified Rankin Disability Scale (MRDS) was significantly higher in patients with hemianesthesia than other stroke patients, p<0.001. MRDS of patients with each of hemihypoesthesia, hemineglect and homonymous hemianopsia was not significantly different than patients without these abnormalities, p=0.44, p=0.23 and p=0.83 respectively. Patients with triad of hemianesthesia, hemineglect and homonymous hemianopsia had significantly higher MRDS than others, p<0.001. Hemianesthesia is the most important clinical effector on MRDS of the stroke patients. Presence of above triad predicts the highest MRDS in these patients. Aphasia is an important effector in disability of stroke patients. Aphasia increases the stroke disability and reduces future recovery following rehabilitation in the stroke patients. An observational study in Persian stroke patients revealed that stroke patients with aphasia had significantly higher MRDS than other stroke patients, p=0.01. Patients with Global aphasia had significantly higher MRDS than
patients without aphasia and patients with Wernicke aphasia; p<0.001, p=0.006 respectively. However, patients with Global aphasia had non-significant difference of MRDS to patients with Broca aphasia, p=0.06. The effectiveness of speech therapy in promoting actual improvement in speech and language function is controversial, although speech therapy is useful in some individuals.

Mortality in Stroke

Estimation of mortality rate of stroke patients depends on methodology and follow up of the stroke patients. Brain herniation, aspiration pneumonia, sepsis, myocardial infarction, pulmonary embolism are common causes of death in the Persian stroke patients. The single best predictor of early death in stroke patients is impaired consciousness.
Chapter VIII

Thrombolysis with rTPA Therapy in Acute Stroke

Thrombolysis by intravenous recombinant (Tissue Plasminogen Activator) TPA

TPA is synthesized and secreted by endothelial cells. TPA and plasminogen bind to the fibrin clot. TPA binds specially to fibrin and activates plasminogen only at the fibrin surface. The most widely used preparation is the single-chain form, Alteplase. Rapid clearance of TPA takes place in humans, largely through the liver, and so the serum half life is about 4-6 minutes. The National Institute of Neurological Disorder and Stroke (NINDS) rTPA stroke study group enrolled and treated 624 ischemic patients within 3 hours of onset of symptoms, half of them within 90 minutes. The dose of rTPA was 0.9 mg/kg (maximum 90 mg), 10% of which was given as a bolus over 1-2 minutes and followed by delivery of the remaining 90% as a constant infusion over a period of 60 min. This study assessed the clinical outcome according to the National Institute of Health Stroke Scale (NIHSS). In the NINDS rTPA trial, 11-13% more patients in the rTPA arm reached an excellent outcome with no increase in mortality, although symptomatic hemorrhage were increased tenfold by thrombolysis (6.4 versus 0.6%). Implying that for every 100 patients treated with rTPA, an additional 11-13 patients would recover compared with 100 patients not treated with rTPA. On the basis of the results, intravenous rTPA was approved in the north America for the use within a 3 hours time window in selected patients. Treatment can be beneficial irrespective of the patients age, gender or presumed cause of stroke. Treatment can be effective for patients with a wide spectrum of neurological deficits including infarctions in the cerebellum and brainstem. In north America only 6 to 7% of the ischemic stroke patients at university teaching hospitals receive thrombolysis.
Guidelines for intravenous rTPA therapy

Exclusion Criteria

1- We should be cautious treating patients with CT evidence of infarction involving more than one-third of MCA territory which is a partial contraindication of tPA therapy. Significant mass effect of ischemic area, as shown by ventricular compression or midline shift, and CT evidence of intracerebral hemorrhage are absolute contraindications to thrombolytic therapy.

2- Patients with extensive neurological deficit (NIHSS score >22) and occlusion of MCA stem are less likely to benefit from IV thrombolysis and the risk of intracerebral hemorrhage is higher in these patients. Caution is advised before giving tPA to patients with severe deficit (NIHSS>22).

3- IV rTPA is not prescribed if blood pressure is more than 185/110 mmHg, unless controlled down by labetalol as with following method. Labetolol should be intravenously infused 10 mg over 1-2 minutes, repeated every 10-20 minutes up to a dose of 150 mg. If blood pressure could be reduced <185/110 and stabilized within 3 hours time window, rTPA management is permitted. The blood pressure should be monitored every 15 min during and 24 hours after rTPA therapy. To minimize risk of intracerebral hemorrhage, treatment must be limited to patients with an initial systolic BP ≤185 mmHg and diastolic BP ≤110 mmHg. Hypertension increases the risk of intracerebral hemorrhage and edema.

4- Use of anticoagulants in the previous 48 hours and a prolonged PTT or an INR >1.7, or PT >15 seconds is a contraindication. Platelet count <100000 is considered as a contraindication. Treatment with aspirin prior to rTPA therapy is not a contraindication. The lack of information about the safety of rTPA in stroke patients who have been on other antiplatelet drugs, does not permit any recommendation.

5- Stroke, SAH or severe head trauma, subdural hematoma or intracranial surgery in the previous 3 months are contraindications to IV rTPA. Symptoms suggestive of SAH is a contraindication. History of SAH beyond 3 months is a contraindication unless the aneurysm has been clipped. Any history of intracerebral hemorrhage is a contraindication.

6- Major surgery or serious trauma within prior 14 days are contraindications.

7- Blood glucose <50 or >400 mg/dL is a contraindication to IV r TPA. Hyperglycemia increases the risk of intracerebral hemorrhage. Patients with hypo or hyperglycemia may not be correctly assessed for intracerebral hemorrhage and edema by clinical examination. If you could correct hypo or hyperglycemia immediately, IV rTPA could be given thereafter.
8- Patients with seizures at stroke onset have been excluded from thrombolytic trials because of potential confusion with post-ictal Todd’s phenomena\textsuperscript{181}. Case series have suggested that thrombolysis may be used in such patients when there is evidence for new ischemic stroke\textsuperscript{181}.

9- Other clinical bleeding, i.e. gastrointestinal or urinary bleeding within prior 3 weeks is contraindication to IV rTPA\textsuperscript{181}.

10- Myocardial infarction within prior 3 weeks is a contraindication for intravenous thrombolysis. Because these patients often receive thrombolysis therapy for MI. At the other side presence of post MI pericarditis and further rTPA therapy increases the risk of hemopericardium.

11- Bacterial endocarditis is a contraindication for IV rTPA therapy due to high risk of secondary intracerebral hemorrhage. However, patients with nonbacterial endocarditis are eligible for the therapy\textsuperscript{115}.

12- The presence of left ventricular thrombus is a contraindication for IV rTPA because it could lyse and fragment the thrombus and may cause additional stroke. This does not mean that TTE should be done in the initial 3 hours to rule out the left ventricular thrombus. It includes a patient who has TTE done for cardiologic indications in recent days and develops a stroke\textsuperscript{115}.

13- rTPA is not used for patients with TIA, rapidly improving neurological signs and minimal deficit (NIHSS score <4), because they have a favorable prognosis even without rTPA therapy. Patients with isolated neurological deficit such as ataxia alone, sensory loss alone, dysarthria alone and minimal weakness have a favorable prognosis even without rTPA therapy\textsuperscript{115,183}.

14- rTPA is not recommended if the time of symptom onset is uncertain, i.e. in aphasic patients without collateral history or in patients who have neurological deficits upon awakening\textsuperscript{183}.

15- Since 2008, thrombolysis with IV rTPA within 3-4.5 h after stroke has been implemented rapidly. Safety and functional outcomes are less favourable after 3 h; but the wider time window now offers an opportunity for treatment of those patients who cannot be treated earlier. Thrombolysis could be initiated within 4.5 h after onset of ischemic stroke, although every effort should be made to treat patients as early as possible after symptom onset.

**Practical notes about thrombolysis with rTPA**

rTPA should be used solely by physicians expert in acute stroke management and interpretation of early signs of significant infarction and intracerebral hemorrhage on brain CT. Immediate CT scanning and facilities
for managing hemorrhagic complications must be readily available every
time in patients candidated for thrombolysis therapy. Early signs of ischemia
including sulcal effacement, loss of grey-white matter differentiation, or
parenchymal hypodensity are associated with an increased risk of
intracerebral hemorrhage but are not contraindications to rTPA therapy.
Stroke neurologists should detect the NIHSS score in the patients who are
considered for IV rTPA protocol. Currently, ischemic stroke patients with
NIHSS > 4 < 22 within 3 hours of stroke onset are eligible for approved IV
rTPA therapy. Stroke neurologist explains to the patient or his/her
responsible family members the risk and benefit of the IV rTPA therapy but
there is no need for the signature of the consent. In stroke patients with
NIHSS score > 22 or after 3 hours time window, stroke neurologist should
take consent signature by the patient or responsible member of family for
starting IV rTPA therapy. Patients with a baseline NIHSS score > 20 or
sever deficit are 11 times more likely to develop a symptomatic
intracerebral hemorrhage than patients with an initial NIHSS score < 5 or
mild deficit. IV rTPA therapy outside of the standard protocol should be
limited to patients who can be treated within 3 hours. No warfarin,
heparin, aspirin or other antiplatelet drugs must be given for at least 24
hours after rTPA therapy. Aspirin therapy 160-300 mg/day is started 24
hours after rTPA therapy for preventing re-occlusion of the opened
artery. Vital signs should be taken every 15 minutes during the drug
infusion, then every 30 minutes for the next 2 hours, then every hour for the
next 5 hours. Placement of an indwelling bladder catheter should be
avoided during rTPA infusion and for 30 minutes after infusion ends.
Insertion of a nasogastric tube should be avoided during the first 24 hours
after the treatment. Patients with obtundation or depressed level of
consciousness caused by the brain stem infarction are eligible for IV rTPA
treatment. In IV rTPA candidates without history of bleeding disorders or
active bleeding who have not been on anticoagulant drugs you could start
therapy with rTPA before receiving PT, PTT, INR and platelet results. If a
stroke patient who received IV or IA rTPA has indication for anticoagulant
therapy, i.e. develops acute MI, anticoagulation could be started 2 weeks
after IV or IA rTPA therapy. Old age is not a limitation for IV rTPA
therapy. Predictors of good outcome in patients treated with IV rTPA
include; age < 70 years, a normal initial CT scan, absence of diabetes,
hypertension or cardiac disease, and low NIHSS score. Poor therapeutic
outcome is more probable to those patients receiving therapy beyond 3
hours. Be cautious for IV rTPA therapy in patients with sever stroke
Intravenous rTPA could be used up to 4.5 hours but the patient or his/her family should sign consent for the management. Because patients treated between 3 to 4.5 hours achieve less benefit and have more chance of developing intracerebral hemorrhage and edema compared to those treated within 3 hours. Post hoc analyses have identified the following potential factors associated with increased risk of intracerebral bleeding complications after rtPA use:

1. Elevated serum glucose
2. History of diabetes
3. Baseline symptom severity
4. Advanced age
5. Increased time to treatment
6. Previous aspirin use
7. History of congestive heart failure
8. Low plasminogen activator inhibitor activity
9. NINDS protocol violations.

However, none of these factors reversed the overall benefit of rtPA. Non-invasive vascular imaging, i.e. TCD, MRA, CT angiography is not required before and after IV or IA rTPA therapy, however in investigational studies these techniques are used for assessment of the vascular reopening caused by thrombolytic therapies.

**Complications of rtPA therapy**

Intracerebral Hemorrhage (ICH) is probable if unexpected neurological deterioration develops following the use of rTPA. The infusion should be discontinued immediately and an emerging CT scan obtained. Neurosurgery consultation may be requested after the fibrinolytic state is corrected. If ICH is suspected, blood should be drawn to measure the patient hematocrit, hemoglobin, platelet count, PT, PTT, INR, fibrinogen and cross match. 6-8 units cryoprecipitate or fresh frozen plasma and 10 units of single donor platelet should be infused urgently. In some instances active bleeding can be controlled mechanically, i.e. arterial and venous puncture sites can be compressed. The case mortality rate is also similar to that for spontaneous ICH. ICH after IV rtPA therapy is less frequent in vertebrobasilar than carotid territory infarcts. Presentation of symptomatic ICH in the setting of IV rTPA therapy is similar to that of spontaneous ICH. Decline in the level of consciousness, headache, nausea and vomiting, abrupt raise in the systemic blood pressure, increase in the initial focal neurological deficit or
the appearance of the new neurological deficit should prompt an emergency CT scan\textsuperscript{83,115,182}. Systemic hemorrhage is a rare but serious complication of IV rTPA therapy\textsuperscript{12}. Risk factors of secondary ICH in patients receiving IV rTPA include; later time to treatment, higher dose of thrombolytic agent, elevated blood pressure, severity of neurologic deficit and early ischemic changes, i.e. hypodensity on the initial CT\textsuperscript{12}. Symptomatic ICH after thrombolysis therapy develops within 36 hours after rTPA therapy with \( \geq 4 \) points increase of NIHSS. Sever brain edema is other complication of IV or IA thrombolysis, Sever brain edema in the infarcted region is caused by delayed lysis of a thrombus following irreversible neuronal injury and reperfusion. It could be due to direct harmful effect of thrombolytic enzymes and free radicals on blood brain barrier, leaking out in to the ischemic brain tissue due to necrosis of microvasculature. It is not possible to separate evolving edema secondary to the primary injury from edema secondary to clot lysis and reperfusion by clinical manifestations and neuroimaging\textsuperscript{83,115}. IV rTPA rarely causes life threatening upper respiratory obstruction due to angioneurotic edema. Intravenous thrombolysis has the potential to dislodge further embolic material from the source of the original symptom-producing thrombus in the cardiac, aorta or cervical arteries\textsuperscript{184}. Unintended embolism could result from the therapeutic fragmentation of the original occluding thrombus. For example, when the thrombus within the MCA stem is broken up by thrombolysis, the resulting smaller particles may be large enough to lodge and occlude downstream distal MCA branches\textsuperscript{184}. Stroke patients who receive IV rTPA therapy, get benefit frequently from the therapy despite this benefited group often have an infarct in deep basal ganglia area\textsuperscript{115}.

A standard protocol of intravenous thrombolysis with rTPA is attached for guiding of our neurologists.

**Standard acute ischemic stroke thrombolytic protocol**

**PHYSICIAN TO COMPLETE**

**INCLUSION CRITERIA SHOULD BE YES**

YES  NO

- Clinical diagnosis of acute cerebral hemisphere, brain stem or cerebellar ischemic stroke
- Clearly identified onset of symptom less than 3 hours
- Patient evaluated and approved for alteplase (rTPA) by staff neurologist/stroke team
CT INCLUSION
YES  NO
☐ ☐ No intracranial hemorrhage
☐ ☐ No early infarct or edema involving
   >1/3 MCA territory or cerebellar hemisphere

EXCLUSION CRITERIA
YES  NO
☐ ☐ Active bleeding
☐ ☐ Severe hypertension (systolic >185, diastolic >110)
   persisting despite therapy
☐ ☐ Intracranial bleeding risk (head trauma, AVM, recent stroke,
   aneurysmal hemorrhage or cranial surgery within last 3 months
☐ ☐ Bleeding diathesis (including presence of petechiae or history of
   advanced hepatic or renal disease)
☐ ☐ Platelets <100,000
☐ ☐ INR >1.7
☐ ☐ IV heparin within 48 hours and PTT >1.5 normal
☐ ☐ Seizure at onset of stroke
☐ ☐ Suspected stroke due to
   amphetamine/cocaine use
☐ ☐ Surgery, biopsy, trauma or subclavian puncture within past 14 days
☐ ☐ Gastrointestinal or genitouriinary hemorrhage in previous 21 days
☐ ☐ Arterial puncture at non-compressible site within past week
☐ ☐ Blood glucose <50 or >400 mg/dL
☐ ☐ Concurrent Myocardial Infarction
☐ ☐ Hemorrhagic diabetic retinopathy
☐ ☐ Pregnant or postpartum
Date and Time [ ]
Physician Name [ ]
Physician Signature ------------------------
STROKE TEAM MEMBER TO COMPLETE

The NIH Stroke Scale
1a. Level of Consciousness (LOC): ☐
The patient is asked about his/her medical history
0=Alert: keenly responsive
1=Not alert: rousable by minor stimulation to obey, answer or respond
2=Not alert: requires repeated stimulation to attend, or is obtunded and requires strong or painful stimulation to make movements (not stereotyped)
3=Responds only with reflex motor or autonomic effects or totally unresponsive, flaccid, areflexic

1b. LOC Questions: □
The patient is asked the current month and his/her age.
0=Answers both questions correctly
1=Answers one question correctly
2=Answers neither question correctly

1c. LOC Commands: □
Say to the patient, open your eyes, now close your eyes, and then make a fist, now open your hand.
0=Performs both tasks correctly
1=Performs one task correctly
2=Performs neither task correctly

2. Best Gaze: □
0=Normal
1=Partial gaze palsy, gaze is abnormal in one or both eyes but forced deviation or total gaze paresis are not present
2=Forced deviation or total gaze paresis not overcome by the oculocephalic maneuver

3. Visual: □
0=No visual loss
1=Partial hemianopsia
2=Complete hemianopsia
3=Bilateral hemianopsia including cortical blindness

4. Facial Palsy: □
0=Normal symmetrical movement
1=Minor paralysis (flattened nasolabial fold, asymmetry on smiling)
2=Partial paralysis (total or near total paralysis of lower face)
3=Complete paralysis of one or both sides (absence of lower and upper facial movement)
5. Motor Arm:  5.a Left arm  5.b Right arm
0=No drift: limb holds 90° or 45° for 10 seconds
1=Drift: limb holds 90° or 45°
2=Some effort against the gravity: limb can not get to be maintain (if cued)
90° or 45° drifts down to bed.
3=No effort against gravity: limb falls
4=No movement

6. Motor Leg:  6.a Left leg  6.b Right leg
0=No drift: leg holds 30° position for 5 seconds.
1=Drift: leg falls by the end of 5 seconds period but does not hit bed.
2=Some effort against the gravity: leg falls to bed within 5 seconds.
3=No effort against gravity: leg falls to bed immediately.
4=No movement

7. Limb Ataxia:  Right arm  Left arm
   Right leg  Left leg
0=Absent (if 0 then go to question 8)
1=Present in one limb (score for each limb)

8. Sensory:
0=Normal: no sensory loss
1=Mild to moderate sensory loss: patient feels pinprick is less sharp or is
dull or there is loss of superficial pain but patient is aware of being touched
2=Sever or total sensory loss: not aware of being touched

9. Best Language:
0=No aphasia: normal
1=Mild to moderate aphasia: some obvious loss of fluency or facility of
comprehension without significant limitation on ideas expressed or form of
expression.
2=Sever aphasia: all communication is through fragmentary expression;
great need for inference, questioning and guessing by the listener. Range of
information that can be exchanged is limited.
3=Mute, global aphasia; no usable speech or auditory comprehension

10. Dysarthria:
0=Normal
1=Mild to moderate: patient slurs some words
2=Sever: patients speech is so slurred as to be unintelligible, in the absence
of or out of proportion to any dysphasia or is anarthric
11. Extinction and Inattention: □
0=No abnormality
1=Visual or tactile inattention and extinction in bilateral stimulation
2=Profound hemineglect, does not recognize own hand or orients to only one side of space. Both visuospatial and tactile inattention in bilateral stimulation.

TOTAL SCORE ITEMS 1-11: □
DATE AND TIME
STROKE TEAM MEMBER NAME
SIGNATURE--------------

Nursing care in thrombolysis with rTPA/Alteplase

TPA dose is determined by weight, 0.9 mg/Kg (see below table). TPA total dose is not exceeded 90 mg; maximal assumed patient weight is 100 Kg. TPA is administered over 60 minutes. Dissolve a vial of alteplase with diluent supplied 100mg/100mL=1mg/mL. Do not shake, set up IV line with NS 20mL.

Bolus dose-----(mg=mL)+Infusion dose-----(mg=mL)=Total dose-----(mg=mL)

Ten percent of the calculated drug is given as a bolus dose. Withdraw bolus dose from TPA vial. Give bolus dose----mg over 2 min IV push. Infusion dose should be given over 60 minutes. Set the pump volume at----mL. Set the rate at-----mL/hr.

Table 19 is a guidance for calculation of alteplase/TPA dosing (mg/kg/hr)

Vital signs each 15 min during infusion and 1 hour thereafter, then each 30 min during next 6 hours, then each 1 hour during next 16 hours should be recorded. Systolic BP >180 or diastolic BP >110mmHg if remaining elevated for 15 min or more/and BP <140/85 mmHg is reported. Observe for brusing and bleeding, avoid unnecessary invasive procedures. Delay placement of nasogastric tubes, indwelling bladder catheters, or intra-arterial pressure catheters115. Patient should be underwent cardiac monitoring for 24 hours. Avoid heparin, warfarin, antiplatelet agents and NSAID for 24 hours following infusion of TPA. The administration of aspirin as an adjunctive therapy within 24 hours of thrombolytic therapy is not recommended115.
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**Table 19:** Calculation guide for iv Alteplase/TPA doseing (mg/kg/hr)

<table>
<thead>
<tr>
<th>Weight Kg</th>
<th>Bolus Dose 0.09mg/kg</th>
<th>Infusion Dose 0.81mg/kg/h</th>
<th>Total Dose 0.9mg/kg/h</th>
</tr>
</thead>
<tbody>
<tr>
<td>40-42</td>
<td>3.7</td>
<td>33</td>
<td>36.7</td>
</tr>
<tr>
<td>43-45</td>
<td>4</td>
<td>36</td>
<td>40</td>
</tr>
<tr>
<td>46-48</td>
<td>4.2</td>
<td>38</td>
<td>42.2</td>
</tr>
<tr>
<td>49-51</td>
<td>4.5</td>
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<td>47.8</td>
</tr>
<tr>
<td>55-57</td>
<td>5</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>58-60</td>
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<td>48</td>
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</tr>
<tr>
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<td>5.9</td>
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</tr>
<tr>
<td>100+</td>
<td>9</td>
<td>81</td>
<td>90</td>
</tr>
</tbody>
</table>

Responders to intravenous TPA are defined as improvement in NIHSS ≥ 4 points at 24 hours or reaching to modified Rankin scale ≤ 1 at 90 day\textsuperscript{185}. Clinical outcome at 3 months follow up and mortality rate is similar in patients with carotid versus vertebrobasilar territory stroke undergoing intravenous rTPA therapy\textsuperscript{185}. Although intravenous rTPA therapy in ischemic stroke related to extracranial carotid dissection seems to be safe, the benefit in outcome is less than other causes of stroke\textsuperscript{185}.

**Practical notes about NIH stroke scale scoring**

In a globally aphasic, mute or anarthric patient, evaluation of sensory, extinction and inattention is impossible and the patient gets score 0 in these regards. In a hemiparetic or hemiplegic patient, the affected limbs are not testable for ataxia and the patient gets score 0 for limb ataxia. Patients with limb amputation or joint fusion do not get calculable scores in examination of motor arm, motor leg and limb ataxia. Patient who is intubated or has other barrier does not get calculable score in examination of best language and dysarthria. In Level of Consciousness (LOC) questions; aphasic and
comatous patients who do not comprehend the questions will get score 2. Patients who are unable to speak due to endotracheal intubation, orotracheal trauma, language barriers, and anarthria are given score 1 for LOC questions. It is important that only the initial answer be scored and that the examiner do not help the patient with verbal or non-verbal clues. The answer must be correct. There is no practical credit for being closed to correct. LOC 1a is scored 3, only if the patient makes no movement other than reflexive posturing in response to noxious stimulation. For test of LOC commands, use the nonparetic limb. If amputation or other physical impediment prevents the response, use other suitable one step command. Comatous patients who do not comprehend the LOC commands will get score 2. In aphasic patients who do not respond to command, the task should be demonstrated to them by pantomime and score the result.

The Modified Rankin Disability Scale (MRDS)
MRDS is defined as\textsuperscript{12}: Score 0= No symptoms. Score 1= No significant disability, able to carry out all usual activities. Score 2= Slight disability, unable to carry out some of previous activities but able to look after own affairs without assistance. Score 3= Moderate disability, requiring some help but able to walk without assistance. Score 4= Moderately severe disability, unable to walk without assistance and unable to attend to own bodily needs without assistance. Score 5= Sever disability, bedridden, incontinent and requiring constant nursing care and attention.

Challenging comparison of stroke disability scales
A reproducible and valid method for quantification of the neurological deficit that occurs after stroke is essential for monitoring patients and many stroke scales have been proposed for this purpose. Stroke scales represent useful tool for estimating the severity of stroke at onset and for assessing prognostic information in hospital. In general, a stroke scale consists of several variables for observing the signs and symptoms, and each variable is categorized for scoring. In developing an ideal stroke scale, issues of simplicity, reliability, validity and popularity of use must be pursued, especially if a scale is to be used by a broad array of practitioners\textsuperscript{2}. Reliability of a stroke scale is known to improve with personal and videotape training. Acceptability and average completion times need to be considered in any outcome measure, but especially for use in stroke given the potential cognitive problems and feelings of tiredness that may be experienced after stroke\textsuperscript{3,11}. Stroke scales can be classified as parametric or clinicometric
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scales on the basis of physical deficit and functional impairment, handicap scales. Evaluating the impact of new treatments requires the use of reliable and valid outcome measures\textsuperscript{1}. The development of stroke outcome classification systems is predicted on the belief that neurological deficits often lead to permanent impairments, disabilities, and compromised quality of life. The National Institute of Health Stroke Scale (NIHSS) is the most frequently used stroke deficit scale in routine clinical practice and clinical trials\textsuperscript{188}. In spite of its great success, there are problems with the NIHSS. NIHSS contains items with poor reliability and has been criticized for its redundancy and complexity\textsuperscript{189}. The NIHSS overall reliability is clear, however assessments have consistently shown specific items that yield low interrater reliability. The items with poorer NIHSS reliability included facial palsy, ataxia, dysarthria and level of consciousness\textsuperscript{190}. Among over 15000 individuals who have taken online NIHSS certification, the NIHSS items with poorer interrater reliability included facial palsy ($\kappa=0.25$), ataxia ($\kappa=0.15$), level of consciousness ($\kappa=0.43$), dysarthria ($\kappa=0.46$) and gaze ($\kappa=0.44$)\textsuperscript{191}. These elements may contribute to difficulties in practitioner communication, incorrect hospital care patterns that are based on the NIHSS; e.g., decisions to give thrombolytics, variable trial enrollments and even possible difficulties with assessing patient outcome in clinical trials\textsuperscript{192}. Given the unreliability of some of the NIHSS items, patients may score high on the NIHSS when they actually have mild strokes but questionable other findings. Alternatively, patients may score as mild even if they have more severe deficits, because unreliability may result in certain items being unscored\textsuperscript{192}. Patient with severe stroke may not be able to receive NIHSS scores for ataxia or dysarthria because their arousal state may preclude testing these items. Because these items are not scored abnormal unless patients produce testable behaviours, these patients may be too sick to score on these items\textsuperscript{192}. Though the patients may clinically improve, their NIHSS scores may artificially worsen since now items such as ataxia and dysarthria can receive the scores that were previously unscored\textsuperscript{192}. Since these items have been removed from the modified NIHSS, these difficulty can be avoided, or at least lessened. A modification of NIHSS was designed which maintains similar internal structure. Level of consciousness was redundant and dropped from the new scale. Ataxia showed poor reliability, so was excluded. Facial palsy and dysarthria showed poor reliability, and were redundant, so they were eliminated. The sensory item was simplified due to poor reliability. With fewer items and simpler grading, the modified NIHSS was intended to be simpler and easier to administer\textsuperscript{193}. The resulting
modified NIHSS has shown significantly higher reliability and validity than NIHSS\textsuperscript{194}. In the NIHSS, 7 of 42 points are related to language function, while only 2 of 42 points are attributed to neglect functions. Redundant items noted in the NIHSS have been deleted from the modified NIHSS, resulting in a more balanced clinical scale. Therefore, lateralization bias may be minimized\textsuperscript{192}. The author suggests scoring 0-3 to language function and including mute or global aphasia in score 3 as severe aphasia. This scoring strategy improves hemisphere balance between language and neglect items in modified NIHSS\textsuperscript{194,195}. Both NIHSS and modified NIHSS failed to accurately or reliably detect stroke severity in patients with posterior circulation findings\textsuperscript{194,195}. With the removal of the ataxia item, there may be concern that the modified NIHSS would be even less able to assess brainstem strokes. However, since ataxia is a poorly reliable NIHSS item anyway, the benefit of using a scale that inconsistently assesses the posterior circulation, may not outweigh the consistency of modified NIHSS. Many clinical trials routinely include only anterior circulation strokes, so there is less need to measure posterior circulation deficit for this purposes. However, stroke severity scale specialized for posterior circulation strokes has been developed and validated\textsuperscript{196}. The Scandinavian Stroke Scale is easier than NIHSS for clinical practice in acute stroke and has been used in many clinical trials\textsuperscript{12}. The Canadian Neurological Scale developed for assessment of acute stroke patients\textsuperscript{197}. Despite advantages of modified NIHSS and Scandinavian Stroke Scale comparing to the NIHSS (including their simplification and less interrater variability), most of the stroke neurologists around the world continue using the NIHSS because they have used to work with it for more than two decades, although it could not be an acceptable reason. At the other side, results of previous stroke trials which are basis of stroke management guidelines are driven using the initial NIHSS. The basic self-care tasks for quality of life and outcome measures after stroke are feeding, grooming, dressing, bathing, toileting, sphincter control, mobility, and transferring from place to place\textsuperscript{1,2}. These are called basic activities of daily living. Independence in these activities could enable the stroke patient to live at home with help from family or community providers for meals and other household tasks as needed. More complex activities of daily living are called instrumental activities of daily living. These tasks are performed to maintain independence in the home and community and include shopping, using transportation, telephoning, preparing meals, handling finances, and maintaining a household\textsuperscript{1,2}. Other instrumental activities of daily living that affect quality of life are work
skills, religious activities, leisure time and recreational activities\textsuperscript{2}. Leisure activities demonstrated the strongest association to subject well-being. The MRDS and Barthel Index (BI) are widely used functional impairment, disability scales which have been proven to be valid and reliable for defining outcome in stroke patients. Despite BI, distinction between grades of MRDS are poorly defined\textsuperscript{1}. Interrater variability introduces noise into trial outcome assessments and reduces the power of clinical trials to detect treatment outcome. A variety of approaches to minimize interrater variation of MRDS have been proposed, including: 1- use of a formal structured interview, 2- training and certification programs using written and video case vignettes, and 3- central panel adjudication of local site-recorded video assessments. However, the instruments and approaches developed to date have not consistently been shown to reduce interrater variability for MRDS. The clinicometric stroke scales only partly explain functional health and impact of impairments on functional outcomes seems to be underestimated by the stroke scale weights. Despite development of better functional impairment scales, stroke neurologists around the world continue using the MRDS and BI, because they have used to work with these scales for decades, although it could not be an acceptable reason. At the other side, results of previous stroke trials which are basis of stroke management guidelines are driven using the initial MRDS and BI. There is little consensus on the optimal implementation of the BI and MRDS as outcome measure in acute stroke trials and it is unclear which outcome scale is preferable.

Development and validation of the Asian Stroke Disability Scale (ASDS)

The ASDS was developed by the author as a nonclinicometric disability score like MRDS and Bartel Index\textsuperscript{199}. The procedure for developing the ASDS can be summarized as follows: 1- select the variables, 2- categorize the variables, 3- evaluate the categorization for their distribution and sensitivity, 4- modify and reevaluate the categorization, 5- repeat procedures 1 through 4 until the appropriate categorizations are obtained. Three items including; self-care, mobility, and daily activities were selected as variables for development of the ASDS based on the contribution of each item to the prognosis and a review of currently available stroke scales. The variables were provisionally graded on a 2- to 4-point scale based on importance of each item. Each of the variables was categorized into 3 categories. Each of the categories was expressed in a concrete way, avoiding abstractive expression, so that the same grade could be obtained regardless of the level of training of the rater. The total score for a patient could be calculated from the sum of the scores for each of the variables ranging from 0-8. Table 20 shows details of the ASDS\textsuperscript{199}. 


Five residents of neurology assessed the score of stroke patients based on the MRDS, Bathel Index (BI) and ASDS at 7 days post event. We included only later 25 stroke patients which consists of 125 rater-patients assessment for each of the MRDS, BI and ASDS in this analysis to eliminate any potential training effect. The MRDS and BI are widely used stroke disability scales which have been proven to be valid and reliable for defining outcome in stroke patients. Therefore we compared the interrater variability of ASDS with MRDS and BI assumed as gold standard. Each assessor performed score detection based on the MRDS, BI and ASDS in succession with neither assessor present in the room during the other's evaluation and the assessors were blinded to the others rating. For categorization of functional impairment as minor or major, the scores of MRDS, BI and ASDS were dichotomized at ≤2, >2; ≥90, <90 and <3, ≥3 respectively. The quantitative variability of BI, MRDS and ASDS scores between 5 raters was not significant; (df=4, F=1.061, 95% CI=52.639-62.400, p=0.379), (X²=1.758, df=4, p=0.780), (X²=1.454, df=4, p=0.835) respectively. Interrater variability of MRDS, BI, and ASDS scores by whole of the 5 raters based on the qualitative categorization was not significant; (X²=0.553, df=4, p=1), (X²=0.869, df=4, p=0.978), and (X²=1.434, df=4, p=0.901) respectively. The paired interrater variability of MRDS, BI and ASDS scores based on qualitative categorization was not significant for the three methods, p>0.05. The quantitative and qualitative interrater variability of ASDS in the validation study was similar to the MRDS and BI. The ASDS is a simplified functional impairment and handicap scale. The ASDS
is easy to use, requires less than 1 minute to perform the test and is as valid as MRDS and BI in assessment of functional impairment of stroke patients.

**Thrombolysis with other thrombolytic agents**

Intravenous administration of streptokinase or prourokinase out side of clinical trials is not recommended as an approved treatment for acute ischemic stroke. Intravenous streptokinase was associated with an unacceptable risk of hemorrhage and death. Desmoteplase is a highly fibrin specific plasminogen activator which has potential to safely extend treatment upto 3-9 hours post stroke onset. Intravenous desmoteplase is used in clinical trials in selected patients with a perfusion diffusion mismatch based on MRI or CT perfusion technologies. Intravenous desmoteplase administered 3 to 9 hours after stroke in these patients was associated with a higher rate of reperfusion and better clinical outcome, compared with placebo. Intra-arterial thrombolytic treatment of proximal MCA occlusion using Pro-Urokinase (PUK) within 6 hours was significantly associated with better outcome.

**Thrombolysis with Intra-Arterial rTPA Therapy**

Intra-arterial thrombolysis is an option for treatment of selected patients who have major stroke of <6 hours duration due to occlusions of the MCA and who are not otherwise candidates for intravenous rTPA. Intra-arterial thrombolysis is reasonable in patients who have contraindications to use of intravenous thrombolysis such as recent surgery. IA rTPA therapy is also used for carotid artery occlusions due to dissection following by angioplasty and stent insertion. This technique involves performance of a cerebral arteriogram, detecting the location of the occluding clot and then navigation of a microcatheter to the site of the clot. The clot is usually penetrated and thrombolytic agent (i.e. rTPA) is administered over 30-120 min. Intra-arterial rTPA therapy is investigational and needs patient or his/her family consent signature. Patients who could be treated within 6 hours with an acute stroke due to MCA stem occlusion are eligible for angiography and IA rTPA therapy, if the baseline NIHSS score is >4 and <20. Hyperdense MCA sign is characteristic of MCA stem occlusion. Other potential candidates of IA rTPA therapy are terminal ICA and BA occlusion. Intra-arterial rTPA therapy is more beneficial than intravenous rTPA in stroke associated with hyperdense MCA sign or terminal ICA occlusion even though intra-arterial route is started later. However this technique is not used for MCA branch occlusions, because IV rTPA works
enough in these circumstances\textsuperscript{12}. Dot sign on the initial CT at silvian fissure means MCA branch occlusion. If a stroke patient has hyperdense MCA sign in the initial CT and is within 3 hours window, IV rTPA therapy alone is possibly not going to good results. In this condition, both IV and IA rTPA could be administered\textsuperscript{185}. The dose of rTPA in combined therapy is intravenous route of 0.6 mg/kg (maximum 60 mg) and intra-arterial delivery of 0.3 mg/kg (maximum 30 mg). If the patient is out of 3 hours window you could start only IA rTPA therapy (0.3 mg/kg, maximum 30 mg), because approved IV rTPA therapy is often started within 3 hours\textsuperscript{200}. Intra-arterial thrombolysis is associated with increased risk of symptomatic ICH as compared to intravenous thrombolysis (15\% versus 5\%)\textsuperscript{184}.

**Thrombolysis Therapy with rTPA in Iran**

In Iran, ischemic stroke patients eligible for IV rTPA therapy, admitted to the hospital within 3 hours are around 1\%. At the other hand the health insurance program does not cover Alteplase vial. There are a few stroke neurologists in Iran. If Iranian health insurance would cover Alteplase, the author suggests IV rTPA therapy with approved standard protocol in some university hospitals. A prospective observational study was carried out in all of the patients with ischemic stroke admitted in Ghaem hospital, Mashhad during 2009\textsuperscript{201,202}. Ghaem hospital is a tertiary care hospital and a referral neurology center in east of Iran. Ghaem hospital contains Neurology, Emergency Neurology and Neuro-ICU divisions. Eight neurology faculties including 2 stroke neurologists are recruited in this center. CT, MRI and MR angiography, conventional angiography, emergency team, emergency laboratory, residents of neurology and neurosurgery are available in Ghaem hospital 24 hours per day and 7 days per week\textsuperscript{201,202}. Duplex sonography of neck arteries, Transcranial Doppler, Transthoracic and Transesophageal echocardiography are available in Ghaem medical center 6 hours per day in non-holidays. Patients demographics, stroke onset to hospital entrance time\textsuperscript{203}, hospital entrance to completed investigations time\textsuperscript{203} and method of patient transportation to the hospital was recorded in a data bank. Selection of patient delivery method had been made by the patients or their relatives. The para-medics team did not have any special training for requirements of thrombolysis therapy in stroke patients and there was no priority for triage of stroke patients in the emergency division\textsuperscript{201,202}. Presence of contraindications for intravenous thrombolysis with tPA based on the standard protocols was evaluated in stroke patients who arrived hospital within 3 hours time window after stroke onset\textsuperscript{203,204}. Although the chance of a complete or nearly
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complete recovery among patients with sever stroke, NIHSS≥25 improved by tPA treatment but overall success in this group of critically ill patients was low. Therefore NIHSS≥25 assumed as an exclusion criteria in our study. Economic capability for payment of 1400 USD for vial of tPA by the stroke patients was questioned in whom arrived hospital in 3 hours time window. A signed inform consent was taken by patients or their first degree relatives. Six hundreds twenty five ischemic stroke patients (344 males, 281 females) with mean age 62.1;SD: 10.7 were investigated for eligibility of intravenous thrombolysis with rTPA in our center. In this group, 50 stroke patients (30 males, 20 females); 8% arrived hospital within 3 hours time window. Among this 50 stroke patients, 25 patients were delivered to the hospital by ambulance and other half transported by personal vehicles. The mean stroke onset to hospital entrance time in ambulance and non-ambulance groups of these 50 stroke patients is 75.4 and 98.3 minutes respectively and ranged 10-340 minutes. The mean hospital entrance to completed investigations time in ambulance and non-ambulance groups of these 50 cases was 116.2 and 116.6 minutes respectively and ranged 20-360 minutes. Forty four percent of this early arrived 50 stroke patients remained within 3 hours time window at completed CT and laboratory tests. 18 stroke patients (18/50=36%) had hospital entrance to completed investigations time less than 60 minutes. Forty two percent of these 50 patients had no contraindication. Table 21 represents frequency of contraindications or exclusion criteria of intravenous thrombolysis in 50 cases who arrived hospital in 3 hours after stroke onset.

Table 21: Frequency of contraindications or exclusion criteria of intravenous thrombolysis in our 50 cases

<table>
<thead>
<tr>
<th>Type of contraindication</th>
<th>Number of patients</th>
<th>percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncontrolled hypertension</td>
<td>15</td>
<td>30%</td>
</tr>
<tr>
<td>Sever stroke-NIHSS&gt;25*</td>
<td>13</td>
<td>26%</td>
</tr>
<tr>
<td>Evidence of extensive infarction in CT</td>
<td>6</td>
<td>12%</td>
</tr>
<tr>
<td>Age above 80 years</td>
<td>4</td>
<td>8%</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Prior stroke in recent 3 months</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Prior stroke in diabetics</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Oral anticoagulant therapy</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Heparin therapy and increased PTT</td>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>Recent major surgery</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>1</td>
<td>2%</td>
</tr>
<tr>
<td>Multiple contraindications</td>
<td>15</td>
<td>30%</td>
</tr>
<tr>
<td>Minor stroke</td>
<td>3</td>
<td>6%</td>
</tr>
</tbody>
</table>

*Assumed as exclusion criteria in our patients
Among these early arrived group of our stroke patients, 15 cases (12 males, 3 females); 30% were capable for payment of tPA expense by themselves. Sixty percent of these rich candidates had a contraindication for thrombolysis therapy and 46.6% of them remained within 3 hours time window at completed CT and investigations. Only 20% of these rich candidates had no contraindication and remained within 3 hours window at completed investigations. Within 625 stroke patients, seven patients (1.1%) including 5 males and 2 females were eligible to intravenous thrombolysis. Meanwhile 86% of early arrived group of our stroke patients (43/50) missed thrombolysis therapy due to delay in investigations and presence of the contraindications.

In summary, contraindications of thrombolysis with tPA were found in 58% of Iranian early arrived stroke patients. Fourteen percent of our early arrived stroke patients and 1.1% of whole ischemic stroke patients were eligible for intravenous thrombolysis. The most important barrier of thrombolysis with tPA in our center is its uncoverage by Iranian health insurance systems in stroke patients. Although about 14 hospitals have this resource and infrastructure in Iran, however these medical centers cover less than one third of Iranian stroke patients. These limitations diminishes the chance of Iranian stroke patients for taking thrombolysis with tPA.

Fourteen Persian stroke patients received IV rTPA in our center in within six months. Two of these cases died due to development of intracerebral hemorrhage and brain edema.

Protocol violation was the main cause of this complication and poor outcome in our patients. At the other hand Persian race seems to have more probability for development of intracerebral hemorrhage following IV TPA. The same problem was reported in other Asian nations, e.g Pakistan and Japanese people. The author recommends below guidelines of thrombolysis therapy with tPA for modification of its expense in stroke patients of developing countries.

- Thrombolysis therapy should be used preferably in stroke patients younger than 60 years old who are economically active people.
- Intravenous thrombolysis should be initiated only in 3 hour time window exactly based on the standard protocol and patients with any contraindication should be excluded.
- Intravenous and intraarterial tPA therapy should be performed only in hospitals which have resources and infrastructure of this type of therapy.
- Although intraarterial thrombolysis with tPA extends the therapeutic time window up to 6 hours or more, however number of neurointerventionists in developing countries is too low and coverage of this route of thrombolysis by health insurance systems will not make significant increase of thrombolysis expenses.
Barriers of thrombolysis therapy in developing countries

The stroke in developing countries has grown to epidemic proportions\(^\text{207}\). Two-thirds of global stroke occurs in low- and middle-income countries\(^\text{207}\). Most of the available stroke data from these countries are hospital series\(^\text{44,207}\). There has been limited progress in management of patients with stroke in developing countries and data on stroke care in these countries are sparse\(^\text{208}\). Guidelines are continuously developed and updated in the developed world but their practicality for use in developing regions is unrealistic\(^\text{209}\). The number of stroke patients receiving r-tPA in third world is extremely low\(^\text{210}\). Stroke thrombolysis is currently used in few developing countries like Brazil, Argentina, Senegal, Iran, Pakistan, China, Thailand, and India\(^\text{210,211,212}\).

Prehospital barriers

One of the most important pre-hospital barriers of thrombolysis therapy in developing world is non-recognition of stroke warning signs by patients at risk, families, general public and even health workers in some places\(^\text{213}\). There is poor recognition of stroke symptoms in developing countries\(^\text{214}\). The people at highest risk have the lowest knowledge regarding vascular disease including limitations to ascertain mild and transient symptoms as stroke\(^\text{215}\). Most stroke patients attending a university hospital in India were not aware of the importance of the time window in stroke management\(^\text{216}\). Only one in 25 patients attending a stroke clinic and 27% of patients presenting to the stroke services in a tertiary care hospital in India were aware that they had suffered a stroke\(^\text{216}\). Production and broadcasting of stroke awareness programs by TV and other media could reduce the stroke onset to hospital entrance time\(^\text{217}\). There are also cultural and religious barriers that impede early presentation, even when stroke is recognized. Half of the patients with stroke in Bolivia do not go to hospital or see a doctor, thus consideration of health behavior is important in different population\(^\text{218}\). In developing countries, there is great variation in the time taken by patients to arrive hospitals\(^\text{213}\). The median time to admission of stroke patients in Gambia and Ethiopia is 8 hours and 13.5 hours respectively\(^\text{213}\). The proportion of stroke patients who reached the hospital within the 3-hour window period in Iran and India is 8% and 14.7% respectively\(^\text{201,219}\). Although there is hardly any ambulance service especially in rural areas in most of the developing countries\(^\text{208,210}\), in Iran there is a well organized ambulance service which covers the rural areas\(^\text{202}\). However about half of the Iranian urban population choose to deliver their patients by personal vehicles\(^\text{201,202,211}\).
Financial constraint

One of the main reasons of low utilization of thrombolytic therapy in these countries is financial constraints because recombinant tissue Plasminogen Activator (r-tPA) in developing countries has high cost (US$1400 per person)\textsuperscript{210,211}. The developing world, with a population five times the size of developed world, has at its disposal only 25% of the global gross domestic product\textsuperscript{220}. The budget allocation to health care is often meager, most of which goes to establishment and running costs\textsuperscript{220}, e.g. governments of Pakistan and Iran spend 0.72% and 5.4% of gross national product on health care which equals to about US$3.5 and US$7.5 per person per year respectively\textsuperscript{221,222}. Thrombolysis with r-tPA for stroke is not registered by governments in most of the developing countries and health insurance companies do not cover the high cost of thrombolysis therapy for stroke patients because the governments do not pay for this expensive therapy to these companies\textsuperscript{210}. Countries in the developing world where r-tPA is approved by the local regulatory authorities for use in acute ischemic stroke include; China, Philippines, Malaysia, Turkey, Thailand, Argentina, Brazil, Peru, Bulgaria, Czech Republic, Estonia, Slovakia, Ukraine and Poland\textsuperscript{210,211}. At the other words most governments in developing countries are not in a position to provide thrombolysis therapy in public sector hospitals to patients in need\textsuperscript{208,210,211}. Furthermore, stroke physicians are not paid for thrombolysis therapy by government and health insurance companies in some of the developing countries such as Iran\textsuperscript{211}. Therefore thrombolysis therapy is feasible in hospitals of private sectors which cover a limited number of stroke patients. Stroke patients in these countries should cover the cost of r-tPA by their own personal savings or not receive treatment\textsuperscript{210}. Only 30% of Iranian stroke patients could pay the cost of r-tPA by their own savings and thrombolysis therapy in India is mainly performed in some private hospitals\textsuperscript{201,202}. A study from south India reported that 30% of stroke patients reached hospital within 3 hours post event and 16% were eligible for thrombolysis therapy but all of these eligible patients belonged to a lower socioeconomic group and could not afford the therapy due to its high cost\textsuperscript{219}. Among 23 stroke patients admitted in a private hospital in northwest India who were eligible to intravenous thrombolysis, only five actually received the drug and the remaining patients were unable to afford the high cost of the treatment\textsuperscript{222}. The cost of r-tPA in India amounts to EUR 1300 per patient. The approximate cost for the secondary prevention of stroke in India is EUR 9 per month for each patient (using two antihypertensives, one antiplatelet agent and a statin) which is much cheaper
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...than r-tPA\textsuperscript{210}. Some health maintenance organizations in developing countries; e.g., Argentina, do not cover/reimburse for thrombolytic therapy despite its approval for stroke therapy by health authorities\textsuperscript{210,225}. The Argentina health system annual revenue in recent years has been approximately 7% of the gross national product. However, 40% of the Argentine population does not have medical insurance which receive medical attention free of cost at public hospitals\textsuperscript{224}. Governments must understand the importance of vascular disease prevention, treatment and assign sufficient resources for this purpose. In Spain as developed country, the impact of thrombolysis on society's health and social budget indicates a net benefit after 6 years and the improvement in health grows continuously\textsuperscript{225}.

**Lack of infrastructure**

Infrastructure is another barrier against thrombolysis in developing world. A general overview shows that the quality and quantity of stroke care is largely patchy in low developed and medium developed countries with areas of excellence intermixed with areas of severe need depending upon location and socioeconomic status\textsuperscript{214}. Centers with resources and infrastructure for thrombolysis in stroke patients are very limited in the developing world\textsuperscript{210,211}. A national survey in Poland showed that only 15% of stroke patients were admitted in specialized stroke units\textsuperscript{226}. Although about 14 hospitals have this resource and infrastructure in Iran with 75 million population and stroke units are increasing up to 20, however these medical centers cover less than one third of Iranian stroke patients\textsuperscript{201,202}. About 15 stroke units in India with more than 1 billion population use r-tPA for acute stroke\textsuperscript{210}. Unfortunately, most of the centers with the resources to facilitate thrombolysis therapy in India are in private sector. Hyperacute thrombolysis was found useful and safe in selected patients with ischemic stroke in India\textsuperscript{227}. In China, 40% of 1500 Neurology departments have the infrastructure to facilitate thrombolysis therapy for a population of 1.3 billion\textsuperscript{228}. Stroke patients who underwent either CT or MRI in China and Iran constitute 83% and 95% of these patients respectively\textsuperscript{201,202,228}. In African continent the situation of stroke care is much worse; only northern African countries and South Africa have an appropriate number of CT and some MRI scanners\textsuperscript{229}. Nine percent of stroke patients in Nigeria and 38% of the stroke patients in Ethiopia could afford to have CT scans\textsuperscript{229,230}. The stroke unit model of care in South Africa has not been widely implemented despite compelling evidence of efficacy\textsuperscript{231,232}. Currently there is 1 comprehensive acute stroke unit in Cape Town\textsuperscript{232}. Therefore thrombolysis therapy with r-tPA
in Africa is a dream\textsuperscript{229,230,231,232}. Except Brazil and Argentina, well-organized stroke services in the government sector are virtually absent in South America\textsuperscript{210,211}. There are about 20 hospitals in Brazil where intravenous thrombolysis is administered\textsuperscript{217}. The majority of stroke patients are treated in public hospitals in Brazil through a united health system. Emergency ambulance services are being widely available in Brazil\textsuperscript{217}. The health care system in Argentina provides limited incentives to health care providers and hospitals to offer specialized care for stroke patients\textsuperscript{224}. Seven stroke units have been build in Argentina, however 1.3\% of stroke patients in Argentina receive thrombolysis therapy and 6.9\% are admitted in the stroke units\textsuperscript{223,224}. Thus availability of skilled manpower to deliver thrombolysis and multidisciplinary care in a dedicated stroke unit is very limited in developing countries\textsuperscript{211}. The mean hospital entrance to completed investigations time in early arrived Iranian stroke patients was 116 minutes\textsuperscript{201,202}. Delay in performance of CT and laboratory tests excluded 56\% of Iranian early arrived stroke patients from 3 hours time window and is a problem of this therapy in Iran\textsuperscript{201,202}. This delay is due to lack of priority for candidates of thrombolysis in performance of triage, CT and laboratory tests\textsuperscript{201,202,211}. Avoidance of this delay increases upto 2-3 times the number of eligible Iranian stroke patients for intravenous r-tPA\textsuperscript{201,202}. Lack of priority of stroke patients in Emergency division and CT scan facility caused a high mean door to needle time (120 minutes) in Pakistan\textsuperscript{221}. The mean door to needle time was 27 min in a public sector hospital in New Delhi and 72 min in Thailand and 21 min in Taiwan\textsuperscript{205,233,234}. A study on stroke evaluation in Buenos Aires university hospital revealed that 24\% of stroke patients arrived within 2 hours post event to the emergency room and 2\% had a CT under 2.5 hours\textsuperscript{235}. Fourteen percent of stroke patients who received thrombolytic therapy with r-tPA in Pakistan developed fatal hemorrhage and 10\% of them had non-fatal hemorrhage\textsuperscript{221}. Protocol violations were found in 33\% of these treated stroke patients\textsuperscript{221}. A similar situation was found in IV TPA treated Persian stroke patients who developed intracerebral hemorrhage as explained before. This may be a part of learning curve and it clearly identifies a need of educating physicians involved in stroke care. Another possible explanation for increased rate of the intracranial hemorrhage in Pakistan and Iran could be related to genetic variability\textsuperscript{221}. Higher rates of r-tPA-related intracranial hemorrhage among Asians due to racial differences in blood coagulation-fibrinolysis factors is reported in Japanese stroke patients\textsuperscript{236}. These racial differences in developing and developed countries of Asia could affect the cost and benefit ratio of thrombolysis therapy in this
continent. The number of medical centers with interventional facilities for intraarterial thrombolysis with r-tPA in some developing countries like Brazil and Senegal is surprisingly more than stroke units. In most of the developing countries; e.g, Iran and Pakistan this condition is reverse. However number of Iranian stroke patients who have been treated with intraarterial r-tPA is surprisingly more than patients who administered intravenous r-tPA. There are two reasons for this discrepancy. First, dose of r-tPA for intraarterial administration is one-third of its dose for intravenous route and this matter makes intraarterial thrombolysis cheaper in Iran and some of the developing countries. Second, Intraarterial r-tPA therapy extends therapeutic time window upto 6 hours or more and only 44% of early arrived Iranian stroke patients remain within 3 hours time window at completion of CT and laboratory workup due to lack of priority of these patients for triage and investigitations.

**Promotion of infrastructure**

Some of the developing countries have been promoting infrastructure for stroke care in recent three years. The Brazilian program for establishment of stroke network initiated in 2008. Four levels of stroke hospitals defined in Brazilian program: (1) Level A: a comprehensive stroke center; (2) Level B: a hospital with neurologist and CT available 24 h a day but without MRI or endovascular interventions; (3) Level C: a remote center for thrombolysis with telemedicine connected to a Level A center (for areas without neurologist; and (4) Level D: a hospital without structure for thrombolysis. In each state, the program was tailored according to the local conditions (infrastructure and technical staff). The program will be expanded to 15 of the 26 states. A stroke program has been created in Russian Federation since 2007, in which each region of Russia will have 1 to 3 comprehensive stroke centers (1 center per 1.2 to 2 million population). Each comprehensive center will be connected to a network of 3 to 6 primary stroke units with telemedicine. The program is financed from federal budget and from budgets of constituent territories of the Russian Federation. Four hundred sixty-three patients received treatment with rtPA during over the 9 months of 2009 within Russian stroke program. The new system of stroke care will be deployed in all 83 regions of Russia by 2013. In South Africa with only one comprehensive stroke unit, a stroke training course was developed for nurses and allied professionals and has attracted staff from other local hospitals. This stroke unit has assisted in the establishment of stroke services and units at other hospitals in both the public and private
sector\textsuperscript{212}. Some recent reports support the use of thrombolytic therapy in stroke patients in previously inexperienced centers by using guidelines created by clinical trials of intravenous thrombolytic therapy\textsuperscript{238,239}.

**Organization of Stroke Care Units**

Primary Stroke Center (PSC) is defined as centers with neurologist on call, radiologist on call and stroke trained physician available 24 hours per day in 7 days a week. Intravenous rTPA therapy is available in PSC 24 hours per day in 7 days a week\textsuperscript{240}. PSC should have stroke trained nurses. Physiotherapy and speech therapy should be started within 2 days post stroke in PSC\textsuperscript{240,115}. Brain CT, automated monitoring of pulse, blood pressure, temperature and ECG are available in PSC 24 hours per day in 7 days a week. General ICU, Emergency department and stroke clinic are present in PSC\textsuperscript{83,115,240}. Extracranial duplex sonography and transthoracic echocardiography are available in the PSC. Stroke awareness programs and stroke prevention programs are defined in PSC\textsuperscript{83,115,240}. Comprehensive Stroke Center (CSC) is defined as centers with stroke faculty on call, interventional neuroradiologist on call, neurosurgeon on call and vascular surgeon on call. CSC should have stroke trained physician 24 hours per day in 7 days a week. Brain CT, MRI (T\textsubscript{1}, T\textsubscript{2}, Flair, MRA), CT angiography, cerebral catheter angiography, TCD, extracranial duplex sonography, intravenous and intraarterial rTPA therapy should be available 24 hours per day in 7 days a week in CSC\textsuperscript{83,115,240}. CSC should have stroke trained nurses. Automated monitoring of pulse, blood pressure, temperature and ECG should be available 24 hours per day in 7 days a week in CSC\textsuperscript{240}. General ICU, Emergency department, stroke data base, transthoracic echocardiography, transesophageal echocardiography and stroke clinic are available in CSC\textsuperscript{83,115,240}. Physiotherapy and speech therapy start within 2 days post stroke in CSC. Stroke awareness programs and stroke prevention programs are present in CSC. Surgery for hematoma, ventricular drainage, carotid endarterectomy, decompressive craniotomy, and aneurysmal surgery should be available in CSC\textsuperscript{83,115,240}. Extracranial and intracranial angioplasty and stenting, should also be available in CSC\textsuperscript{83,115,240}.
Chapter IX

Hemorrhagic Stroke in Clinical Practice

In Intra-Cerebral Hemorrhage (ICH) the dynamics of macropathological changes after appearance of the primary lesion include hematoma growth, perihematomal edema and/or ischemia, hydrocephalus or secondary intraventricular hemorrhage. All of these complications also can potentially increase ICP by mass effect resulting in neurological deterioration. The hypertensive ICH is typically a one time event. This characteristic of hypertensive ICH clearly differentiates these cases from those due to ArterioVenous Malformation (AVM) and aneurysm. Rapid resolution of neurologic deficits in clinical course indicates ischemia rather than hemorrhage. Multiple simultaneous hematomas occurs in 2% of ICH cases who are usually normotensive. This is an uncommon but characteristic feature of cerebral amyloid angiopathy, trauma, cerebral venous thrombosis, metastasis, hematologic disease, thrombolytic and anticoagulant therapy. Single ICH in normotensive patients occurs in AVM, cerebral amyloid angiopathy, brain tumor, anticoagulation, vasculitis and primary ICH. The causes of lobar ICH are hypertensive in 30%, AVM in 7-14%, tumors in 7-9%, blood dyscrasias or anticoagulation in 5-20% of the patients. In neuroimaging, resolving hematomas frequently shows post contrast ring enhancement after 1-6 weeks which disappears after 2-6 weeks. This phenomenon is due to hypervascularity and disruption of blood brain barrier at the periphery of resolving hematoma. CT with contrast is indicated if an AVM, tumor or hemorrhagic metastasis is suspected in patients with ICH. Enhancement at edges of hematoma can be seen after a week even without above causes. In hemorrhagic strokes the indications of catheter angiography are; 1- suspected aneurysm, 2- suspected AVM or dural fistula, 3- suspected vasculitis, 4- suspected Moyamoya syndrome. It is not practical to perform frequent imaging studies in these patients. Catheter angiography is
usually performed in ICH due to AVM and saccular aneurysm. Angiography is not urgent in vascular anomalies because rebleeding occurs usually after months or years but it is urgent in saccular aneurysms. Measurement of hematoma volume is done based on the Broderick formula: \( \text{ABC}/2 \) (Cm\(^3\)). Where A is the largest diameter of the hematoma in CT slice with largest area of ICH. B is the largest diameter of the hematoma perpendicular to line A. C is the number of 1-Cm-thick slices with hematoma. If the hemorrhage area for a particular slice is greater than 75% of the area seen on the slice where the hemorrhage is largest, the slice is considered 1 hemorrhage slice for determining C. If the area is approximately 25% to 75% of the area, the slice is considered half of a hemorrhage slice. If the area is less than 25% of the largest hemorrhage area, the slice is not considered a hemorrhage slice.

**Current Recommendation Regarding Surgical Treatment in hypertensive ICH**

1- Lobar ICH: Surgical evacuation for supratentorial hematoma is only indicated in patients presenting with lobar clots within 1 Cm of surface. If patient is drowsy or lethargic with progressive decline in consciousness and hematoma volume is 30-60 Cc then consider surgery. Evacuation could be considered in patients with lobar ICH >30 cm\(^3\) who show signs of progressive neurologic deterioration.

2- Putaminal ICH: If patient is alert and hematoma volume is <30 Cc, the case is non-surgical. If patient is comatose and hematoma volume is > 60 Cc, the case is nonsurgical. If patient is drowsy with hematoma volume 30-60 Cc, then consider surgery.

3- Caudate ICH: If patient is drowsy with intraventricular hemorrhage or hydrocephalus, then consider ventriculostomy.

4- Thalamic ICH: If patient is lethargic or drowsy with blood in third ventricle or hydrocephalus then consider ventriculostomy. Thalamic hematomas have frequent ventricular extension reflecting location of the hematoma and a high frequency of hydrocephalus which may allow a successful shunting.

5- Pons & Midbrain ICH: These are nonsurgical in every case.

6- Cerebellar ICH: Patients with cerebellar hemorrhage >3 Cm who are deteriorating or who have brain stem compression and/or hydrocephalus from ventricular obstruction should have surgical removal of the hemorrhage as soon as possible. Smaller cerebellar hemorrhage without brainstem
compression that are managed medically do reasonably well in the case series. In cerebellar hematomas there are two groups of patients. The first group have abrupt onset, a more severely depressed level of consciousness and a tendency toward progressive deterioration while the second group has a more benign and stable course. The first group requires immediate surgical treatment whereas the second group do well on a medical therapy. CT scan of the first group shows hematomas >3Cm in diameter and/or obstructive hydrocephalus and/or effacement of the quadrigeminal cistern (ventricular extension of the hematoma). These features are absent in the second group. There is strong impression that surgery saves lives in patients with cerebellar ICH who have clinical evidence of brain stem compression. The development of obtundation and extensor plantar response is ominous and usually follows a fatal outcome without surgery.

No clear evidence at present indicates that ultra-early craniotomy improves functional outcome. Minimally invasive or stereotactic surgery in ICH patients have some benefits; 1- reduces the operative time, 2- is performed under local anesthesia, 3- reduces tissue trauma. However this technique is not able to treat AVM and aneurysm. The use of intraventricular instillation of rTPA for clot evacuation in patients with sever intraventricular hemorrhage is reported. Patients who underwent stereotactic removal of ICH did well with instillation of Urokinase in to the bed of the clot. Minimally Invasive Stereotactic Surgery plus rTPA for ICH Evacuation (MISTIE) tests the following hypothesis: 1- Early use of minimally invasive surgery plus intraclot delivery of tPA during first 3 days is safe for treatment of ICH and 2- This therapy reduces clot size compared with medically treated patients. Of all the surgical therapies described for treating ICH, craniotomy has been the most extensively studied and 7 of the 9 randomized controlled trials of ICH evaluated craniotomy. Most of these trials are small, single center studies that randomized fewer than 125 patients. None of these small studies found convincing evidence of surgical benefit. A direct surgical approach is considered frequently in patients with lobar or cerebellar hematomas, whereas patients with brainstem, caudate and thalamic hemorrhage are rarely, if ever surgical candidates. Putaminal hemorrhage occupies an intermediate position and is most controversial. Epidemiologic studies illustrated that hypertensive ICH commonly occurs during change from cold to hot seasons and reverse. Most of these hypertensive ICHs occur at the early morning.

Arterio-Venous Malformations (AVM)
ICH in young normotensive patients without coagulopathy should be assumed as AVM. Typical features of AVM include: 1-ICH in 50-60% of cases, 2-History of focal seizure or progressive neurological deficit, 3-Throbbing headaches with or without auras always located to one side of the cranium (more common in occipital AVMs and AVMs with meningeal supplies from external meningeal arteries), 4-Cranial bruits. Brain stem AVMs and cavernous angiomas may present with fluctuating neurologic dysfunction and simulate multiple sclerosis. In the spinal cord level, AVMs present with back pain, myelopathic and radiculopathic symptoms. Catheter angiography is essential for surgical and interventional management of every AVM. Normal angiograms may be seen in AVMs with: 1-Obliteration of the arterial feeders by pressure of the hematoma, 2-Spontaneous thrombosis of the AVM or self cure, 3-Cavernous angioma, because they have no direct arterial feeder. Local high flow velocity with low pulsatility index in TCD in only found in AVM. This high velocity is related to amount of arterial supply to AVM but is not related to the risk of hemorrhage and rupture. Cavernous angiomas are often multiple and can be familial. Seizure and progressive neurological deficit in cavernous angiomas and venous angiomas are more common than AVM. Cavernous angiomas characteristically appear on T2 weighted images as irregular lesions with a central core of mixed (high and low) signal surrounded by a halo of hypodensity corresponding to hemosiderin deposition (eyes of Tiger). MRI does not show space occupying effect in cavernous angiomas and catheter angiography is normal. Venous angiomas are the most common incidentally discovered vascular anomaly. Several dilated veins (caput medusa) is pathognomonic neuroimaging finding of venous angioma. Surgery of venous angiomas could be disastrous and make venous infarction.

**Cerebral Amyloid Angiopathy (CAA)**

CAA usually occurs sporadically and is not associated with systemic amyloidosis. ICH due to CAA rarely occurs before age 55. CAA is associated with Alzheimer or senile dementia in 30% of cases. CAA could cause TIA and focal seizure. ICH in CAA is usually lobar in location, sometimes affecting cortex and meninges. ICH of CAA has tendency to recur in other sites over periods of months to years. CAA is the cause of recurrent, sometimes multiple ICH in elderly normotensive individuals.
Neuroimaging features suggesting ICH due to brain tumors

Some neuroimaging findings favor diagnosis of ICH due to brain tumors. These patterns are explained following.

1- Presence of low density indentation or digitate pattern of edema at periphery of ICH\textsuperscript{12}.
2- Amount of surrounding edema and mass effect is disproportionate to hematoma volume\textsuperscript{12}.
3- Presence of post contrast irregular ring enhancement in acute phase of ICH, ring enhancement is usually seen in subacute phase of ICH\textsuperscript{1,12}.
4- Presence of the enhancing nodules adjacent to the hemorrhage on contrast CT.
5- The appearance of the other lesions.
6- Bleeding into tumors tends to be lobar or occur in sites that is rarely affected by primary ICH such as corpus callosum\textsuperscript{1,12}.

ICH due to anticoagulation

Risk factors of ICH in anticoagulated patients include; age $>$70 years, hypertension, brain infarction, aspirin administration and increase in INR values\textsuperscript{1}. The HAS-BLED score could also be useful in this aspect\textsuperscript{119}. Characteristic leisurely progression of the focal neurologic deficit during 48-72 hours occurs in half of these cases. Volumes of hematomas in these cases are larger on average than those in other cases and have higher mortality comparing with other similar sized hematomas\textsuperscript{1}. Location of hematoma in these cases are similar to hypertensive ICH. A high frequency
of cerebellar hematomas may be found in these patients who have INR>2.5. Characteristic fluid-blood level within hematoma, a horizontal interface between unclotted serum and sedimented red cells, occurs in up to half of these cases\cite{1,2}. ICH is more common after warfarin than heparin therapy because heparin therapy is usually performed in hospitalized patients who have better control of coagulation tests. ICH may occur within 24-48 hours after onset of anticoagulation therapy in patients with brain infarction. Large infarct size, uncontrolled hypertension and increase in INR are risk factors of ICH in patients with brain infarction\cite{83}. In patients with heparin induced ICH, protamine sulfate 1 mg/100 unit Heparin which is infused within the previous hours, should be given slowly to prevent hypotension and bradycardia\cite{1,241}. In patients with enoxaparin induced ICH or other hemorrhagic complications, protamine sulfate 1 mg/1 mg enoxaparin received within recent 8 hours is administered. If patient received enoxaparin before recent 8 hours, protamine sulfate 0.5 mg/1 mg is administered intravenously and this dose can be repeated if bleeding due to enoxaparin does not stop. For ICH due to warfarin therapy, the first step is discontinuation of warfarin. The second step is infusion of Fresh Frozen Plasma (FFP) 15cc/kg, about 1 liter for adults, with intravenous injection of 5 mg VitK\cite{1,241}. If patient who is on warfarin has very high INR without hemorrhage, stop warfarin and use intravenous 0.5 mg Vit K. Infusion of FFP is not indicated in these cases. Aspirin very rarely causes ICH and dose of aspirin is not related to the risk of ICH\cite{1,241}. In patients with aspirin induced ICH, the first step is discontinuation of aspirin and the second step is infusion of platelet. In cohort studies, aspirin use at the time of ICH compared to no aspirin use was independently associated with increased mortality but not with poor functional outcome\cite{243}. ICH should not be attributed to thrombocytopenia unless the platelet count is below 20000\cite{1}. ICH secondary to fibrinolysis occurs early after onset of TPA therapy. Fibrinolysis induced ICH is usually lobar and in 30% multiple with high mortality. Myeloid leukemia is complicated by ICH in 20% of cases, whereas ICH is rare in other types of leukemia\cite{1,241}. ICH in leukemia is usually multifocal and part of a generalized bleeding tendency\cite{1}.

**ICH due to vasculitis**

Vasculitic ICH is often lobar and usually occurs in the setting of chronic headache, progressive cognitive decline, seizure and recurrent cerebral infarction\cite{1,12}. Due to its primary cerebral location systemic features of vasculitis and elevated ESR are absent in vasculitic ICH. Angiography may show beading pattern in multiple vessels of these cases\cite{1,12}.
ICH due to Moyamoya syndrome

Moyamoya syndrome causes multiple TIA and infarction in children. While, ICH and SAH constitutes the presenting patterns of Moyamoya syndrome in young adults. Because the anastomotic network is located in deep hemispheric regions, hemorrhage in Moyamoya cases usually occurs in putamen, thalamus and caudate.\textsuperscript{1,11,12}

ICH due to bacterial endocarditis

Bacterial endocarditis may cause ICH by making mycotic aneurysm which is often multiple and peripheral. A lobar ICH is rarely due to endocarditis in a patient without recent malaise, fever, weight loss and heart disease.\textsuperscript{1,12}

Aneurysmal ICH and Sub-Arachnoid Hemorrhage (SAH)

SAH is occasionally associated with ICH. These ICHs are often located in basal or medial frontal lobe and middle temporal lobe. These aneurysmal cases of ICH and SAH usually do not show intraventricular hemorrhage. Primary ICH usually reaches the subarachnoid space by way of the ventricles. Association with cisternal hemorrhage is characteristic in aneurysmal ICHs.\textsuperscript{1}

The most distinctive feature of SAH headache is its sudden onset. However only one-quarter of patients with sudden onset severe headache have SAH.\textsuperscript{2,3}

Because common headaches (i.e. migraine and tension headache) can infrequently raise suddenly. Headache with gradual onset, if occurs in SAH patients is more common in cases with non-aneurysmal perimesencephalic hemorrhage.\textsuperscript{2} If a patient have sudden onset headache and oculomotor nerve palsy, rupture of posterior communicating artery aneurysm is highly possible.

Neck stiffness caused by meningismus does not occur immediately after SAH. It takes 3-12 hours and may not develop at all in deeply comatose patients or in patients with minor SAH. Back and leg pain may follow SAH because blood irritates lumbosacral nerve roots.\textsuperscript{3} If SAH is suspected clinically but the brain CT is normal, look carefully at the interpeduncular and quadrigeminal cisterns. In the CT negative suspected SAH patient, lumbar puncture should be performed after 12 hours post event, even if noninvasive neurovascular imaging such as CT angiography or MRA rules out aneurysm.\textsuperscript{3}

Because xanthochromia after centrifuging CSF appears after 12 hours and provides distinction of a traumatic tap from SAH. In suspected cases of SAH with normal CT and lumbar puncture performing catheter angiography is not indicated. Hematomas from aneurysmal hemorrhage can be reliably diagnosed by association of the cisternal hemorrhage and its typical location.\textsuperscript{2} MRA has sensitivity of 95\% for detection of aneurysms more than 5 mm and
50% for aneurysms less than 5mm. CT Angiography (CTA) is readily available less invasive alternative to catheter angiography and has demonstrated sensitivities approaching equivalent to catheter angiography for larger aneurysms. For aneurysms ≥5 mm, CTA has a sensitivity more than 95% and when aneurysms are <5mm, it has a sensitivity about 70% compared to catheter angiography. Among aneurysms detected on CTA and then undergoing surgery, a total correlation was observed between CTA and catheter angiography. CTA can also be used to supplement information obtained by catheter angiography. CTA is better able to define aneurysmal wall calcification, intraluminal aneurysm thrombosis, orientation of aneurysm with respect to intraparenchymal hemorrhage and the relationship of the aneurysm with bony landmarks. The use of CTA continues to evolve and in the future, CTA will increasingly supplement or selectively replace conventional angiography in the management of acute SAH. Selective catheter cerebral angiography is currently the standard for diagnosing cerebral aneurysms as the cause of SAH. About 25% of cerebral angiograms performed for SAH will not indicate a source of bleeding. Repeating angiography after 1 week will disclose a previously unrecognized aneurysm in an additional 2% of the cases. Catheter angiography in patients with SAH should be performed only with a view to surgical or endovascular treatment. Angiography negative SAH is present in below situations: 1-Technical reasons, i.e, insufficient use of oblique projections, 2-Narrowing of blood vessels by vasospasm, 3-Thrombosis of neck or whole of the aneurysm, 4-Obliteration of aneurysm by pressure of an adjacent hematoma, 5-Presence of microaneurysm. In other series of patients with normal initial catheter angiogram, repeated angiogram showed the aneurysm in up to 17%.

![Diagram of aneurysms](image_url)
Prescribing orders in patients with hemorrhagic stroke

1- Elevation of the head of the bed to 30° improves jugular venous outflow and lowers ICP. The head should be in midline and head turning to either side should be avoided.

2- Intravenous sedation with diazepam is needed in unstable patients who are intubated for maintenance of ventilation.

3- Mannitol is an intravascular osmotic agent that can draw fluid from both edematous and non-edematous brain tissue. Mannitol decreases blood viscosity, which results in reflex vasoconstriction and decreased cerebrovascular volume. The major problem associated with mannitol is hypovolemia. In a clinical trial, 128 patients with primary ICH within 6 days of onset were randomized to mannitol 20%, 100mL every 4 hours for 5 days tapered in the next 2 days. The control group received placebo infusion. At 1 month 25% of patients in each group died and at 3 months the outcome was not significantly different. However, mannitol is infused during herniation in ICH patients with below protocol. The initial dose of mannitol is 500cc of 20% solution infused during 30 minutes and followed by 125cc every 6 hours.

4- Normal saline serum is infused, 1-1.5 liter/day for ICH and 3 liters/day for SAH patients.

5- Antacid is given in ICH and SAH patients for prevention of stress ulcer. Laxatives are prescribed in SAH for prevention of aneurysmal re-rupture during valsalva maneuver.

6- Analgesics are used for decreasing sever headache. Morphine may be used for analgesia.

7- It is generally agreed that sources of fever should be treated and antipyretic medication should be administered to lower temperature in febrile patients with ICH.

8- Early mobilization and rehabilitation should be done in patients with ICH who are clinically stable.

9- Evidence indicates that hyperglycemia >140 mg/dL during the first 24 hours after stroke is associated with poor outcomes and hyperglycemia should be treated. Elevated glucose concentration >180 mg/dL and possibly >140mg/dL should be treated by insulin.

10- Low dose subcutaneous heparin or enoxaparin may be considered in patients with hemiplegia after 3 to 4 days from onset of ICH after documenting cessation of bleeding for prevention of DVT and pulmonary embolism. Patients with ICH who develop an acute proximal venous thrombosis are considered for acute placement of vena cava filter.
11- Nimodipine reduces the vasospasm and poor outcome in SAH patients. Nimodipine is administered with 60 mg tablets every 4 hours or IV route for 3 weeks. If the patient is unable to swallow, the tablets should be crashed and washed down by NG tube. Dose of nimodipine should be half in patients with hypotension. Hypotension and headache are its side effects. In patients with symptomatic cerebral vasospasm, volume expansion, inducing hypertension and hemodilution (triple-H therapy) is indicated. Volume expansion is done by administration of 500 cc colloid such as 5% albumin or haemaccel on 4 hours. Transluminal angioplasty and/or selective intraarterial vasodilator therapy is used for vasospasm in SAH, unresponsive to hypervolumic therapy and nimodipine prescription.

12- Antiepileptic therapy should be used for treatment of clinical seizures in patients with ICH. Initial choice of medications includes benzodiazepines such as lorazepam or diazepam followed by intravenous phenytoin. A brief period of antiepileptic therapy soon after ICH onset may reduce the risk of early seizures, particularly in patients with lobar hemorrhage. Choice of medication for prophylaxis should include one that can be administered intravenously as needed during hospitalization and orally after discharge. Prophylactic use of antiepileptics is controversial in SAH and ICH. The routine long-term use of anticonvulsants is not recommended in SAH patients but may be considered for patients with prior seizure, parenchymal hematoma, infarct or MCA aneurysm.

13- Prospective cohorts have shown that for untreated ruptured aneurysms, there is 4% risk of rebleeding in the first day after the initial ictus and a 2% per day risk in the first month. Urgent investigation and treatment of patients with suspected SAH is therefore recommended. Aneurysm operation and endovascular embolization for aneurysm is indicated as soon as possible in patients with SAH. The major complications following SAH are due to ischemic deficit (27%) and hydrocephalus (12%). However the most feared complication for survivors of the initial hemorrhage is recurrent bleeding, which occurs in 15-20% of the patients and is associated with a 40-78% mortality. The definitive method for prevention of rebleeding is to secure the aneurysm as soon as possible. Early surgery may not be appropriate for every patient with SAH but every attempt should be made to secure the aneurysm as soon as possible to prevent rebleeding. Early treatment of aneurysm reduces the risk of rebleeding after SAH and certainly allows more aggressive and early management of cerebral vasospasm by hemodynamic therapy and interventional management. Endovascular treatments are associated with lower complication rates and higher recurrence.
Chapter IX: Hemorrhagic Stroke in ...

rates than surgical clipping. In addition there is a 16% reduction in risk of in-hospital death in institutions that use angioplasty for vasospasm\textsuperscript{244}.

14- Antifibrinolytic drugs, i.e. tranexamic acid 1 gr IV prevents rebleeding but increases the risk of cerebral ischemia. However the overall outcome is not different by antifibrinolytics management\textsuperscript{1}.

15- Temporary or permanent CSF diversion is recommended in symptomatic patients with chronic hydrocephalus after SAH. Ventriculostomy can be beneficial in patients with ventriculomegaly and diminished level of consciousness after acute SAH\textsuperscript{244}.

16- Elevated blood pressure may increase the risk of ongoing bleeding from ruptured small arteries and arterioles during the first hours. Conversely, overaggressive treatment of blood pressure may decrease cerebral perfusion pressure and worsen brain injury, particularly in the setting of increased ICP by inducing cerebral ischemia in the edematous region that surrounds the hemorrhage\textsuperscript{241}. The rational for lowering blood pressure is to avoid hemorrhagic expansion from potential sites of bleeding. This is especially true for hemorrhage resulting from ruptured aneurysm or AVM in which the risk of continued bleeding or rebleeding is highest. Enlargement of hematoma occurs most frequently in patients with elevated systolic blood pressure. Reduction of blood pressure to a target <160/90 mmHg is associated with improved outcome if BP is lowered within 6 hours of hemorrhagic onset\textsuperscript{241}. Repolarization abnormalities are frequent in ECG of patients with hypertensive ICH\textsuperscript{245}. The presence and degree of these ECG findings depends on location and volume of hematoma\textsuperscript{245}.

**Recommended guidelines for Treating Elevated Blood Pressure in ICH**

1- If systolic blood pressure is >200 mmHg or mean arterial pressure is >150 mmHg, then consider aggressive reduction of blood pressure with continuous intravenous medication with frequent blood pressure monitoring every 5 minutes\textsuperscript{241}. 2- If systolic blood pressure is >180 mmHg or mean arterial pressure is >130 mmHg and there is evidence of elevated ICP, then reduce BP using intermittent or continuous intravenous medication\textsuperscript{241}. 3- If systolic blood pressure is >180 mmHg or mean arterial pressure is >130 mmHg and there is not evidence of elevated ICP, then make a modest reduction of blood pressure; target blood pressure of 160/90 mmHg, mean arterial pressure of 110 mmHg\textsuperscript{241}. Intravenous medications that may be considered for control of elevated blood pressure in patients with ICH and SAH include labetolol 5-20 mg every 15 minutes, 2 mg/minute (maximum 300 mg/day) and nitroglycerine 20-400 microgram/minute\textsuperscript{241}.
Recombinant activator factor VII (Novoseven)

Factor VIIa is approved to treat bleeding in patients with hemophilia. Interaction of rFVII and tissue factor stimulates thrombin generation. rFVIIa also activates factor X on the surface of activated platelets, which leads to an enhanced thrombin burst at the site of injury. Thrombin converts fibrinogen to fibrin which produces a stable clot. Recombinant activator VII (Novoseven) is administered within 4 hours of symptom onset in patients with spontaneous ICH diagnosed by CT. Novoseven was used in doses of 40, 80 and 160 microgram per kilogram body weight in a clinical trial. Reduction of hematoma volume within 24 hours, lowering mortality and improvement of functional outcome within 90 days were evaluated. Overall novoseven in dose of 40 microgram per kilogram has the best results and cost effectiveness. Up to 4% of ICH patients are eligible to early haemostatic therapy. Four hundreds patients with ICH within 3 hours of onset were randomized to receive placebo or rFVII with doses 40, 80, 160 microgram/kg. The mean increase in hematoma volume in placebo group was 29% compared to 16%, 14% and 11% in the above groups of given rFVII respectively. Sixty nine percent of placebo treated patients died or were severely disabled as defined by modified Rankin scale 5-6, compared to with 55%, 49% and 54% of patients who were given above doses of rFVIIa respectively, \( p=0.004 \). Based on this clinical trial, treatment with rFVII within 3 to 4 hours after onset of spontaneous ICH may cause slowing progression of bleeding. rFVII has been used in cases with warfarin associated ICH.

Comparison of medical and surgical treatments of ICH in a developing country

Consecutive Persian patients with primary ICH admitted in Ghaem hospital, Mashhad, Iran during 2005-2009 enrolled a prospective clinical study. Diagnosis and localization of primary ICH was made by neurologist based on brain CT. All of the ICH patients received a standard medical management including 1.5 liter of normal saline per day, control of hypertension, analgesics and other conservative managements. Activated coagulation factor VII is not available in our hospital for medical management of primary ICH patients. Selection of ICH patients for surgical evacuation was performed by neurosurgeons. Craniotomy and evacuation of hematoma is the routine surgical technique in our hospital. Shunting for hydrocephalus and drainage of intraventricular blood with or without evacuation of hematoma was performed based on the neurosurgeon
decision. Stereotactic surgery with or without thrombolysis is rarely performed in our hospital and none of the reported patients with primary ICH underwent this surgical approach. Neurologists ruled out other causes of ICH based on the medical history and neuroimaging\textsuperscript{12}. ICH patients suspected to tumoral lesions underwent MRI with contrast and patients suspected to arteriovenous malformation had MRI, MRA and catheter angiography\textsuperscript{12}. In-hospital death was recorded in two therapeutic groups of primary ICH patients. Mean ICH onset to death time was recorded in whole of the deceased ICH patients. In surgical group of the patients, mean ICH onset to surgery time and in deceased subgroup of surgically managed patients, mean surgery to death time was recorded. One hundred ninety three ICH patients (52% females) with mean age 61±3 years enrolled the study. In medical group 72 patients (58% females) with mean age 62.9±4 years and in surgical group 121 patients (48% females) with mean age 60±4 were investigated\textsuperscript{249}. Table 22 represents localization of hemorrhage in two therapeutic groups of our patients.

<table>
<thead>
<tr>
<th>Therapeutic group/ Location</th>
<th>Lobar Number (%)</th>
<th>Putaminal Number (%)</th>
<th>Thalamic Number (%)</th>
<th>Cerebellar Number (%)</th>
<th>Brainstem Number (%)</th>
<th>Isolated IVH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical(72)*</td>
<td>29(40.3%)</td>
<td>21(29.2%)</td>
<td>11(15.3%)</td>
<td>4(5.5%)</td>
<td>5(6.9%)</td>
<td>2 (2.8%)</td>
</tr>
<tr>
<td>Surgical (121)**</td>
<td>51(42.2%)</td>
<td>24(19.8%)</td>
<td>16(13.2%)</td>
<td>22(18.2%)</td>
<td>0(0%)</td>
<td>8 (6.6%)</td>
</tr>
</tbody>
</table>

IVH: Intraventricular Hemorrhage

Infratentorial localization consisted 12.5% of medical and 18.2% of surgical groups of our ICH patients. This difference in frequency of infratentorial localization of ICH in two therapeutic groups of our patients is due to more tendency for evacuation of cerebellar hematomas. The mean ICH onset to death time in medical and surgical groups of our deceased ICH patients is 14.8 days ranged 1-40 days and 15.4 days ranged 1-23 days respectively\textsuperscript{249}. In deceased subgroup of our surgically treated ICH patients mean ICH onset to surgery time and mean surgery to death time is 2.2 days ranged 1-16 days and 14.1 days ranged 1-52 days respectively. In-hospital mortality rate for medical and surgical therapeutic groups of ICH patients was 50% and 65.6% respectively\textsuperscript{249}. Distribution of in-hospital mortality was not significantly different in two therapeutic groups of our ICH patients; $X^2=2.34$, df=1, $p=0.126$. The influence of gender on in-hospital mortality was not significant in medical and surgical groups of our ICH patients;
(X^2=1.02, df=1, p=0.31) and (X^2=0.201, df=1, p=0.65) respectively. Influence of surgery on mortality of ICH patients was analyzed based on ICH localization. The effect of surgery on mortality of the ICH patients was not significant in lobar, putaminal, cerebellar and thalamic subtypes of our patients (X^2=0.16, df=1, p=0.77), (X^2=2.34, df=1, p=0.126), (X^2=0.01, df=1, p=1) and (X^2=3.09, df=1, p=0.08) respectively. However surgery had a nonsignificant benefit in patients with lobar hematoma and a nonsignificant harm in patients with thalamic hematoma. Thirty seven ICH patients underwent ventricular shunting which was performed with surgical evacuation of hematoma in 13 cases. Table 23 demonstrates details of surgical approach and mortality of 37 ICH patients who underwent shunt insertion.

<table>
<thead>
<tr>
<th>ICH location</th>
<th>Only Shunting</th>
<th>Shunting with hematoma evacuation</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lobar (n=2)</td>
<td>1</td>
<td>1</td>
<td>100%</td>
</tr>
<tr>
<td>Putaminal (n=5)</td>
<td>5</td>
<td>-</td>
<td>75%</td>
</tr>
<tr>
<td>Thalamic (n=12)</td>
<td>8</td>
<td>4</td>
<td>80%</td>
</tr>
<tr>
<td>Cerebellar (n=10)</td>
<td>2</td>
<td>8</td>
<td>75%</td>
</tr>
<tr>
<td>Isolated IVH (n=8)</td>
<td>8</td>
<td>-</td>
<td>100%</td>
</tr>
<tr>
<td>Total (n=37)</td>
<td>24</td>
<td>13</td>
<td>86%</td>
</tr>
</tbody>
</table>

Distribution of mortality was not significantly different in two therapeutic groups of our ICH patients. The effect of surgery on mortality was not significant in lobar, putaminal, cerebellar and thalamic subtypes of our ICH patients. Our results shows that surgery does not reduce in-hospital death rate in ICH patients and surgery may be harmful in patients with thalamic hematomas.

Comparing surgical and medical treatments of ICH in developed countries

The International Surgical Trial in Intracerebral Hemorrhage randomized 1033 patients from 107 centers in developed countries over an 8-year period. Surgery was associated with a statistically insignificant absolute benefit of 1.2% for preventing death and statistically insignificant absolute benefit of 4.1% for preventing sever disability. Subgroup analysis identified those subjects with GCS score of 9 to 12, those with lobar clot and those with clot <1cm from the surface that may have been helped by early surgery, but this did not reach statistical significance. In contrast, those presenting with deep coma tend to do better with medical management.
Together, the data from this trial and other smaller trials suggests that surgery does not appear to be helpful in treating most supratentorial ICHs and is probably harmful in those presenting with coma\textsuperscript{250}. Randomized trials of surgery did not include patients with cerebellar hemorrhage due to ethical reasons. Non-randomized treatment series of patients with cerebellar hemorrhage in developed countries reported good outcomes for surgically treated patients who have large (>3cm) cerebellar hemorrhages or cerebellar hemorrhage with brainstem compression or hydrocephalus\textsuperscript{251}. In these patients, medical management alone often results in bad outcomes. Smaller cerebellar hemorrhages without brain stem compression that are managed medically do reasonably well in the case series\textsuperscript{1,251}. Overall, craniotomy and surgical evacuation of hematoma has not been better than conservative management in developed countries\textsuperscript{241}. Six randomized clinical trials compared surgical with nonsurgical treatment of ICH, and the results were generally inconclusive, mostly because of methodological issues\textsuperscript{252}.

**Comparison of surgical and medical managements of aneurysms in a developing country**

Unfortunately many Persian SAH patients are admitted to hospitals without facilities for catheter angiography, aneurysmal coiling, or direct aneurysmal surgery. Even in tertiary care hospitals with these facilities, many of the SAH patients are admitted after 3 days following the ictus and for this reason the surgical or endovascular treatment is delayed for up to 3 weeks post event. Unfortunately there is no policy of urgency in Iranian emergency departments to direct the patients with SAH for appropriate management. Additionally, some of the Persian SAH patients refuse surgery on cultural or economic grounds. Consecutive Persian patients with SAH admitted in Ghaem hospital, Mashhad during 2005-2009 were enrolled in a prospective clinical study\textsuperscript{253}. Ghaem hospital is a university tertiary care center in north east of Iran. Neurologists, neurosurgeons and radiologists are available 24 hours per day and 7 days per week in Ghaem hospital. SAH patients who died before arriving to hospital were excluded from this study. The initial Hunt and Hess scale of each SAH patient on arrival to the hospital was recorded in both therapeutic groups. Diagnosis of SAH was made based on a brain CT scan. Patients suspected to have a SAH but with normal brain CT scan underwent a FLAIR MRI scan and lumbar puncture\textsuperscript{1,11}. Catheter cerebral angiography is a routine diagnostic investigation in our SAH patients and is performed by general radiologists. SAH patients with an initially normal cerebral angiography usually
underwent a second angiography after 3 weeks. Patients who did not have cerebral angiography due to poor medical condition or early death in hospital or allergy to contrast material were excluded. Positive angiograms for aneurysm was found in 63.5% of our SAH patients. SAH patients were usually admitted for 3 weeks in either Neurology or Neurosurgery divisions. In our center, cerebral angiography followed by aneurysmal clipping is usually performed on patients with SAH within the first 72 hours post SAH. Patients who arrive to hospital after this time or were initially comatose were usually medically treated and diagnostic procedures and surgery if required, were performed in this group of cases after 3 weeks post event. SAH patients who underwent craniotomy and aneurysmal clipping were categorized as a surgical therapeutic group. Aneurysmal clipping with the aid of a microscope is the usual type of surgical procedure in our hospital for these patients. Aneurysmal wrapping is not performed and endovascular coiling was not available in our hospital during study period. Patients who underwent ventricular shunting for hydrocephalus without aneurysmal clipping were included in the medical therapeutic group in respect to aneurysmal therapeutic approach. Surgical decision of the patient for aneurysm was made by a neurosurgeon. General medical condition of the patients were assessed by anesthetists and patients with poor cardiopulmonary or medical condition were excluded. SAH patients with Hunt and Hess scale of 5 were also excluded. Despite neurosurgical recommendation, some of our patients refused surgery due to cultural aspects or lack of funds. The medical management was standardized in both surgical and medical groups of SAH patients. Principles of medical management included; analgesia, nimodipine, sedatives, laxatives, control of blood pressure and 3 litres of normal saline per day. Demographic features, risk factors, cerebral CT findings, clinical manifestations and aneurysm characteristics were evaluated in all patients. Mortality and complications in SAH, including rebleeding, hydrocephalus and brain infarction due to vasospasm, were recorded in both medical and surgical groups of patients during hospitalization. The time was recorded and comparison made in each therapeutic group from SAH onset to hospital arrival, SAH onset to death, SAH onset to surgery (where applicable) and surgery to death (where applicable) in all patients. The results of the treatment of one hundred and twenty SAH patients (63 females, 57 males) with a mean age 50.6 ±7 years were prospectively evaluated. Patients with exclusion criteria are not considered in these 120 SAH cases. SAH was detected on cerebral CT in 95% of the cases. The patients were divided into two therapeutic groups. Among our SAH patients, 62.5% with mean age
52.4±5 received medical treatment and 37.5% with mean age 49.7±3 were subjected to surgery. Hypertension, smoking, oral contraceptive medication, past trauma and over dosage of oral anticoagulation therapy were found in 41.6%, 19.1%, 0%, 0% and 0.8% of patients respectively. Fifty six patients were subjected to surgery, of whom 45 underwent craniotomy and aneurysmal clipping, while 11 cases had CSF shunting without aneurysmal clipping and were included into the medically managed group. Overall mortality was 44.2% of all SAH patients (60.4% of females and 39.6% of males). There was no statistically significant difference in the death rate between the two therapeutic groups (X²=1.54, df=1, p=0.11) and no significant difference between the females and males (X²=0.73, df=1, p=0.39). The mean SAH onset to admission time in whole of our SAH patients and in their medical and surgical groups was 66±4, 84±1 and 24±7 hours respectively. The overall mean timing from the onset of SAH to death was 14.1±2 days. In the surgical group, the mean length of time from onset of SAH to surgery was 8.4±3 days and of those who died, the mean length of the time between surgery and death was 5.9±3 days. Table 24 compares the clinical characteristics between surgical and medical groups.

Table 24: Distribution of Hunt Hess Scale scores in surgical and non-surgical groups of our SAH patients

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Surgical (n:45) (F: 25, M: 20)</td>
<td>1</td>
<td>14</td>
<td>24</td>
<td>6</td>
<td>-</td>
<td>28 (62.2%)</td>
</tr>
<tr>
<td>Medical without aneurysm (n: 58) (F: 29, M:29)</td>
<td>1</td>
<td>12</td>
<td>26</td>
<td>11</td>
<td>8</td>
<td>18 (31%)</td>
</tr>
<tr>
<td>Medical with aneurysm (n:17) (F:9, M:8)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>7</td>
<td>10</td>
<td>7 (41.2%)</td>
</tr>
<tr>
<td>Total (n:120) (F:63, M:57)</td>
<td>2</td>
<td>26</td>
<td>50</td>
<td>24</td>
<td>18</td>
<td>53 (44.2%)</td>
</tr>
</tbody>
</table>

H-H-S: Hunt Hess Scale
* None of our SAH patients had Hunt Hess scale 0.

The effect of therapeutic type of aneurysm management on mortality was not significant; X²=0.16, p=0.77. Rebleeding occurred in 4.4% of patients in the surgical group (before aneurysm clipping) and 4% in the medical group and the difference was not statistically significant; X²=0.014, p=0.91. Among 5 SAH patients with rebleeding, 2 had an anterior communicating artery aneurysm and 3 had a normal angiography. The influence of rebleeding on the overall mortality was not statistically significant; X²=2.54, p=0.14. None of the studied patients had rebleeding before admission to hospital. However rebleeding may have occurred in patients who died before arriving...
to the hospital and these were not included in this study. Hydrocephalus was found in 17 patients and its frequency was significantly different in the two therapeutic groups; $X^2=5.58$, $p=0.03$. Out of 17 SAH patients with hydrocephalus, 13 (76%) died and the effect of hydrocephalus on the mortality of these patients was significant; $X^2=7.93$, $p=0.007^{253}$. Cerebral infarction due to vasospasm occurred in 7(5.8%) patients, 4.4% of the surgical and 6.7% of the medical group. The choice of aneurysmal therapeutic strategy on frequency of cerebral infarction was not significant; $X^2=0.25$, $p=0.71^{253}$. Out of seven patients with brain infarction due to vasospasm, three cases died. The effect of cerebral infarction on the overall mortality of SAH patients was not significant; $X^2=0.005$, $p=1$. Table 25 represents distribution of complications in two therapeutic groups of our SAH patients.

<table>
<thead>
<tr>
<th>Therapeutic group/</th>
<th>Rebleeding</th>
<th>Death due to rebleeding</th>
<th>Hydrocephaly</th>
<th>Vantricular shunting</th>
<th>Infarction due to vasospasm</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical (n:45)</td>
<td>2 (4.4%)*</td>
<td>-</td>
<td>2 (4.4%)</td>
<td>2 (4.4%)</td>
<td>2 (4.4%)</td>
<td>28 (62.2%)</td>
</tr>
<tr>
<td>Medical (n:75)</td>
<td>3 (4%)</td>
<td>2 (2.7%)</td>
<td>15 (20%)</td>
<td>11 (14.7%)</td>
<td>5 (6.7%)</td>
<td>25 (33.3%)</td>
</tr>
<tr>
<td>Total (n:120)</td>
<td>5 (4.2%)</td>
<td>2 (1.7%)</td>
<td>17 (14.2%)</td>
<td>13 (10.8%)</td>
<td>7 (5.8%)</td>
<td>53 (44.2%)</td>
</tr>
</tbody>
</table>

Rebleeding occurred before aneurysm clipping

Aneurysms were found in the angiography of 62 patients (45 in the surgical and 17 in the medical group). The distribution was as follows: Anterior communicating artery 41.9%, middle cerebral artery 23.1%, internal carotid artery 14.5%, basilar artery 4.8%, anterior cerebral artery 4.8%, posterior communicating artery 6.4% and multiple aneurysms 3%^{255}. Among 62 SAH patients with aneurysm on angiography, 45 patients (72.6%) underwent aneurysm surgery and 17 cases (27.4%) received only medical management. Death was recorded in 48.9% of SAH patients with aneurysm who underwent aneurysm surgery (22/45) and 41.2% of patients with aneurysm who only received medical management (7/17). High Hunt and Hess scale, poor general medical condition and refusal of patients constituted reasons of excluding these 17 cases with aneurysm from surgical group in 58.8%, 29.4% and 11.7% respectively^{253}. The difference in the mortality rate in 62 SAH patients with angiographically confirmed aneurysms in two therapeutic groups was not statistically significant; $X^2=0.16$, $p=0.77$. Table 26 illustrates causes of death in surgical and medical groups of our SAH patients.
Table 26: Causes of death in surgical and non-surgical groups of our SAH patients

<table>
<thead>
<tr>
<th>Cause of death/Therapeutic group</th>
<th>Medical (n: 75)</th>
<th>Surgical (n: 45)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral infarction</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rebleeding</td>
<td>2</td>
<td>-</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>13</td>
<td>-</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Electrolyte balance derangement</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Ventricular tachycardia</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Acute tubular necrosis</td>
<td>-</td>
<td>1</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Intraoperative</td>
<td>-</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>Total</td>
<td>28</td>
<td>25</td>
</tr>
</tbody>
</table>

This study concerned SAH patients admitted alive, thus the pre-hospital mortality is unknown in our SAH patients. Our hospital-based study revealed an incidence of negative angiography in 58/120 (48.3%). In other study from Iran, the incidence of negative angiography among SAH patients was reported to be 35/108 (32.4%)\cite{254}. This is strikingly different from findings in developed countries, were studies have reported a 15-20% negative angiography result in SAH\cite{255}. The mean time of onset to surgery in our SAH patients was 8 days which is longer than reported in western countries\cite{256}. This significant delay in the timing of aneurysmal surgery in our patients, could be the main reason for failure to decrease mortality in our patients. During this period of delay a number of complications may occur in the surgical group. There was no statistical significance between type of management with mortality and complications in our patients. The impact of rebleeding despite presence of hydrocephalus on mortality was not significant in our patients\cite{253}. This is inconsistent with results in developed countries\cite{12}. The late presentation of the SAH patients in our center, compared to developed countries is a local issue and this leads to late treatment. Management of Persian SAH patients is still suffering from major difficulties. Whether the obstacles are situated mainly on the diagnostic, technical or intensive care level and the barriers to improving treatment should be investigated in next studies.

**Surgical managements of aneurysms in developed countries**

In aneurysmal surgery, delay in treatment is associated with increased rates of pre-operative rebleeding, in both retrospective and prospective studies\cite{244}. Recently it has been associated with higher rates of poor
outcome\textsuperscript{244,256}. The International Co-operative Study on the Timing of Aneurysmal Surgery, analysed management of 3521 patients, of whom 83\% underwent surgical repair of the ruptured aneurysm\textsuperscript{257}. The timing of surgery after SAH was significantly related to the likelihood of pre-operative rebleeding. Patients who underwent early surgery had a significantly lower pre-operative rebleed rate than those who underwent later surgery (3\% versus 11\%)\textsuperscript{257}. In recent years, there has been a trend towards early surgery for ruptured aneurysms, especially in good and moderate grade patients\textsuperscript{244,256}. In addition, early surgery facilitates the possibility of aggressive therapy of vasospasm\textsuperscript{244}. However, it is also reported that there were no overall differences in outcome in patients operated on early (0-3 days post SAH) or late (11-14 days post SAH)\textsuperscript{256}. Surgical mortality was higher with early surgery due to brain swelling, disturbed autoregulation and haemorrhage\textsuperscript{256}. The surgical treatment was most hazardous between days 7 and 10 due to the combined risks of rebleeding and vasospasm\textsuperscript{256}. A prospective study, from three centers, indicates that despite attempts to do early surgery, rebleeding is still a significant problem, because only one half of the patients were operated on within 72 hours, and 35\% of the patients with poor outcome had suffered rebleeding\textsuperscript{258,259}. In addition, some SAH patients with acute hydrocephalus may benefit from early placement of a ventricular drain in the hospital\textsuperscript{260}. Acute hydrocephalus is more frequent in patients with poor clinical grade. The clinical significance of acute hydrocephalus after SAH is uncertain because many patients are apparently asymptomatic and do not deteriorate\textsuperscript{244}.

Summary

Review of stroke literature reveals that almost all of stroke texts are provided in the developed countries especially in north America and Europe. Despite presence of guidelines for stroke medicine in Asia\textsuperscript{261}, an Asia-specific stroke text does not exist. The Asian continent contains ancient civilizations and is a mixture of developing and developed countries. Clinical practice guidelines for stroke have been provided in a few developed and developing countries of Asia\textsuperscript{262,263}. This handbook is provided for physicians residing in Asia.

\[\text{[From inability to let well alone; from too much zeal for what is new and contempt for what is old; from putting knowledge before wisdom, science before art, and cleverness before common sense; from treating patients as cases, and from making the cure of the disease more grievous than the endurance of the same, Good Lord, deliver us.-Robert Hutchinson, British Medical Journal 1971, 4: 221-223.]}\]
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