The 2nd International
And the 8th National Iranian
Stroke Congress

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The 2nd International And the 8th National Iranian Stroke Congress

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In the Name of GOD

WELCOMEING NOTE

Dr. Mohammad Hadi Imanieh
President of Congress

Stroke is a life-threatening disease with a significant impact on mortality and morbidity. It is recognized as the third cause of death and leading cause of morbidity in developed countries causing a severe economic burden. Stroke patients in the Middle East and Central Asia regions are believed to be younger and have a higher rate of mortality as compared to those in the Western countries. Therefore, there is an urgent need for the neurologists in these regions of the world to gain more knowledge of and experience with both prevention and treatment strategies pertaining to stroke. Moreover, it is crucial for policymakers to allocate more resources to deal with this disease within these regions.

It is our pleasure to announce that the Clinical Neurology Research Center at Shiraz University of Medical Sciences will host the 2nd International Iranian Stroke Congress in Shiraz, Iran, from September 23rd to 25th, 2015. Iran is situated in the crossroads of civilizations in the Middle East and Central Asia, and Shiraz is the capital of art and culture in the region. Several international keynote lecturers from prestigious American and European academic institutions will present their experiences in the treatment of cerebrovascular disease and stroke throughout the conference.

On behalf of the organizing committee, we look forward to seeing you for the Stroke Congress in Shiraz.
Ladies and Gentlemen,
On behalf of the scientific and organizing committees it is my pleasure to invite you to participate to the 2nd International Iranian Stroke Congress in Shiraz, Iran, from September 23rd to 25th, 2015. This conference focused on novel advances in research in the field of cerebrovascular disease. First-time incidence of stroke occurs almost 17 million times a year worldwide; one every two seconds. Stroke continues to be the second leading cause of death worldwide and accounts for about 1 in 10 deaths or 5.7 million deaths a year. Globally, over the past 4 decades, stroke incidence rates have fallen by 42% in high-income countries and increased by >100% in low- and middle-income countries. There is substantial variation in the distribution of stroke burden by geographic region and by country—the level that may be most relevant for policy and program development.
Unfortunately, it seems that stroke prevalence and mortality rate in Iran are higher than the global rate. Demographic and vascular risk factor trends suggest that there will be an even greater burden of disease from stroke in coming years and will represent a major public health challenge moving forward. This concentration of stroke burden suggests that a targeted approach for addressing stroke in the developing world may be warranted.
Such congresses is an outstanding opportunity to share our knowledge to find scientific solution and improve burden of disease for stroke. We aimed this congress fulfill the expectations of the audiences and organizers in that a number of emerging concepts will be presented and discussed.
I wish all of you a pleasant and productive time.
It would be pointless to talk about the importance of stroke since it is clear for everybody. Throughout the world, it is one of the major priorities and serves as a criterion for evaluating physician’s collective action. However, something that needs to be highlighted is the fact that our country fails to keep up with the developments in this field, hence not fulfilling this criterion.

Hopefully, the persistent endeavors of neurologists and many other health experts and managers have helped getting a little closer to the goal. It is due to the fact that since the beginning of this year, the Ministry of Health and Medical Education has announced the treatment of stroke as one of its major national plans. In other words, the government aims at guiding and programing its collective wisdom, which emerges in the Ministry of Health and Medical Education. It also aims at using all its facilities to plan the treatment of stroke. It implies more concrete and important responsibilities on the part of neurologists as well as neurology and stroke communities, who are the true embodiment of this corporate group.

Undoubtedly, by implementing the plans hitherto defined or to be defined by national stroke associations, neurologists' responsibilities go beyond issuing warnings, sending requests, or not taking action with an excuse of lack of facility.

The active treatment of CVA at all levels opens the floor for neurologists to enter a highly neurological and highly required field. Consequently, it promotes the position and status of this group of medical experts. It gives
them a status they truly deserve, but have not hitherto attained. The fact that some highly educated experts actively and wisely engage in a social activity in line with other parts of the society, show the scientific results of this social activity, and endeavor to solve probable shortcomings, undoubtedly and in various forms, greatly influences the public culture.

A major part of the 8th congress is committed to the more general aspects of treating stroke and the coordination required for the further spreading of CVA treatment in Iran.

This is, in fact, what makes the 8th Iranian Stroke Congress in Shiraz, Iran, unique and important. Being the first event following the new approaches and changes in the field of stroke, this congress provides an exceptional opportunity for the peers to reunite, not in a virtual network, but in a real environment, in order to renew their pledge for the journey ahead. It also provides an opportunity for them to take steps in improving international connections, which are a prerequisite to such developments.
The 2nd International And the 8th National Iranian Stroke Congress

In the Name of GOD

Congress co-chairs

Dr. Abdolhamid Shariat
Dr. Afshin Borhani Haghighi

Dear Colleagues,

The idea of holding the international Stroke congress in Shiraz was with us for several years, but there were some executive obstacles for realizing this dream. Fortunately, the Iranian Neurological Association and the Iranian Stroke Association accepted Shiraz as the congress venue for 2015. The congress was endorsed by international institutions such as the World Stroke Organization and the Society of Vascular and Interventional Neurology.

Prestigious speakers have been invited to cover the edge-of-the science aspects of cerebrovascular medicine. Many Iranian colleagues were also invited to participate as keynote lecturers. About sixty original research articles have been submitted to the congress website which were accepted for either oral or electronic-poster presentations. There will be several debates in the congress, focused on some controversial issues related to the stroke. Four workshops of hands-on training will be held as well as Students desks and Nurses sections. The latter two will be crucial parts of our congress. It should be mentioned that 14 CME points for platform sessions and 6 CME points for workshops have been accredited.

Social events such as visiting the Persepolis and having a gala dinner in Shapuri’s house have been considered for the recreation of our guests.

Hereby, we would like to express our sense of appreciation and gratitude to the president of Shiraz University of Medical Sciences (SUMS) and to the chair-person of the congress, the vice-chancellor of research of SUMS, the board of directors of Iranian Neurological Association and Iranian Stroke
The 2\textsuperscript{nd} International And the 8\textsuperscript{th} National Iranian Stroke Congress

Association, members of strategy, scientific and executive committees, Chatre Sefid company, and all the pharmaceutical and device-producing companies which sponsored our congress. We would also like to thank our students and all the others who helped us to hold this congress in our beloved homeland, Shiraz.

In the end, we wish to invite all to our congress with Hafiz’s words:

\textit{The chamber of vision of my eye is the dwelling of Thine, Show courtesy, and alight, for this house is the House of Thine.}
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Brain CT scan in cerebral vascular accidents

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In patients came with suspicious cerebrovascular accidents, CT scan can play a major roll for diagnosis and treatment planning. In these patients we can do non contrast enhanced CT scan followed by perfusion CT scan and CT angiography. This multimodal CT evaluation can help us to roll out hemorrhage, other differential diagnosis, identify the site of vascular occlusion, the infarcted zone and the salvageable tissue, also we can assess collateral circulation. This multimodal CT scan take about 10 to 15 minutes. Each of the mentioned CT scan are described in following words separately.

Non contrast enhanced CT scan
First on CT scan unite, non-contrast enhanced CT scan is performed. In this CT scan, hemorrhagic CVA should be rule out, then other differential diagnosis for CVA such as tumors and AVM should be rule out. Then signs of infarction should be searched in the CT scan; such as blurring of corticomedulary differentiation, insular ribbon sign and obscuration of lentiform nucleus sign and dense vessels sign. First image should be reviewed with standard window width and level setting approximately at 40-20 HU, then for improving sensitivity of image interpretation, the CT scan must be reviewed with window width and level setting as 20-35 HU. In the latter setting subtle hypo attenuation and obscuration of the gray white matter differentiation and obscuration of the lentiform nucleus sign and loss of insular ribbon and visualization of the dot sign or hyper attenuation vessels sign can be better seen in the second windowing (1). The previous mentioned signs have poor prognosis for thrombolytic treatment but there are not contraindications for treatment. (1)

Diagnosis and interpretation of the mentioned signs are hard for radiologist and they have low sensitivity. Hyper attenuating and dense vessel sign is only seen in about 30% of patient and it is hard to interpret and some conditions such as elevated hematocrit and vessel wall calcification and dolicoectasia are pitfalls. Also the mentioned signs are not helpful for differentiation between ischemic penumbra and the central core of infarction (2).

Several methods have proposed for assessment of non-contrast CT scan in patients with CVA. The most famous one is ASPECTS ( Alberta stroke program early Ct score ), this CT score is time consuming but it has acceptable inter observer reliability. (3, 4)
Perfusion CT

Perfusion CT is performed by monitoring first passed bolus of contrast agent into the brain tissue. In this method continuous imaging for about 45 seconds over the same slab of the brain tissue during dynamic contrast administration was done, the arterial ROI is placed on ACA territory and venous ROI is placed on superior sagittal sinus or over Torcular Herophili. Then color encoded perfusion map was performed by cerebral blood volume mean transit time (MTT) and cerebral blood flow. The relation between these parameters is: cerebral blood flow = cerebral blood volume/MTT. Then quit visual assessment of the perfusion maps by radiologist was done and the ischemic penumbra can differentiate from central core of infarction.

One limit of perfusion CT scan is limited field of view, because only about 4cm slap at the level of basal ganglia for depiction of the territory of ACA, MCA and PCA were done in routine perfusion CT scan, so visualization of infra tentorial region is not well possible.

Based on the fact that, in cerebrovascular accident the central core of infarction is dead brain tissue but the stunned cells around the central core of infarction is ischemic penumbra and can be saved by early revascularization by performing intravascular thrombolysis within three to four and a half hours since attack. (5)

The CBV map can showed infarcted brain tissue that is compatible with diffusion restricted area in DWI image whereas CBF map show the area of reversible ischemia compatible with perfusion MRI. The ischemic tissue shows increased MTT with decreased CBF and normal or mild increased CBV whereas infarcted area show significant decreased CBF and increased MTT with significant decreased CBV. The at risk brain tissue is equivalent to CVF-CBV.

The patient selection for performing IV thrombolysis is: disabling neurological deficit + less than three hours interval between the onset of symptoms and start of treatment + rolled out other criteria such as hemorrhage in non-contrast enhanced CT scan. Findings of perfusion CT scan is still not included in patient selection.

Therefore, if no penumbra was detected in perfusion CT scan thrombolysis is still can be done for the patient. Also areas of abnormality in CBV and diffusion restricted area are not always irreversible brain tissue damage. (6)

CT angiography

After performing CT perfusion then CT angiography can be done for the patient. The goal of CT angiography is too see cranial arterial system. The site of arterial occlusion can be show. The site of arterial stenosis can also be seen. We can search for arterial dissection. Collateral blood flow is visible. The state of atherosclerosis
oral
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can be seen. CTA angiography can be useful guidance for intra-arterial thrombolysis. (5)
Intra-arterial thrombolysis is a good modality for occlusion of the ICA, MCA stem and basilar artery occlusion. Also it is good modality for treatment planning. Also CT angiography is good modality for evaluation of vertebral basilar system because posterior fossa can hardly be visible in non-contrast enhanced CT scan and usually is not included in CT perfusion.
In CT angiography from aortic arch up to vertex should be seen with thin section slices, especially it is good for evaluation of the carotid arteries and vertebral artery and the circle of Willis.
The evaluation of the intracranial arteries can be well done by performing reformatting or by MIP (maximum intensity projection with thickness about 20mm). It is best to make reformatting with MIP scadule in, two axial, one sagittal and two coronal images.
More over leptomeningeal arterial collaterals can be seen in CT angiography because the patients with good collateral circulation from the leptomeningeal vessels have better prognosis. In addition CT angiography of the cervical vessels can show plaque irregularity or ulceration and also quantification of calcification and vessels stenosis can be well seen.
With assessment of post contrast images also hypo attenuating hypo vascular areas can be well seen better that noncontract enhanced CT scan. For evaluation of infarcted zone, the optimum window width and level for evaluation of post contrast images can be 25-35HU.

CONCLUSION
Cerebrovascular accident is one of major causes for hospital admission. One acceptable treatment is thrombolysis. by performing CT scan early hemorrhage can be seen, if hemorrhage was ruled out then perfusion CT scan for evaluation of penumbra and at risk brain tissue can be done, then CT angiography can be performed for visualization of the site of occlusion and to visualize collateral circulation and for assessment of carotid atherosclerotic disease.
This multimodal CT scanning (non-enhanced CT scan, perfusion CT scan and CT angiography) can be performed rapidly and can be interpret easily by radiologist.
Questions
1. A 66 y/o man came with right sided hemiplegia for about 2 hours ago. In multimodal CT, no penumbra was found in CT perfusion. No hemorrhage is noted. Occlusion of left MCA is seen in CT angiography. What is true about the case?
   A. IV thrombolysis can be helpful.
B. IA thrombolysis is not a choice.
C. MRI is the next step for diagnosis.
D. Carotid color Doppler ultrasound is an emergent work up.

2. In the previous case what is true?
A. Check of BUN and Cr is mandatory before contrast enhanced CT
B. Perfusion CT should be searched for vertebrobasilar system
C. Area of decreased CBV is always dead tissue.
D. The CT protocol can be done in about 10 to 15 minutes.

Moyamoya disease in south west of Iran

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Moyamoya disease is a rare cerebrovascular disorder with unknown etiology. To both clarify the current incidence of clinicoepidemiological features of Moyamoya disease in Shirza, Iran, we investigate the incidence of Moyamoya in Namazi hospital from 2009-2015.

The age of onset of Moyamoya disease was between 2-12 years old, but just one patient was 44 years old. The female to male ratio was 2.3:1. The incidence of CVA among Moyamoya patients was about 50%, and the incidence of seizure was about 40%. Associated diseases were in patients presented intermediate thalassemia. Intracerebral hemorrhage was seen just in one patient. One patient had both down syndrome and moyamoya. Also some patients had splenomegaly and unilateral weakness and hemilplasia. After diagnosis ITP in one of patients, they reported moyamoya as a secondary disease. 40% of patients was undergoing surgery with successful results.

Moyamoya disease isn’t as rare as previously imagine in Iran.
Post stroke epilepsy

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Stroke is one of the leading causes of long-term disability which is the cause of 10–15% of epilepsies, especially more prevalent in patients above 60 years of age. Intracranial venous thrombosis (ICVT) is much more likely to induce seizure in their acute and chronic phases. Among the arterial causes of stroke intracranial hemorrhage, ischemic infarction with hemorrhagic transformation and cortically located lesions are much more likely to produce seizure. Early post stroke seizures (≤ 7 days) are associated with more severe strokes. Clinical presentation of seizure besides continuous electroencephalography (cEEG) may be helpful for early detection of non-convulsive status epilepticus (NCSE) and optimal treatment of post-stroke epilepsy. There is currently no consensus on the optimal management of post-stroke seizures. The latest studies regarding post-stroke seizure treatment showed that 'new-generation' drugs, such as lamotrigine, gabapentin and levetiracetam, in low doses would be reasonable because of long-term seizure-free periods, improved safety profile, and fewer interactions with other drugs, especially anticoagulant ones, compared with first-generation antiepileptic drugs (AEDs).

Keywords: Stroke, Seizure, Antiepileptic drugs

Background:
One in the six people in the world will suffer a stroke in their lifetime with an annual incidence of 117 per 100,000 person-years in developing countries. It has also been shown which stroke is the cause of 10–15% of epilepsies and is more prevalent in patients above 60 years of age. The incidence of early seizures (≤ 7 days) in acute stroke ranges 3–33%, with 50–78% of the seizures occurring within the first 24 hours early seizure. Occurrence of seizures within 24 hours of stroke is associated with higher 30-day mortality, which may be a reflection of severe neuronal damage (1-3). Hyper-excitability due to alteration in intracellular ion concentrations and cellular biochemical dysfunction are thought to be etiologies for early seizures in acute stroke, and late seizures on the other hand are suggested to be a result of gliosis or hemosiderin remaining (4).

Causes of post-stroke epilepsy:
Compared with people with strokes resulting from arterial occlusion, those with intracranial venous thrombosis (ICVT) are much more likely to experience...
seizures at the initial presentation and during the follow-up. In the study of 142 participants with ICVT (5), 34% experienced seizures within the first two weeks of the event, and 10% experienced seizures after the first two weeks. Among children with ICVT, the frequency of seizures may be even higher. In a series of 58 children with ICVT, 58% experienced seizures on admission, and those presenting with seizures were more likely to have a bad outcome (6). The risk factors of early seizures in patients with ICVT were having motor and sensory deficits and in those with computed tomography (CT) or MRI evidence of focal brain edema, venous infarction, or intracerebral hemorrhage. In addition, patients with early seizures and those with CT or MRI evidence of hemorrhage were at risk of late seizures (5). However, some studies have not found any relationship between post-ICVT seizures and outcome (5) while the others have identified seizures as a poor prognostic indicator (7). There are some conflicting results in the findings reported by some studies on post arterial stroke seizures. Procacciati et al. (2) studied 2,053 patients with acute stroke admitted to the Stroke Unit from 2004 to 2008 and reported that 66 patients (8 hemorrhagic and 58 ischemic strokes), aged 73–88 years and mean age 82 years, presented seizures in the first week after stroke onset. Cardioembolic ischemic stroke was the most frequent cause of post stroke seizure in their study. Clinical presentations of epilepsy were simple and complex partial seizures and generalized convulsive. In addition, status epilepticus (SE) was observed in 13 patients. Furthermore, the patients with early seizure had more severe strokes compared with those who had no seizure (National Institutes of Health Stroke Scale >14 in 50 vs. 25%) so mortality (30 days) was higher (29 vs. 14%). Independent seizure predictors were total anterior circulation infarct, hemorrhagic transformation, hyperglycemia, and the interaction term diabetes × hyperglycemia. Moreover, Beghi et al. (8) studied 714 patients with acute stroke, after multivariate analysis, compared to cerebral infarction (CI), primary hypertensive hemorrhage (PIH) carried the highest risk for induction of seizures (odds ratio [OR] 7.2; 95% confidence interval [CI] 3.5-14.9) followed by cerebral infarction with hemorrhagic transformation (OR 2.7; 95% CI 0.8-9.6). Cortical involvement was a risk factor for PIH (OR 6.0; 95% CI 1.8-20.8) and CI (OR 3.1; 95% CI 1.3-7.8). In summery hemorrhagic stroke and cortical lesion were independent predictors of acute symptomatic seizures. Early post stroke seizure may be considered as a marker of stroke severity.

Management of post-stroke epilepsy:
There is currently no consensus on the optimal management of post-ICVT seizures. Because of the high risk of seizures and their potential adverse physiological effects, some experts recommend prophylactic treatment with antiepileptic drugs.
(AEDs) for all people with ICVT (9) while the others have more recently recommended reserving prophylactic treatment only for those who have already had a seizure, i.e., for secondary prevention only (10, 11).

However, some researches were specific in recommending that prophylactic treatment should be used in those with proven risk factors (e.g. those who have already experienced seizures or who have CT or MRI evidence of haemorrhage) for seizures. Overall, it remains unclear which people with ICVT should receive prophylactic AEDs and which drug, at what dosage and for how long, should be taken (11). Any potential benefits of using AEDs should also be balanced with their potential side effects.

Additional metabolic burden and damage to the blood–brain barrier can be prevented with early detection of seizures and subsequent effective treatment which may improve recovery and the overall outcome. Clinical seizures, which can readily be recognized at bedside, result in prompt medical intervention. In contrast, electrographic seizures with subtle or no clinical sign and non-convulsive status epilepticus (NCSE) may escape clinical observation and be left untreated. Patients with electrographic seizures can be better identified and medically treated more quickly with the use of continuous electroencephalogram monitoring (cEEG). Since up to 75% of these patients have been found to develop early post-stroke seizures, the presence of isolated and periodic epileptiform patterns on electroencephalogram (EEG), in addition to electrographic seizures, suggests the need for medical treatment. A controversial issue is the optimal timing and type of AED treatment for patients with post-stroke seizures. Many population- and hospital-based studies have been performed, ending with generalized recommendations, but the decision to initiate AED treatment after a first or second seizure should be still individualized. Prospective studies in the literature showed that immediate treatment after a first unprovoked seizure does not improve the long-term remission rate. However, prophylactic treatment should be considered after a first unprovoked because of the physical and psychological influences of recurrent seizures event in an elderly person at high risk of recurrence. The individuality of the patient and a discussion with the patient and his/her family about the risks and benefits of both options should be taken into consideration. In spite of the fact that post stroke epilepsy is more prevalent in elderly population, the chosen ADEs should have wide spectrum of activity, few side effects and at least drug-drug interactions. The latest studies regarding post-stroke seizure treatment showed that it would be reasonable to use ‘new-generation’ drugs, such as lamotrigine, gabapentin and levetiracetam, in low doses because of their high rate of long-term seizure-free periods, improved safety profile, and fewer
interactions with other drugs, especially anticoagulant ones, compared with first-generation AEDs (12). On the other hand, first-generation drugs, such as phenytoin, carbamazepine and phenobarbital, have the potential to have a harmful impact on recovery, bone health, cognition and blood sodium levels and may interact with other treatments used by the elderly population.

References

Debate: New oral anticoagulants for embolic stroke

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Since several years ago, anticoagulant therapy was used in acute ischemic stroke. Recently randomized clinical trials (RCT) have shown the role of anticoagulants more clearly in prevention and treatment of stroke. In the present article we aimed to review the effects of four groups of new anticoagulant (Xa Inhibitors, Direct Thrombin Inhibitors) on stroke for either treatment or prophylaxis.

Xa Inhibitors
Factor Xa inhibitors competitively inhibit activated factor X. Factor Xa is the common factor in both intrinsic and extrinsic pathways. So inhibition of this factor affects the entire coagulation cascade.

Rivaroxaban (Xarelto) as a direct inhibitor of factor Xa has been approved for treatment and prevention of nonvalvular atrial fibrillation and deep vein thrombosis and pulmonary embolism after large joint replacement. ROCKET AF, as a large double-blind RCT concluded rivaroxaban can be a safer option than warfarin for stroke prevention in AF cases. Also ROCKET AF showed the tolerability of rivaroxaban and warfarin and also the rate of overall bleeding are similar. Sub analysis showed that prevalence of gastrointestinal bleeding was lower with use of warfarin, while fatal and intracranial bleeding were lower with rivaroxaban.

Apixaban (Eliquis) is direct inhibitor of factor Xa that has been approved by FDA in 2012 for stroke prevention in AF. It is a newer edition of new anticoagulants than rivaroxaban. The ARISTOTLE study about the effect of apixaban on decreasing thromboembolic events including stroke in Atrial Fibrillation (AF) was shown apixaban is more efficient than warfarin in prevention of embolism and stroke with less bleeding that reduced rate of mortality.

Edoxaban (Savaysa) is an anticoagulant that inhibit factor Xa directly and is the third factor Xa inhibitor approved by the FDA in early of 2015 for prophylaxis of stroke and systemic embolism in cases with nonvalvular AF. In the ENGAGE AF-TIMI 48 trial (n=21,105) has been revealed that edoxaban has no priority to warfarin in stroke or systemic embolism prevention. However the bleeding and mortality rate of edoxaban were significantly lower than warfarin.

2. Direct Thrombin Inhibitors
The direct thrombin inhibitors (DTIs) directly inhibit the enzyme thrombin. DTIs are categorized into two groups: the bivalents, which bind to both the thrombin active site and exosite-1, and the univalents that bind only to the active site.
Bivalirudin (Angiomax) is a synthetic analog of hirudin that acts as a bivalent DTI. Bivalirudin has been approved for use in patients with heparin-induced thrombocytopenia and in patients undergoing percutaneous coronary intervention (PCI) with conditional use of glycoprotein IIb/IIIa inhibitor, patients with/or at risk of heparin induced thrombocytopenia, or in patients with unstable angina undergoing percutaneous transluminal coronary angioplasty. There is only a report about the usage of bivalirudin for acute ischemic stroke therapy. That showed Bivalirudin might be an effective drug for intravenous anticoagulation and intra-arterial thrombolysis. Some RCT are needed to confirm effects of Bivalirudin on acute ischemic stroke.

Dabigatran (Pradaxa) as a monovalent DTI has been approved for prophylaxis of stroke in nonvalvular atrial fibrillation. Also some studies concluded that dabigatran could be efficient in venous thromboembolism. Dabigatran etexilate (BIBR-1048, Rendix), an orally active prodrug of the thrombin inhibitor dabigatran (BIBR-953ZW), is being developed by Boehringer Ingelheim Corp as a potential antithrombotic agent. By March 2003, the compound was in phase IIb/III trials for the prevention of deep vein thrombosis. By November 2005, a phase III trial had been initiated for the prevention of stroke and embolism due to atrial fibrillation and in May 2006 phase III trials for the prevention of secondary venous thromboembolism began. By July 2007, an EU filing for the drug had been made. The effects of dabigatran versus warfarin were compared in the RE-LY trial (N=18113). The RE-LY trial revealed the advantages of dabigatran at decreasing intracranial bleeding and stroke compared with warfarin. In Chinese patients with atrial fibrillation also has been shown that even at the high level of therapeutic range (TTR) quartile, warfarin was associated with a higher stroke and ICH risk than dabigatran.

Ximelagatran (Exanta or Exarta) is a DTI that commonly is prescribed in several European countries but regarding to risk of liver toxicity has not been approved by FDA for stroke prevention in atrial fibrillation. Ximelagatran was compared with warfarin in the SPORTIF trials. SPORTIF III and V were conducted in Europe and North America. Analysis of these studies showed the efficacy of ximelagatran is similar to warfarin for stroke prophylaxis and also ximelagatran was associated with lower rate of bleeding.

Vorapaxar (Zontivity) is a thrombin receptor (protease-activated receptor, PAR-1) antagonist that has been approved by the FDA in risk reduction of MI, stroke, cardiovascular death in 2014. In May 2014, the FDA approved vorapaxar (Zontivity) to reduce the risk of MI, stroke, cardiovascular death and patients undergoing under revascularization procedures. Normally vorapaxar is used in combination with aspirin and/or clopidogrel, not monotherapy. Results of the TRA
2°P TIMI-50 trial (n = 26,499) determined that stroke, MI and death due to cardiovascular events reduced in significantly vorapaxar receiving group. However the rates of bleeding and ICH were more prevalent in vorapaxar group than placebo group.

**Conclusion**
In summary the Factor Xa inhibitors including apixaban, edoxaban, rivaroxaban and the direct thrombin inhibitors including dabigatran and Ximelagatran can be used in patients with stroke as an alternative of warfarin. Evidences has been shown all of these drugs are associated with lower risk of bleeding than warfarin. However for stroke prevention, apixaban and dabigatran are superior to warfarin but rivaroxaban, edoxaban and ximelagatran are comparable with warfarin.

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Pathophysiology of Intracerebral Hemorrhage: Is Recovery Possible!?

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Intracerebral hemorrhage (ICH), the pathological accumulation of blood within the cranial vault, represents the second mostly common cause of stroke, as approximately 15% of all stroke subtypes are hemorrhagic in nature (Qureshi et al., 2005). Despite high mortality and morbidity associated with intracerebral hemorrhage (ICH), treatment options are limited to neurosurgical evacuation, which, for the most part, remain ineffectual (Yu et al., 1992; Morgenstern et al., 1998; Broderick et al., 1999; Steiner et al., 2011). This is due, in part, to the variability in the timing of hemorrhage onset, the location and severity of this condition, along with the incomplete penetrance of genetic mutations predisposing the individual to the condition (Sahni and Weinberger, 2007). The severity associated with ICH stems from the ensuing pathophysiological processes within the cranial vault, typified by hematoma expansion, release of inflammatory mediators and neurological deterioration. As such, strategies geared towards enhancing functional recovery and tissue regeneration are of indispensable value in order to increase survival in these patients. Some tangible progress has been made, particularly using murine models in characterizing the pathophysiology and progression of ICH through a number of interventions, including injection of bacterial collagenase into the basal ganglia (Rosenberg et al., 1990; Clark et al., 1998), infusion of autologous blood into the brain parenchyma (Belayev et al., 2003) and through genetic knockouts (Louvi et al., 2011). However, these mammalian studies are limited by several shortcomings, such as; low expression and reproducibility of the desired phenotype(s), heterogeneity of the resulting hemorrhages, lack of feasibility for real-time/in vivo imaging of hematoma expansion and edema formation, lack of optical clarity, high cost and the high mortality observed in the murine models utilised.

As such, there is a need to utilize a robust vertebrate model in which the aforementioned shortcomings are resolved. The zebrafish (Danio rerio), an excellent vertebrate disease model belonging to the teleost family, exhibits a tendency for fully functional recovery after cerebral injury and intracerebral hemorrhage. This is in sharp contrast with mammalian models in which ICH induces relatively high morbidity and mortality. Zebrafish continued to gain recognition as a reliable model to complement in vitro and clinical studies to
address vascular malformations underlying human pathologies such as ICH (Liu et al., 2007; Buchner et al., 2007; Gore et al., 2008; Kwon et al., 2012; Eisa-Beygi et al., 2013; Hegarty et al., 2013). In addition, zebrafish embryos provide a relatively rapid screening system with the genomic and functional complexity of a vertebrate model organism (Lieschke and Currie, 2007). However, the precise mechanisms through which zebrafish functionally recover from ICH remain elusive and speculative.

Hence, we propose that improved understanding of pathophysiological cascade of events and molecular mechanisms ensuing ICH in an optically transparent paradigm, like zebrafish, can be of clinical relevance in terms of identifying potential targets for new prognosis and therapeutic interventions to ameliorate the progression of this disease *in vivo* and to test the potential involvement of stem/progenitor cells in recovery. More importantly, characterization of the molecular and signalling processes (both extrinsic and intrinsic) facilitating zebrafish neuro-regeneration and vascular remodelling in the wake of hematoma expansion, would enable us to deliver or enhance these regenerative stimuli in patients experiencing ICH and to test whether the mammalian CNS could be coaxed into exhibiting a regenerative response to injury and hematoma expansion.
Endovascular treatment in intracranial atherosclerotic stenosis

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Intracranial stenosis account for the 10% of all strokes[1].
The natural history is variable. It may progress, regress or remain stable during follow up. The natural history depends on location of stenosis and extent of intracranial atherosclerosis. Patient with more than 70% stenosis are at more risk of developing stroke in follow up. Also possibility of progression of stenosis in lesions of middle cerebral artery, anterior cerebral artery and posterior cerebral artery are more than intracranial internal carotid artery. The risk of annual stroke in symptomatic intracranial stenotic group is significantly more than patients with extracranial stenosis[2]. Recurrent annual stroke rates are estimated at 4–12% per year with atherosclerosis of the intracranial anterior circulation and 2.5–15% per year with lesions of the posterior (vertebrobasilar) circulation.

In general, intracranial atherosclerosis occurs in the setting of widespread atherosclerosis. Asians, blacks, and Hispanics are more likely to have intracranial atherosclerosis than whites. Although ICAS is more prevalent in Asians than in Westerners, the reason for racial-ethnic differences is unknown. Possible explanations include inherited susceptibility to intracranial vessel atherosclerosis, acquired differences in risk factor prevalence, and differential responses to the same risk factors. Because both Moyamoya disease (MMD) and ICAS are more prevalent in Asians than in Westerners, the increased prevalence of ICAS may in part be caused by adult-onset MMD that is misclassified as ICAS.

Moyamoya disease (MMD) is a unique cerebrovascular disease characterized by progressive stenosis of the distal internal carotid artery (ICA) and a hazy network of basal collaterals called Moyamoya vessels. It was known that MMD mostly occurs in children in Asia, and the hemorrhage rate is higher among adults than children. However, recent epidemiologic studies of Asians and Westerners revealed that patients with MMD are older and more often ischemic or asymptomatic than previous studies indicated.

One regional, all inclusive data set of newly registered patients with MMD in Hokkaido (Japan, 2002 to 2006) showed that the percentage of patients less than 10 years of age at onset was 15% (compared to 48% in previous studies), and the highest peak was observed at 45–49 years. The data also revealed that the percentage of cases with ischemia increased to 57.4%. Only 21% (previously 42%) of adult MMD patients were hemorrhagic[3].
Risk factor control, aggressive medical management (including statins), and stent placement (in selected patients) are important for preventing stroke in patients with ICAS. The pathophysiology of MMD is still unknown, and no medication can stop or reverse its progression. Several case series consistently showed that the role of stenting in MMD is highly questionable and is associated with a high rate of symptomatic restenosis/occlusion. Revascularization surgery remains the mainstay of treatment for MMD, whereas the recent guidelines do not recommend bypass surgery for ICAS. Therefore, differentiation of MMD from ICAS is important for treating patients with intracranial occlusive disease.

There is also female predominance. Besides sex, race and ethnicity, risk factors associated with intracranial atherosclerosis include hypercholesterolemia, diabetes mellitus, cigarette smoking, and hypertension.

Three modalities of treatment considered for intracranial atherosclerotic disease include medical therapy with aspirin vs warfarin, endovascular revascularization with angioplasty and stent, and extracranial intracranial bypass surgery.

The WASID (Warfarin Aspirin Symptomatic Intracranial Disease) trial demonstrated that aspirin was as effective and safer than warfarin for preventing stroke in patients with symptomatic intracranial stenosis[4], however, neither therapy was particularly effective, especially in patients with more severe stenosis (70%-99%) and recent symptoms.

As shown by the warfarin–aspirin symptomatic intracranial disease (WASID) study, the risk of recurrent ischemic stroke was still high in patients with intracranial artery stenosis even after aspirin therapy and standard treatment of vascular risk factors. The overall rate of any stroke or death at 1 year was 22% in WASID for patients with 50–99% stenosis[5], which can cause disability in nearly half of these patients. In particular, for patients with a high degree of stenosis (≥70–99%), the ischemic stroke recurrence rate at 1 year was 18%.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) and Warfarin Aspirin Symptomatic Intracranial Disease Study (WASID) trials showed the poor effectiveness of medical management of IAS. This is one of the reasons why transluminal angioplasty and vascular endoprothesis arise as useful therapeutic tools.

The first randomized trial to evaluate endovascular therapy for intracranial stenosis was SAMMPARIS (Stenting and Aggressive medical Management for Preventing Recurrent Ischemic Stroke) trial. Enrollment in SAMMPARIS was stopped early because of the higher than expected rate of periprocedural stroke in stenting group (14.7% at 30 days including 10.2% ischemic stroke and 4.5% hemorrhagic stroke)[6].
Criticisms of SAMMPARIS soon followed. One particular concern involved technical aspects of the self-expanding stent used in this trial which requires an over the wire exchange technique after balloon angioplasty, the balloon is removed over long exchanged wire and the stent advanced subsequently and deployed. In contrast a balloon mounted stent requires crossing the lesion and a single time for simultaneous angioplasty and stent deployment. The stent system used in SAMMPARIS trial may theoretically increase the risk of hemorrhagic stroke from wire perforation during the exchange or ischemic stroke from crossing the lesion after angioplasty for stent deployment. So some authors have suggested these periprocedural risks could be lowered by delivering and deploying a balloon-mounted stent in a single-step procedure that leaves less residual stenosis.

So the first randomized trial to use balloon mounted intracranial stent VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) which had similar eligibility criteria to SAMMPARIS which included some sites in China and Europe was done but enrollment was stopped early after only 112 patients were randomized because of higher than expected rate of stroke in stenting group. The periprocedural stroke rate in VASSIT was 25.8% at 30 days (17.2%, ischemic stroke and 8.6%, hemorrhagic stroke).

The SAMMPRIS trial suggested that aggressive treatment was superior to endovascular stenting in patients with severe symptomatic intracranial atherosclerotic stenosis (ICAS) due to high complication rates in patients in the stenting group. Given that 12.2% patients failed aggressive medical therapy in the SAMMPRIS study, it is imperative to perform a multicenter prospective registry study of stenting for patients with ICAS in China. This study aims to evaluate the safety and efficacy of endovascular stenting for patients with symptomatic intracranial artery stenosis and poor collaterals in China and to identify the characteristics of the population that would benefit the most from endovascular stenting in Chinese patients and reported the morbi-mortality about 11.5% which was similar to the last series published[7].

Based on these trials there are some recommendations by AHA for treatment of ICAS as follow[8]:

For patients with a stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, aspirin is recommended in preference to warfarin (Class I; Level of Evidence B)

Endovascular revascularization by intravascular balloon angioplasty and/or stenting may be considered for patients with symptomatic severe intracranial stenoses (70% luminal narrowing) despite optimal medical therapy (Class IIb, Level of Evidence C)
For patients with stroke or TIA due to 70% to 99% stenosis of a major intracranial artery, extracranial intracranial bypass surgery is not recommended (Class III; Level of Evidence B).

Due to intracranial artery morphology which has thin media without robust adventitia, and nearly absent external elastic lamina and vasa vasorum any interventional procedure for overcome the stenosis has own special risks so case selection is important aspect for treatment strategy in these groups of arterial stenotic disease.

So for determining the efficacy of endovascular treatment two important factor should be considered:

1. Patient’s related factor
2. Endovascular feasibility

Regarding first issue endovascular treatment recommended only for patients with more than 70% stenosis of major intracranial vessels and refractory to medical therapy, previous stroke or TIA, neurologic symptoms referable to the target lesion, presence of symptoms during the 6 mo prior to treatment and minimum vessel diameter of 2 mm.

Endovascular feasibility depends on a few factors including stenotic lesion character which is classified by Mori to three types:

1. Type A: <5 mm in concentric or moderately eccentric, smooth stenosis
2. Type B: 5 mm to 10 mm in length, extremely eccentric, or angulated (>45°), or irregular stenosis, or total occlusion (<3 months old)
3. Type C: >10 mm in length, extremely angulated (>90°) stenosis, or total occlusion (>3 months old), or lesion with a number of neovasculatures all around.

Other important factor considering in endovascular treatment is vascular access which also has own classification:

Type I: mild-to-moderate tortuosity and smooth access
Type II: severe tortuosity and/or irregular arterial wall
Type III: excessively severe tortuosity

So patient selection according to above criteria is very important in endovascular cerebral revascularization with stent and angioplasty.

Accepted procedure consist of percutaneous transluminal balloon angioplasty with gateway balloon and deployment of wingspan stent which is self expandable stent with low radial force. Balloon should be 0.5-1 mm smaller than vessel diameter and stent should be 0.5-1 mm larger. Cautions should be done during balloon angioplasty due to vessel dissection that may occur in 20%, acute occlusion, acute vessel recoil and post residual stenosis. So for better outcome deployment of stent advise which has some advantages including avoiding plaque dislodgement, avoiding intimal dissection, avoiding elastic vessel recoil, avoiding plaque regrowth and avoiding late restenosis.
Recently cerebral revascularization with balloon expandable stents are also tried in many cases with good results. This include using stents that are equal to or slightly less than diameter of adjacent distal normal vessel. The length of stent should be slightly more (1-2 mm) than the length of lesion. The balloon then inflated gradually at 6 to 9 atm depending on type of stent and its location.

After technical success was achieved, defined as ≤20% of residual stenosis, the balloon was withdrawn and the microguide wire was left in the original site for 30 minute observation until general anesthesia was discontinued. After ensuring angiographical patency and evaluating the National Institutes of Health Stroke Scale (NIHSS) score, the microguide wire and guiding catheter will be withdrawn.

Residual stenosis at the end of procedure defined as more than 20% stenosis and is due to balloon sub expansion and elastic recoil.

Early detection of complication could be life saving. These complications include: Ischemic stroke, intracerebral hemorrhage, hyperperfusion syndrome, snow plow effect, and restenosis[9].

Timing of ischemic complication could lead us to determine the cause and mechanism of this type of complication. Acute intraoperative strokes that manifest immediately after stent placement may be the result of a “snow plowing” effect, thromboembolism, acute occlusion of perforator ostia by stent struts, or in situ thrombus. Early delayed strokes that develop within the first few days after stent placement may be related to in-stent thrombus, occlusion of perforator ostia, or thromboembolism. Late delayed strokes (≥2 weeks after stent placement) may be related to all of the above in addition to another potential mechanism caused by intimal hyperplasia within and around perforator ostia.

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IV Thrombolysis: An Iranian Proposed Protocol

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Background
Stroke is a leading cause of mortality worldwide. Unfortunately, its incidence is more and the age of occurrence is one decade earlier in our country, Iran (1). About 80-90 percent of stroke etiology is ischemic. The only approved drug treatment for eligible acute ischemic stroke patients is thrombolytic therapy by recombinant tissue plasminogen activator (tPA). Related level of evidence is the highest (1a) which has been approved by FDA following NINDS study since 1996. The first golden time for the use of tPA was less than 3 hours but later it has extended to 4.5 hours following re-analysis of the data since 2009 (2).

In the beginning, related exclusion criteria were strict considering many absolute items; however, some of them have been changed or removed as relative exclusion criteria by practicing and performing researches and analysis of results. It is going to be more simplified. Finally, new published researches extended this therapeutic time window to 6 hours by using mechanical thrombectomy in defined patients not responding to IV thrombolysis (3).

Thrombolysis in Iran
Intravenous thrombolysis has been provided discretely in some universities and private hospitals since 2008. The main limit for this therapy was the lack of coverage by health insurance companies for tPA in Iran. Fortunately, despite this limitation, the team working in Tabriz University of Medical Sciences performed a situation analysis on admitted stroke patients and after finding the related pitfalls, a multidisciplinary stroke team has been established to start systematic thrombolysis in eligible stroke patients since 2010, known as Tabriz Thrombolysis Treatment of Acute Ischemic Stroke (T3AIS) project. Since then, this center has been working more actively on stroke promotion program by collaboration of World Stroke Organization (WSO) to help stroke patients as much as possible. So far, the center in Tabriz, with more than 500 stroke code activation and thrombolysis in more than 155 eligible stroke patients is the most active center in Iran. This, together with the valuable activities of other university hospitals on thrombolysis of stroke (Firoozgar, Namazi, Ghaem, Imam Hossein, Alzahra, Sina, etc.) in metropolitan cities of Iran including Tehran, Shiraz, Mashhad and Isfahan have led the ministry of health to consider stroke as a health crisis. Fortunately, in the current year, the ministry called Iranian stroke association and other relevant
authorities to make National Stroke Program to improve the stroke patients’ situations in Iran. National Stroke Committee with six workgroups (Pre-hospital, Stroke Unit, Intervention, Registry, Post-Hospital care and Education/Prevention) was founded. This program is going to be finalized in the near future. In the first step, this activity leads to the decrease of the drug cost and its coverage by insurance companies.

Intravenous Thrombolysis Guideline
Our stroke team in Tabriz, Imam Reza Medical Center decided to use AHA/ASA as a standard guideline in selecting stroke patients for IV thrombolysis and followed the patients’ three-month outcomes. AHA/ASA 2013 guideline is as the following (4):

“Inclusion and Exclusion Characteristics of Patients with Ischemic Stroke that Could Be Treated with IV rtPA Within 3 Hours from Symptom Onset:

Inclusion Criteria
1- Diagnosis of ischemic stroke causing measurable neurological deficit
2- Onset of symptoms <3 hours before beginning treatment
3- Aged ≥18 years

Exclusion Criteria
1- Significant head trauma or prior stroke in the past 3 months
2- Symptoms suggestive of subarachnoid hemorrhage
3- Arterial puncture at non-compressible site in the past 7 days
4- History of previous intracranial hemorrhage
5- Intracranial neoplasm, arteriovenous malformation or aneurysm
6- Recent intracranial or intraspinal surgery
7- Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)
8- Active internal bleeding
9- Acute bleeding diathesis
10- Platelet count <100 000/mm3
11- Heparin received within 48 hours, resulting in abnormally elevated a PTT greater than the upper limit of normal
12- Current use of anticoagulant with INR >1.7 or PT >15 seconds
13- Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as a PTT, INR, platelet count and ECT, TT or appropriate factor Xa activity assays)
14- Blood glucose concentration <50 mg/dL (2.7 mmol/L)
15. CT demonstrates multi-lobar infarction (hypodensity >1/3 cerebral hemisphere)

Relative Exclusion Criteria
1. Only minor or rapidly improving stroke symptoms (clearing spontaneously)
2. Pregnancy
3. Seizure at onset with postictal residual neurological impairments
4. Major surgery or serious trauma within previous 14 days
5. Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
6. Recent acute myocardial infarction (within previous 3 months)" (4)

“Additional Inclusion and Exclusion Characteristics of Patients With Acute Ischemic Stroke Who Could Be Treated With IV rtPA Within 3 to 4.5 Hours From Symptom Onset:

Inclusion Criteria
1. Diagnosis of ischemic stroke causing measurable neurological deficit
2. Onset of symptoms within 3 to 4.5 hours before beginning treatment

Relative Exclusion Criteria
1. Aged >80 years
2. Severe stroke (NIHSS>25)
3. Taking an oral anticoagulant regardless of INR
4. History of both diabetes and prior ischemic stroke" (4)

T3AIS project results were analyzed after one year considering the treated patients’ three-month outcomes and due to high mortality in aged patients, the stroke team decided to exclude the patients more than 80 years for thrombolysis. Recently, guideline workgroup of Iranian National Stroke Committee suggested a national guideline based on new updates of AHA/ASA guideline that will be announced in the near future.

Time Management
“Time lost is brain lost” and “Time is brain” are slogans in acute cerebral ischemia management and thrombolysis. It means that we should treat stroke patients as soon as possible. In a typical middle cerebral artery occlusion, 2 million nerve cells are going to be lost every minute (5). Time from stroke symptom onset is the most important determining factor in the success of IV thrombolysis. Based on current
AHA guidelines, symptom onset is the last time that the patient was in symptom-free situation or in his/her previous baseline condition. The number of benefited eligible stroke patients in the period of 3-4.5 hours has approximately decreased to ½ in comparison with the treated stroke patients during time period of less than 3 hours. Considering the importance of time, the door to needle time should be less than 60 minutes. Stroke centers should be managed to decrease this time as much as possible. Every effort should be made to shorten any delay at the starting point of thrombolysis as earlier treatments were associated with better outcome. Advanced stroke centers are going to decrease this time to about 20 minutes with the use of telemedicine or mobile stroke units.

Protocol, Complications and Management
Dosage of tPA is 0.9 mg/kg IV infusion (maximum dose 90 mg) over 60 minutes, with 10% of the dose given as a bolus over 1 minute. Patient should be admitted to an ICU or stroke unit for monitoring of blood pressure, neurological situation and probable complications. The standard score for monitoring of neurological status and stroke severity is National Institute of Health Stroke Score (NIHSS). This score should be learned in detail by stroke care personnel and they should record NIHSS of the stroke patients before thrombolysis, at least 24 hours and 3 months later.

The chief complication of IV thrombolysis is intracranial hemorrhage. It may be symptomatic (NIHSS increases 4 scores or more) in about 4-6% or asymptomatic, reported as high as 20%. Others are angioedema/allergic reactions in 1-2%, systemic bleeding 0.4% and oozing up to 30%. If patient develops severe headache, acute hypertension, nausea, vomiting or has a worsening neurological examination, we should discontinue the administration (if IV tPA is still being infused) and obtain emergent brain CT scan. If it shows hemorrhagic changes, you should infuse about 4 units FFP or crayo and 4 units platelet transfusion, measure blood pressure and control neurological assessments every 15 minutes during and after IV tPA infusion for 2 hours, then every 30 minutes for 6 hours, finally every hour for 24 hours after IV tPA treatment starts. If systolic blood pressure is >180 mmHg or if diastolic blood pressure is >105 mmHg, you should increase the frequency of blood pressure measurements and administer antihypertensive medications (usually Labetalol) to maintain blood pressure at or below these levels. We should delay insertion of nasogastric tubes, bladder catheters or arterial pressure catheters if the patient can be safely treated without them. Obtain a follow-up CT 24 hours after IV tPA before starting antiplatelet or anticoagulants agents considering stroke etiology.
Outcome of IV Thrombolysis

The main benefit of thrombolysis is improved final functional outcome by reperfusion and salvage of threatened tissue. Overall, of every 100 patients treated, 32 will have a better and 3 will have a worse final global disability outcome as a result of therapy. The number needed to treat (NNT) for any improvement is 3.1-3.6 and for good clinical improvement is 8. The number needed to harm for thrombolysis was reported to be 30-56 (6).

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Epidemiology of stroke in Iran

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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 heterogenous. 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, clinicoradiologic correlations and outcome of patients with cerebrovascular disease.

Khorasan hospital based 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. 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. 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%). 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. 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. Hypertension and history of ischemic cerebrovascular events were the most frequent risk factors, 53.1% and 22.3% respectively. 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. 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. 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 catogorizes 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 KPCSR. Stabilization consisted the most common early stroke course (57.7%) followed by deterioration (22.1%) and regression (20.2%)\(^4\). 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. 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 trauma 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 100,000 child 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 Persian population.

**Khorasan stroke in young adults registry**

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 mechanism of stroke in Iran is similar to other areas around the world, however rheumatic vavular disease and valvular fibrillation consists the most frequent sources of cardioembolism in Iran despite western countires. 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 complicatons.

**Epidemiologic designed study of stroke in Iran**

The population denominator used in this study was obtained from a census conducted in October and November 2006. This census is conducted every 10 years and is conducted with a door-to-door approach. The Mashhad Stroke Incidence Study (MSIS) was conducted in 3 different health districts of Mashhad, located in the province of Khorasan-Razavi, northeastern Iran. From November 21, 2006, for a period of 1 year, patients with recent stroke in the already defined study areas were identified. The study area was delineated by the main boulevards in Mashhad. According to the 2006 census, the study population comprised 450 229 inhabitants. The only neurology center in Mashhad is Ghaem Hospital, and all neurology emergency care is supplied at this hospital. Ghaem Hospital is 1 of the most important hospitals in the east of Iran. It is the referral hospital for eastern Iran (Khorasen, Sistan, and Baluchistan provinces) and for the region west of Afghanistan. Patients or next of kin calling the emergency services telephone number in Iran and who are identified as having a neurologic condition are transferred to Ghaem Hospital. When a patient with stroke is admitted to another hospital, after having been incorrectly diagnosed with another condition, they will then be transferred to Ghaem Hospital as soon as their diagnosis of stroke is made. This occurs when the hospital does not have a neurologist. In addition, some hospitals have a policy not to admit stroke patients because of the high associated mortality and morbidity and lengthy hospital stay. The other main hospital located in the study region is Hasheminejad Hospital, which has both internal medicine
and neurosurgical wards. The 2 other smaller hospitals located within the region are 17 Sharivar (a welfare insurance hospital) and Imam Hosein (a military hospital). According to the World Health Organization definition, stroke is defined as “rapidly developing signs of focal or global disturbance of cerebral function lasting >24 hours (unless interrupted by surgery or death) with no apparent cause other than a vascular origin. With this clinical definition, silent stroke on imaging is not considered a stroke, and imaging confirmation is not required for stroke diagnosis. First-ever stroke (FES) is defined as a stroke occurring for the first time during a patient’s lifetime. Past history of stroke was determined by using all available information, including hospital records, information provided by patients, and family reports. Neuroimaging was used to classify patients with definite FESs into ischemic stroke (IS), intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH) subgroups. All SAHs were included whether or not there were focal neurologic signs. IS was defined as a stroke for which either computed tomography (CT) performed within 28 days of symptom onset showed a normal appearance or CT or magnetic resonance imaging (MRI) showed an area of recent infarction corresponding to the incident symptoms and signs. ICH was defined as a stroke for which CT or MRI demonstrated blood within the brain parenchyma, with or without extension into the ventricles or subarachnoid space. SAH was defined as an abrupt onset of severe headache, loss of consciousness, or both, with or without focal neurologic signs. In addition, CT demonstrated subarachnoid blood. Lumbar punctures are performed in CT-negative patients with an appropriate history. Alternatively, ICHs, SAHs, or ISs were confirmed on autopsy. An undetermined stroke is a stroke for which a patient did not undergo CT scanning within 28 days of the onset of symptoms and an autopsy was not performed. A possible stroke is considered as any acute episode of neurologic disturbance that is suggestive of stroke but for which there is insufficient information to establish whether the symptoms and duration (<24 hours or >24 hours) fully met the World Health Organization definition for definite stroke. “Possible” and “CT-only” strokes were not included in the incidence figures. Multiple sources were used to identify stroke patients, particularly those who were not admitted to hospital. The following methods were used. The medical records of all patients admitted to the 4 hospitals in the study area were examined every day by expert staff to determine any cases with stroke. Discharge diagnoses were also assessed as a backup procedure. We called every hospital in the study area daily to check for new admissions of patients with suspected stroke. All of these patients were visited by a member of the study team. Cases were included only if they lived in the study area. Two hospitals outside the study area were also contacted for potential cases, as it is possible that cases might have been seen at these hospitals.
These cases were followed up in the same manner when a suspected stroke patient was identified. One of these, Imam Reza Hospital, is a main referral hospital with >800 beds, although there are no beds for either stroke or neurosurgery. Faraby is a smaller welfare insurance hospital. One of the authors provided consultations for difficult neurologic cases, and patients with stroke were referred to the study in return. Despite a referral healthcare structure in Iran, there may be situations where people bypass a primary care contact and self-refer to specialists (private) and hospital outpatient clinics (public). Therefore, family physicians, nursing care homes, outpatient clinics, and particularly neurologists in the study area were informed about the study and were asked to identify stroke patients who were not hospitalized. There are 35 neurologists in Mashhad, and they have official meetings on a 3- to 4-month basis. This served as an opportunity to remind neurologists about the study. Referral from neurologists was the major source of case-finding from the smaller military and welfare insurance hospitals (100 to 200 beds) where hospital records could not be checked. In addition, as an incentive to refer patients to the study, 1 of the authors accepted referrals free of charge for duplex and transcranial Doppler examinations from doctors at these hospitals. Death certificates and reports were reviewed on a monthly basis to identify nonhospitalized fatal stroke cases. Cases were included when there was clinical evidence of a sudden, focal neurologic deficit before death. Further validation of stroke diagnosis was provided in cases where CT or MRI was conducted before death or when an autopsy was performed. Local television (once) and newspapers (twice) provided an opportunity for the research group to inform residents about the study. People were invited to contact the study group if they had suffered a stroke. In 1991, the Ministry of Health of Iran began a new healthcare system in urban areas with support from the United Nations Children’s Fund and the United Nations Population Fund. The main aim of this system is to increase outreach capacity in urban health centers and build partnerships between health centers and the people so that the community itself could take a greater share of responsibility for its health. This was undertaken through the use of community health volunteers (CHVs). CHVs participate in several classes in different health-related aspects, such as water quality and family planning. There is evidence that CHVs have had significant impact on the health of their communities, and since 1994, CHVs have become an important part of the national health policy of Iran. For accurate estimation of nonhospitalized stroke patients, 980 trained CHVs who had enough general knowledge about stroke participated in this study. One of the authors undertook training sessions with the CHVs and their coordinators. Common presentations of stroke were outlined. CHVs lived in the study area, knew their neighbors, and were responsible for checking their neighborhoods for
potential stroke cases. They were asked to refer any person with suspected symptoms of stroke. Each CHV was responsible for between 50 and 100 houses. This translates to ≈500 inhabitants, as the average household in Mashhad includes 5 people (>5 in poor areas). The CHVs provided door-to-door information about most of the inhabitants in the study area by visiting them at least every month. In addition, volunteers would see these neighbors every day in the street and in their homes or at religious meetings. Because these families knew the CHVs, they were comfortable reporting their health problems to them. The CHVs were responsible for reporting any people with a history of sudden onset of weakness, sensory disturbance, dizziness, language disturbance, visual loss, and sudden death to the study investigators. Subjects were then telephoned by the lead investigator, and these subjects were invited to participate. The majority of these patients then attended the office of 1 of the investigators either with or without the CHV. Some individuals could not come to the hospital. In this instance, the investigator carefully checked the history of the event by telephone. Those with symptoms and signs consistent with stroke were then visited in their homes, and a neurologic examination was undertaken. This occurred on fewer than 10 occasions. At the end of the study period, each CHV was asked to check each household for any potential stroke event that might have been missed. At this time, they were also asked to check the regions that did not have any volunteers; ≈20% of the region was not covered by CHVs. Any suspected cases of stroke or death from stroke in the previous year were identified, and a final diagnosis was made by the research team. It took 3 months to undertake this final surveillance. All stroke events within the study period occurring among residents of the defined geographic region were counted in this study. Potential cases were reviewed by a panel of stroke experts before final inclusion. Cases were eligible only if they had been resident within the defined geographic area for at least 1 year before the stroke. This latter criterion was used because Mashhad has a large number of temporary residents not included in census figures. For example, farmers in neighboring areas might work for 6 to 8 months on their farms but then come and stay in Mashhad for the winter. Others, such as elderly people with chronic disease, live in neighboring cities and stay with their families in Mashhad for 2 to 3 months. Three neurology residents and a trained nurse abstracted the medical record of each patient and recorded all of the information regarding the patients’ living arrangements, stroke symptoms and signs, risk factors, diagnostic studies, and treatment. Data entry was performed by a group of computer technicians and 4 medical students. A neurologist supervised the process from the patients’ inclusion up to the time of data entry. Incidence rates (number per 100 000 population per year) are reported as crude rates and as rates age-standardized to the “world” and “European”
populations of Segi. These standardizations allow unbiased comparisons between populations by eliminating the influence of different age distributions. During the period of research, a total of 887 strokes were originally included. After careful review of their records, 2 were excluded because their signs and symptoms did not comply with the study definition of stroke, despite evidence of stroke on CT. There were a further 10 possible strokes, 43 TIA’s, and 1 brain tumor case that were excluded. In addition, an additional 138 were found to live outside the study region, and in another 9, the stroke occurred outside the study time period. This left a total of 684 strokes that complied with the study definition. Four hundred ninety-one cases (71.8%) were admitted to hospital (92% in Ghaem Hospital and 8% in other hospitals), and 193 patients (28.2%) were managed in the community; these latter cases being mainly referred by volunteers and other neurologists. The main ethnic groups were Persian (82.5%), Turk (8.3%), Afghan (4.8%), Kurd (2.8%), Arab (1.2%), and other (0.4%). A final diagnosis of FES was made in 624 (91.2%) individuals, of whom 52.4% were men and 47.6% were women. The crude annual incidence rate of FES was 139 (95% CI, 128 to 149) per 100 000; for men, 144 (95% CI, 128 to 159), and for women, 133 (95% CI, 118 to 148). No strokes were found in children age <15 years. The incidence rates increased significantly with each decade of life and were similar in men and women. A CT scan was performed for 661 events (96.6%). We used MRI as the only form of imaging in another 5 cases. Autopsy was performed in 2 cases, for whom we also had a prior CT, for a definite diagnosis of stroke subtype. Consequently, imaging-autopsy was performed for 666 cases (97.4%) of events and for 614 cases (98.4%) of FES. Pathologic subtypes of FES were classified in all 605 people who either had imaging within 28 days of stroke or had an autopsy examination: 511 (81.9%) patients had IS, 79 (12.7%) had ICH, and 15 (2.4%) had SAH. The crude annual incidence rate per 100 000 inhabitants was 113 (95% CI, 104 to 123) for IS, 18 (95% CI, 14 to 21) for ICH, 3 (95% CI, 2 to 5) for SAH, and 4 (95% CI, 2 to 6) for undetermined stroke. When adjusted to the world and European populations, stroke incidence rates were greater than those of crude incidence rates. Incidence adjusted to the European population aged 45 to 84 years was greater in Mashhad than in all other “ideal” studies conducted since 1995, apart from that in West Ukraine, and was largely attributable to a greater incidence of IS. The incidence of ICH also appeared to be greater in Mashhad than in all other regions apart from Tbilisi, Georgia. Adjusted incidence rates for each subtype of stroke were similar between men and women. We found that the incidence of stroke, adjusted to the European population aged 45 to 84 years, in Mashhad, Iran, was greater than in most Western countries with the exception of the Ukraine. Incidence rates were even higher than those of Novosibirsk, Russia, a region known for its high...
incidence of stroke. Although population-based stroke studies are the best way to determine the real burden of stroke, these studies are scattered and have been performed mostly in developed countries. This is the first population-based study of stroke in a Middle East region that fulfils “ideal” criteria for a stroke incidence study. The incidence of stroke was higher than expected. Indeed, the incidence was approximately double that of the majority of “ideal” studies conducted in the last decade. Importantly, the incidence of stroke was as high in women as in men. In a recent review of the differences between men and women, the overall incidence of stroke was 33% higher in men, apart from a few studies with small sample sizes and consequent low power. The reason for this difference between Iran and most other countries is unclear. Interestingly, although the adjusted incidence rates were high, the crude incidence rate of stroke was relatively low. Low crude incidence rates of stroke may occur when stroke incidence is low or when the source population is young; low crude incidence occurs in a young population because age is strongly associated with stroke incidence. However, despite the relatively young population in Mashhad, ISs are occurring approximately 1 decade earlier than in other countries. That is, a higher age-specific incidence is seen in younger age groups. This explains both the greater age-adjusted stroke incidence observed in Mashhad than in other countries and the fact that a low crude stroke incidence is present in a setting of a high age-adjusted stroke incidence.

References
Intracranial Stenting

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Intracranial arterial stenosis (ICAS) is one of the main causes of ischemic stroke. According to western epidemiological studies, 8-10% of ischemic strokes are attributable to intracranial stenosis. Distribution of intracranial stenosis, as shown by Comparison of warfarin and aspirin for symptomatic intracranial stenosis (WASID) study, is as below:

- Internal carotid 20.3%
- MCA 33.9%
- Vertebral artery 19.6%
- Basilar artery 20.3%
- Multiple Artery 5.9%

It seems that intracranial stenosis is more common in Asia. Asian patients have a higher proportion of MCA stenosis and 33% of strokes in China are because of intracranial stenosis. Considering the population of Asia, intracranial stenosis is the most important cause of stroke in the world.

Risk factors associated with symptomatic ICAS include age, hypertension, hyperlipidemia, smoking and diabetes.

The diagnosis of ICAS may be made through several diagnostic procedures including conventional angiography, transcranial Doppler ultrasound (TCD), magnetic resonance angiography (MRA) and computed tomography angiography (CTA). Conventional angiography remains the gold standard with the advantages of accurate stenosis measurement, differentiation of occlusion from severe stenosis and collateral flow evaluation. Non-invasive neuroimaging techniques may, therefore, be useful as screening tests, but conventional angiography remains the gold standard for confirming the degree of stenosis.

In WASID, high-risk subgroups for vascular events including patients with recent stroke or TIA attributable to high-grade (70–99 %) intracranial major artery stenosis experienced an 18 % risk of recurrent stroke in the 1st year (19 % in the 2nd year).

Warfarin-Aspirin Recurrent Stroke Study (WARSS) found that oral anticoagulation was no better than Aspirin for non-cardioembolic stroke. Additional trials have demonstrated the added benefit of dual antiplatelet therapy over Aspirin alone. These data strongly support the recommendation that patients with symptomatic ICAS should be treated with AMM (Aggressive Medical Management) consisting of antiplatelet therapy (with consideration of dual antiplatelet therapy for the first 90 days) and intensive risk factor management.
There are four options for endovascular revascularization: angioplasty alone, angioplasty followed by placement of a self-expanding stent, balloon expandable stents and balloon expandable drug-eluting stents.

The Stenting and Aggressive Medical Management for Preventing Recurrent Stroke and Intracranial Stenosis (SAMMPRIS) trial, a randomized clinical trial comparing aggressive medical management to stenting with aggressive medical management for symptomatic intracranial stenosis, was prematurely halted when a high rate of periprocedural events was found in the stent arm.

After reviewing the available safety information and trials, the FDA approved Wingspan only for patients who are between 22 and 80 years old who meet ALL of the following criteria:

- have had two or more strokes despite aggressive medical management,
- most recent stroke occurred more than seven days prior to planned treatment with Wingspan,
- have 70-99 percent stenosis due to atherosclerosis of the intracranial artery related to the recurrent strokes, and
- have made good recovery from previous stroke and have a modified Rankin score of 3 or less prior to Wingspan treatment. The Rankin scale is used to measure the degree of disability in stroke patients. Lower scores indicate less disability.

**Conclusion**

At present, medical management should be the first line of therapy for the most patients with symptomatic ICAS. Angioplasty and stenting can be considered in some patients that are unstable or have multiple ischemic events in the territory despite AMM.

Further studies have shown that lesions less than 5mm in length may have significantly less peri-procedural risk as well as restenosis following angioplasty, and patients who fail AMM with these shorter lesions may be more amenable to stenting.

It is reasonable to consider percutaneous transluminal angioplasty and stenting (PTAS) for unstable patients or those with recurrent events despite AMM, although there is no good evidence that PTAS provides a benefit. Future studies of PTAS for ICAS are needed to address the following issues:

1. identify high-risk subgroup of patients likely to benefit from PTAS using non-invasive imaging
2. identify and overcome the mechanisms behind reperfusion hemorrhage
3. identify and overcome the mechanisms for procedural ischemic stroke
4. overcome significant problem of delayed symptomatic stent restenosis.
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Cryptogenic stroke

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Definition: The majority of ischemic strokes are due to cardioembolism, large vessel atherothromboembolism, small vessel occlusive disease, or other unusual mechanisms. However, many ischemic strokes occur without a well-defined etiology and are labeled as cryptogenic. Other terms used in the literature to describe cryptogenic stroke (CA) include cryptogenous stroke and infarcts of unknown, uncertain, or undetermined cause. The cause of CS remains undetermined because the event is sometime transitory or reversible, investigations did not look for all possible causes, or because some causes truly remain unknown. It is necessary to establish the cause of stroke to determine functional prognosis, decrease the risk of future strokes, and select appropriate preventative care. By the TOAST classification, which is the most commonly used in clinical practice, cryptogenic stroke (or stroke of undetermined origin in TOAST terminology) is defined as brain infarction that is not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation.

Epidemiology: Incidence of cryptogenic stroke differs according to study population, diagnostic definitions, extent of diagnostic evaluation, and methodology, age of the patients, the definition of cryptogenic stroke that was used and extent of the etiological investigation. CS accounts for 30 to 40 percent of ischemic strokes in most modern stroke registries and databases. The risk of CS may vary by race, with higher incidence rates in blacks than in whites, but no clear association has been found for age and gender.

Causes of cryptogenic stroke: CS is most frequently due to cardiac embolism, followed by vasculopathy, and coagulopathy. The most frequent causes of cardiac embolism include paradoxical embolism from upstream veins via a patent foramen ovale (PFO), paroxysmal atrial-fibrillation, valvular heart-disease, and atrial septal aneurysm. The most frequent vascular causes of CS are complex aortic plaques and Fabry’s disease.

Common causes of cryptogenic stroke:
1-Cardiac
1a: Frequent
PFO*
Atrial septal defect*
Atrial septal aneurysm (ASA)*
Atrial fibrillation
Heart valve disease*#
Regional myocardial dyskinesia
Dilated left atrium
1b: Rare
Right atrial Chiari network*
Prominent Eustachian valve* (conducts the blood from the caval vein directly into the right atrium)
Spontaneous echocontrast within the right atrium*
Ventricular thrombus*
Left atrial appendage thrombi*
Dilative cardiomyopathy*
Restrictive cardiomyopathy*
Takotsubo syndrome*
Left ventricular hypertrabeculation*
Endomyocardial fibrosis
Left atrial bands*
Papillary fibroelastoma*
Atrial myxoma*

2-Lung
Hereditary teleangiectasia Rendu-Osler
(Paradoxical embolism from pulmonary AV-shunts)

3-Vascular
Atherosclerosis
Large arteries (aortic plaques*), small arteries
Fabry's disease
Aortic dissection*
Mural thrombi over dissected aortic segments*

4-Coagulopathic
4a: Arterial hypercoagulability
Antiphospholipid antibody syndrome
Elevated lipoprotein (a)
Tissue factor mutation
Hyperhomocysteinemia
4b: Venous hypercoagulability
Inherited
Antithrombin-III deficiency
Protein-S deficiency
Protein-C deficiency
Factor II deficiency  
Heparin cofactor II deficiency  
Prothrombin mutations  
Activated protein C (APC)-resistance  
Fibrinolytic system abnormalities (plasminogen or tissue plasminogen activator deficiency, elevated plasminogen activator inhibitor)  
Hereditary hyperhomocysteinemia  
Factor XIII polymorphisms  
Acquired  
Acquired hyperhomocysteinemia  
Neoplasm  

Pathophysiology: Identifying a unifying theory and mechanism for cryptogenic stroke is likely to be difficult, if not impossible. The widespread use of modern technologies, including MRI, transesophageal echocardiography, and specific hematologic tests, has greatly enhanced the certainty of stroke subtype classification.  

Clinical features: CS presents with superficial hemispheric infarction in 62 to 84 percent of patients. Lacunar syndromes are rare, accounting for usually less than 5 percent. The severity of the initial presentation varies but, on average, tends to be milder than cardioembolic strokes and worse than lacunar strokes. The risk factors for cryptogenic stroke are not clearly different from the risk factors for other types of ischemic stroke, although hypertension may be less common in patients with cryptogenic stroke compared with other ischemic stroke types.  

Evaluation and diagnosis: No current guidelines (European or American) on how to manage cryptogenic stroke. Cryptogenic stroke is a diagnosis of exclusion based on a thorough investigation for other potential etiologies. Diagnostic work-up for CS includes transesophageal echocardiography (TEE), long-term ECG-recordings, CT-/MR-angiography of the aorta, transcranial Doppler-sonography, and imaging for venous thrombosis in case of paradoxical embolism, and blood chemical investigations and coagulation tests. For patients with a cryptogenic ischemic stroke or transient ischemic attack (TIA) and no evidence of atrial fibrillation on electrocardiography (ECG) and 24-hour cardiac monitoring, (Current guidelines recommend at least 24 hours of ECG monitoring after an ischemic stroke to rule out atrial fibrillation) we suggest prolonged ambulatory cardiac monitoring for several weeks. Paroxysmal atrial fibrillation is present in approximately 25 percent of patients with cryptogenic stroke, depending on the method of detection. It may be undetected on standard cardiac monitoring such as continuous telemetry and 24 or 48-hour Holter monitors. The optimal monitoring method (eg, continuous telemetry, ambulatory electrocardiography, serial electrocardiography,
transtelephonic ECG monitoring, or implantable loop recorders) is uncertain, though longer durations of monitoring (e.g., 21 to 30 days or even longer) are likely to obtain the highest diagnostic yield.

While retrospective data suggest that there is an increased prevalence of patent foramen ovale (PFO) and atrial septal aneurysm (ASA) in patients who have had a cryptogenic stroke, particularly in patients <55 years old, population-based studies suggest that PFO and large PFO are not independent risk factors for stroke. In addition, prospective data suggest that PFO alone is not associated with a meaningfully increased risk of recurrent stroke or death in patients who have already had a cryptogenic stroke, although a small increase or decrease in risk cannot be excluded.

The main tests for CS evaluation:

Useful
- TEE
- Long-term ECG-recording
- CT- or MR-angiography of the aorta and its thoracic branches
- TCD
- Venous ultrasound, MR-venography, phlebography

Ordinary blood investigations
- Blood cell count (polycythemia vera, thrombocytosis)
- (82), D-dimer, urine protein

Coagulation test
- Arterial hypercoagulability (lupus anticoagulant, anticardiolipin antibodies, lipoprotein A, tissue factor mutations, hyperhomocysteinemia)
- Venous hypercoagulability (activated-protein-C (APC) resistance, deficiency of protein-C, protein-S, or antithrombin-III, heparin cofactor II deficiency, prothrombin gene mutations, fibrinolytic system abnormalities (factor XIII polymorphisms), hyperhomocysteinemia)
- Alpha galactosidase (GLA genetics)

Questionable
- 3D-MRI
- Multidirectional 3D-MRI velocity mapping
- FDG-PET
- Cardiac MRI
- Intracardiac echocardiography

Biological assays

Prognosis: Compared with other stroke subtypes, cryptogenic stroke tends to have a better prognosis at three months, six months, and one year. Mortality rates are
lower than those for cardioembolic stroke but higher than those for small artery disease. Overall, the short-term risk of recurrent stroke after cryptogenic stroke is intermediate between the high early risk after large artery atherosclerosis stroke and low risk after small artery disease stroke.

Treatment: Because the pathophysiology of cryptogenic stroke is heterogeneous, decisions regarding treatment for such patients are challenging. Nevertheless, there are no convincing data that acute management should differ by stroke subtype. Intravenous thrombolysis with tPA (alteplase) is beneficial for eligible patients with ischemic stroke who can be treated within 4.5 hours of stroke onset. Acute management for patients with cryptogenic stroke who are not eligible for thrombolysis is also similar to patients with other ischemic stroke subtypes. For most patients with cryptogenic stroke, antiplatelet therapy is recommended as the mainstay of antithrombotic therapy for secondary prevention.
New Oral Anticoagulants (NOAC)

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Introduction
Atrial fibrillation (AF) as the most common cardiac arrhythmia, affects more than 6 million European people and more than 2.2 million people in the United States(1-3). This cardiac arrhythmia is represented by 2% to 3% of Europe and North America population, whereas in developing countries the rates are about 0.4% for females and 0.6% for males(4). AF confers a 4 to 5-fold increase of ischemic stroke risk and one fifth of every stroke is caused by AF. AF associated strokes are often fatal, while others who survive, may suffer from a long term disability and a higher potential of recurrence in comparison to other stroke causes. AF related stroke is associated with double risk of death and a 1.5-fold increase in costs of care.(5-8) Therefore prevention of stroke can play an important rule for patients with this arrhythmia.

Vitamin K antagonists (VKA like warfarin) are highly effective in prevention of stroke and warfarin has been the only orally anticoagulant since 60 years ago. However, this anticoagulant is problematic for the patients due to food and drug interactions. In addition warfarin has narrow therapeu tic index and needs frequent coagulation monitoring (international normalised ratio (INR)) and dose adjustments (6, 9-11). Therefore the necessity of new oral anticoagulants(NOAC) for prevention of stroke and thromboembolism is more clear, that the U.S. Food and Drug Administration has been working on NOAC during past decade(11). These new oral anticoagulants are dabigatran(direct thrombin inhibitor) and rivaroxaban and apixaban (factor Xa inhibitor). Large randomized trials demonstrated that NOAC are at least as effective as warfarin, while they have several advantages in comparison to VKA, including a predictable dose response, less food and drug interactions, less risk of bleeding and also no need for frequent coagulation monitoring (international normalised ratio (INR))(6, 11-16).

NOAC have some major concerns, including rapid decline in there anticoagulant effect in patients with poor compliance and unavailable specific antidotes for the cases of life-threatening bleeding(13, 17). However, there are some suggested specific antidotes(e.g. idarucizumab, andexanet alfa, and ciraparantag) which may be provided in near future(14). ES Eerenberg et. al found prothrombin complex
oral

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concentrate (PCC) as an immediate effective antidote for rivaroxaban but with no anticoagulant influence on dabigatran (18).

Dabigatran etexilate

Dabigatran etexilate is a potent, reversible and competitive direct thrombin inhibitor (DTI) that inhibits thrombin and generation (19). This drug has a predictable pharmacokinetic (PK)/pharmacodynamic (PD) profile which allows a fixed-dose regimen without needing frequent coagulation monitoring (17, 20). In healthy volunteers, 2 hours after oral administration of dabigatran, peak plasma concentrations are reached. Half-life elimination of the drug is 12-14 hours. Dabigatran etexilate has predominantly renal excretion. Therefore in patients with renal function impairment the drug doses should be adjusted. Dabigatran is a prodrug that will be activated by carboxylesterases but cytochrome P-450 isoenzyme system is not involved in its metabolism. No food interactions is observed about dabigatran and low drug-drug interactions mentioned (also no interactions reported in case of concurrent use of it with atorvastatin, diclofenac or digoxin) (16, 19, 20). One of the most important features of dabigatran PK is its consistent pharmacokinetic in different populations, origin, body weight, gender and moderate hepatic impairment (19).

There are several studies reported efficacy of dabigatran in treatment of venous thromboembolism (VTE), prevention of VTE for patients undergoing elective total hip and knee replacement and stroke prevention in non-volvular atrial fibrillation patients (16, 17, 19). Dabigatran has been approved for VTE and stroke prevention in AF patients by the Food and Drug Administration since Octobr 2010 and the European Medicines Agency has accepted it for VTE prevention in undergoing total hip and knee replacement patients in March 2009 (16).

There are some paradoxical results about dabigatran in different studies. RE-LY study has reported that dabigatran is as efficient as warfarin with less potential for extracranial bleeding and equal or superior effect in prevention of embolism and non-fatal stroke, thus as RE-LY study dabigatran is recommended instead of warfarin (12, 20, 21). In the study of JW Eikelboom et. al, dabigatran administration in mechanical volvular heart patients was associated with higher bleeding and thromboembolism complications in comparison with warfarin that led to less compliance for its administration (22).

Stangier J et. al reported mild to moderate headache and dose dependent bleeding that was mild to moderate in intensity, as adverse effects of dabigatran (23), but in other study increased rate of ACS or MI was reported that suggests clinicians to consider this serious cardiovascular effects in case of dabigatran administration for patients (24).
In performed studies, two different doses of dabigatran has been evaluated, including 150-mg dose and 110-mg dose. Due to RE-LY study, administration of 150-mg dose for twice a day in comparison with warfarin, has reducted the rate of unspecified and ischemic stroke but with similar rate of major bleeding. Twice daily administration of 110-mg dose, was shown to be associated with a same rate of stroke as warfarin, but lower extracranial bleeding(25). In Miller et al. meta analysis, they administered only 150-mg dose BID, as 110-mg dose BID was not confirmed in United States for non-vovular AF. This issue may overestimate dabigatran effect in stroke prevention as compared with warfarin(26) whereas in the study of JW Eikelboom et al. both doses were included because of Europe acceptance and also RE-LY study that showed no difference in efficacy of different doses in long term use of the drug(27). In case of life threatening bleeding, there is no specific antidote for dabigatran, however idarucizumab has been suggested(14) and in other study prothrombin complex and recombinant activated factor VII have been considered as prohaemostatic agents which are non-specific(17).

In renal impairment, adjusted doses of dabigatran is required. For stroke prevention, 150mg BID for CrCl >30 mL/min, 75mg BID for CrCl 15-30 mL/min is accepted but for CrCl <15 mL/min or dialysis, there is no evidence and dabigatran administration is nor recommended(28).

Dabigatran is contraindicated in:
1) active pathological bleeding
2) hypersensitivity reaction
3) mechanical prosthetic heart valve(29)

Rivaroxaban:
Rivaroxaban is the second new oral alternative which inhibits free and clot-bound Factor Xa (FXa) and Factor Xa in the prothrombinase complex (30-32).

Rivaroxaban will be absorbed rapidly and maximal plasma concentrations will be reached within 2-4 hours after tablet intake(30, 31, 33-35). Within 3 hours after intake, Factor Xa inhibition would be at peak(33, 34). Bioavailability of oral administered rivaroxaban is dose dependent(35), as it reaches 80-100% irrespective of food intake for 10 mg doses(30) whereas 80% bioavailability of 15mg and 20mg doses will be achieved by concurrent food intake(36). Half life of rivaroxaban has been reported 5-9 hours for healthy youth and 11-13 hours for healthy adults(30). Inhibition of FXa will return to baseline within 24-48 hours after drug administration(35, 37). These statistics show that rivaroxiban will be absorbed and affect rapidly and would be eliminated rapidly after therapy.
Like dabigatran, rivaroxaban doesn't need dose adjustments and is not dependent to age, gender, ethnicity and body weight and also does not require frequent coagulation monitoring. In addition, low food interactions has been reported(31, 35).

According to Weinz C et al. study, rivaroxaban pharmacological effects are associated with unchanged drug(37). Two-thirds of rivaroxaban will be metabolized via co-administration of cytochrome P450 (CYP) 2J2 and 3A4, plus other CYP-independent mechanisms such as P-glycoprotein substrates/moderate inhibitors. As rivaroxaban metabolism doesn't have inhibitory effect on CYP3A4, Bcrp (ABCG2) inhibitors and P-glycoprotein, no significant drug-drug interactions have been reported(30, 31, 34).

Renal excretion(66%) of rivaroxaban is the predominant way of drug elimination and remained drug is eliminated by hepatobiliary route(37-39). 43% of the drug is excreted unchanged, 36% in urine and 7% in feces(37).

There are several studies in which rivaroxaban has been evaluated in orthopedic surgeries for prevention of venous thromboembolism disorders and in non-volvular AF for stroke prevention(32, 36, 40, 41).

In the study of D Kubitza et al. rivaroxaban maximum factor Xa inhibition increased from 68% resulted from 30 mg dose administration to 75% by administration of 40 mg dose but no further change by 50 mg dose. In this study, doses above 50 mg weren't evaluated and adverse effects elevated by 50 mg dose administration(42).

There are some studies in which rivaroxaban administration showed no inferiority in comparison to warfarin or enoxaparin(32, 40, 43). Diener HC et al. study presented same major bleeding rates by 36 mg administration of rivaroxaban twice daily as compared with INR adjusted dose (INR, 2.0 to 3.0 included) of warfarin, whereas the rates of major plus minor bleeding were less than warfarin(43).

Approved dose of rivaroxaban for thromboembolic disorders prevention and treatment are 10 mg, 15 mg and 20 mg(36).

In other studies patients with 30-49 ml per minute creatinine clearance underwent 15 mg or 20 mg dose of rivaroxaban therapy and others administered warfarin adjusted dose (targeted INR of 2.0 to 3.0)(32, 44).

The most important complication of rivaroxaban is bleeding. Although the rates of major bleeding in rivaroxaban were similar to warfarin, but fatal and critical bleedings like intracranial bleeding and hemorrhagic strokes occurred less than warfarin. In contrast, upper and lower gastrointestinal bleedings and rectal ones even those which led to blood transfusion were presented in higher rates(10, 32, 45-47).
As mentioned above, one of the most important problems for administration of NAOC is lack of antidote but prothrombin complex concentrate (PCC) has been found as an immediate effective antidote for rivaroxaban (18).

For rivaroxaban in renal impairment dose adjustment is needed as below:
- CrCl > 50 mL/min: 20 mg/day with the evening meal
- CrCl 15-50 mL/min: 15 mg/day with the evening meal
- CrCl < 15 mL/min: Avoid use (48)

Rivaroxaban contraindications are active pathological bleeding and hypersensitivity (49).

**Apixaban**

The second NOAC which has direct reversible factor Xa inhibition is apixaban (50-52).

As apixaban is not a pro-drug, it does not need any biotransformation to become active. After oral administration, apixaban maximum plasma concentrations can be measured within 3 hours. This drug has a 12-hour half life and 48 to 72 hours are required for all effects to be eliminated (50, 51). Apixaban undergoes oxidative liver metabolism predominantly by cytochrome P-450 (CYP) 3A4/5 but CYP2C8, CYP2C9 and CYP2C19 have less importance in its metabolism (53-55). Apixaban has 25% of renal excretion and more than 50% is eliminated in feces (50). There are controversial ideas about age and sex effects on apixaban administration but generally, this drug is not clinically affected by age and gender (56, 57). In a study, female patients presented more ischemic strokes as compared with male patients but these rates were completely related to prior stroke or transient ischemic attack (TIA) and also age (56). Food consumption before or after apixaban does not affect the drug (58) but because of predominant metabolism of the drug by CYP3A4/5, there are some drug-drug interactions with CYP3A4/5 substrates or inhibitors (e.g., antihypertensives, statins, antibiotics, antiretrovirals), but because 50% of drug is eliminated unchanged, the potential of drug-drug interactions will reduce (53, 55). Apixaban as an other NOAC is approved for prevention of venous thromboembolism in patients undergone hip and knee replacement surgery and stroke prevention in non-volvular atrial fibrillation patients (59, 60).

In a study, 5 mg twice daily administration of apixaban in comparison with warfarin resulted in 21% of reduction in systemic embolism or stroke, 31% decrease of major bleeding and 11% decrease of death, presenting superiority of apixaban (25, 60). In other study apixaban administration was at least as efficient as warfarin (57).
Although bleeding is the most important complication of apixaban as other NOAC, lower risk of intracranial bleeding leads to higher compliance for apixaban in contrast to warfarin (61).

In non-vovular AF 2.5mg BID is the accepted dose for apixaban, and limitations for this drug administrations are:
1) Weight ≤60 kg
2) Age ≥80 years
3) Serum creatinine ≥1.5 mg/dL

In mild to moderate renal impairment, no dose adjustment is required but for patients with 2 of 3 above items, apixaban administration dose adjustment should be considered (62).

Active pathological bleeding and hypersensitivity are contraindications of apixaban (63).

References


Evidence based national program for prevention of stroke

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A healthy diet, physical activity and BP control are key elements of effective prevention of stroke. Mediterranean diet supplemented with nuts is now advised to lower the risk of stroke. The benefit of successfully reducing blood pressure through individualized approach as well as supportive environment is of utmost importance.

There are shred factors between men and women, but women are disproportionately affected by stroke as they have extra risk factors influenced by hormones, reproductive health, pregnancy, childbirth and other sex-specific factors.

Our categories of missed opportunities for stroke/TIA prevention will be sought: untreated high blood pressure in patients eligible for treatment (either blood pressure ≥160/100 or ≥140/90 mm Hg in patients at high cardiovascular disease (CVD) risk); patients with atrial fibrillation with high stroke risk and no anticoagulant therapy; no lipid modifying drug therapy prescribed in patients at high CVD risk or with familial hypercholesterolaemia.
Color Doppler Sonography of Neck in Stroke Patients

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Abstract
Color Doppler, the study of carotid and vertebral arteries, is a non-invasive, reliable and also easily available, cost-effective method for screening and follow-up of patients at risk of stroke to differentiate patients in need of surgery or intervention from those who could be followed by medical management. A comprehensive understanding this procedure needs knowing detailed anatomy, techniques for doing the exam, using obtained data for detection of atherosclerotic changes and characterization of atheromatous plaques, grading of stenosis secondary to atherosclerotic plaques, predicting any cardiovascular or intracranial diseases, either vascular or extravascular, which influence Doppler spectral waveform and finally ability to evaluate cervical portion of vertebral arteries. Mentioned subjects will be discussed in this article.

Introduction
Color Doppler study of carotid and vertebral arteries is a non-invasive, reliable and also easily available, cost-effective method for screening and follow-up of patients at risk of stroke to differentiate patients in need of surgery or intervention from those who could be followed by medical management (1, 2). It is the most common imaging modality used for the evaluation of carotid arteries diseases (3). Nowadays in many centers, it is the only imaging modality before endarterectomy or stent insertion (4).

The anatomy of carotid and vertebral arteries, the technique of color Doppler study of these vessels including B-mode or gray scale scanning, Color flow mapping and Spectral analysis, characterization of atheromatous plaques, grading of stenosis secondary to atherosclerotic plaques, predicting any cardiovascular or intracranial diseases, either vascular or extravascular, which influence Doppler spectral waveform will be discussed Subsequently.

Anatomy
Brain is supplied through four vessels, two carotid and two vertebral arteries, and receives 15% of cardiac output. Right common carotid artery (5) originates from brachiocephalic artery but left CCA originates from aortic arch directly. Both sides CCA ascend on both sides of neck and are divided into internal and external carotid
arteries (6). The origin of right CCA can be seen behind right sternoclavicular joint, but the origin of left CCA cannot be seen by ultrasound.

The level of bifurcation of CCAs is variable, but it is usually at about the level of the upper border of the laryngeal cartilage. In about 90% of cases, ICA rests posterolateral or lateral to the ECA. The distal end of CCA at the level of bifurcation is widened to form the carotid bulb. But in some cases, bulb only involves proximal ICA (4, 7).

The right and left vertebral arteries (VA) originate from right and left subclavian arteries, respectively. They ascend through the posterior aspect of each side of neck and traverse foramina of sixth till second cervical vertebrae and then curve around the atlas and enter intracranial fossa to join together and form basilar artery (4, 8) (9).

**Figure 1** shows the schematic anatomy of major carotid and vertebral arteries.

There are few variations in carotid and vertebral arteries. Rare cases of common origin of left CCA and subclavian artery or left brachiocephalic artery and/or direct origin of right and left VA from aortic arch can be seen (4, 10, 11).

It is common for one vertebral artery to be larger than the other; usually left VA is larger and right VA is hypoplastic (4, 9).

**Technique**

As other parts of body, the examination consists of three steps:

1. B-mode or gray-scale scanning
2. Color flow mapping
3. Spectral analysis

And also to conclude the exam, it will be followed by the evaluation of cervical portion of vertebral arteries and finally record and then report the exam and any limitations related to exam (7).

**B-mode Scanning**

During this step, the exam will be started in axial plane for rapid evaluation of carotid vessels including common carotid artery (5), level of bifurcation and possibly parts of internal carotid artery (ICA) and external carotid artery (ECA). Attention to the existing branches from ECA and also relative position of mentioned artery and ICA at the level of bifurcation, it is possible to differentiate these vessels from each other in axial plane (4, 7).

Any atheromatous plaque can be detected in this step and then its cross-section will be evaluated regarding shape and maximum thickness and the content.
After early evaluation, the exam will be continued in longitudinal plane through CCA and level of bifurcation and visualized parts of ICA and ECA. **Figures 2 and 3** show the normal shape of carotid arteries in gray scale.

At first, intima-media thickness (IMT) will be measured at the level of the posterior wall of carotid bulb and ICA origin by using magnified view to overcome error in measurement (**figure 4**). After that, any atheromatous plaque which is seen at axial plane, will be evaluated longitudinally to see and measure the length, content (calcification, lipid component or hemorrhage) and careful evaluation of intimal surface of plaque (to exclude ulceration). These features help us to characterized the atheromatous plaque (**figure 5**).

**Color Flow Mapping**
Using color flow box, the vessels are evaluated rapidly in longitudinal plane to see the pattern of flow and to detect any flow disturbance at the site of atheromatous plaques. Hemodynamically significant stenoses caused by atherosclerotic disease result in flow disturbance at the site and just above the level of stenosis which will be as a mixture of bright colors (color flow aliasing)**(3, 4)**. **Figure 6** shows significant aliasing of flow at the site of severe atherosclerotic stenosis **(3)**. Power color Doppler can provide additional data for the evaluation of surface of plaque and measurement of related stenoses, especially in large complicated plaques **(12, 13)** (**figure 7**) **(14)**.

**Spectral Analysis**
Spectral waveform should be first obtained at CCA, ICA and ECA to evaluate flow in the mentioned vessels which can be influenced by local, far proximal or distal atherosclerotic disease and or by systemic, cardiac or intracranial diseases. Then, the spectrum should be obtained at the site of any atheromatous plaque for further estimation of degree of stenosis **(15)**. **Figure 8** shows spectral waveform which is obtained from CCA.

**Vertebral Arteries Evaluation**
Finally, to conclude the exam in longitudinal plane, cervical portion of vertebral arteries between transverse processes of cervical spines should be evaluated by color flow mapping, for detection of any possible congenital hypoplasia, flow direction and any possible stenotic changes (**figures 9 and 10**).

**IMT Evaluation**
IMT should be measured on posterior wall of carotid bulb and ICA origin and a cutoff of 0.8mm should be kept in mind. The IMT 0.8-1mm is considered indeterminate, while an IMT greater than 1.1mm is more accepted abnormal value **(3, 7)**.
Plaque Characterization
Any atheromatous plaque should be evaluated in B-mod using axial and longitudinal planes for measuring length and maximum thickness, shape (circumferential, curvilinear, irregular, etc.), content (calcification, lipid or hemorrhage), surface (echogenic cap, irregularity and ulceration) (3, 4, 7). The plaques could be classified by the degree of associated stenosis, ultrasound morphology and intimal surface (table 1) (16) and (figure 11).

Estimation of Degree of Stenosis
Regarding aliasing of flow at color flow mapping, the area of significant stenosis can be detected, and then, mentioned stenotic area will be evaluated by spectral waveform (figures 12 and 13).
Parameters such as peak systolic velocity (PSV), end diastolic velocity (EDV) of C.C.A, I.C.A & E.C.A, Spectral broadening and intra-stenotic PSV to C.C.A PSV are calculated. Using available data from previous studies, the degree of stenosis is estimated. The importance of estimation of degree of stenosis is based on two large trial studies, i.e. the North American Symptomatic Carotid Endarterectomy Trial (NASCET) and the European Carotid Surgery Trial (ECST) which used two different method-based on angiography for calculating the percentage of stenosis and both showed the benefit of performing carotid endarterectomy in patients with significant ICA disease (figure 14) (4, 17). NASCET showed maximum benefit in patients with 70-99% of diameter stenosis and lesser but significant benefit in patients with 50-69% of diameter stenosis. ECST showed maximum benefit in patients with 80-99% of diameter stenosis and lesser but significant benefit in patients with 70-79% of diameter stenosis. Subsequent comparison of the two showed that a 50% NASCET stenosis was broadly equivalent to a 70% ECST, while a 70% NASCET stenosis broadly equated an 85% ECST (6, 18).
Table 2 shows the recommendations for grading of stenosis based on NASET method, derived from the Society of Radiologists in Ultrasound Consensus Conference which took place in San Francisco, Calif, October 22–23, 2002 (19).

Changes of Spectral Waveform by Extra Carotid Causes
By evaluation of spectral waveform of both-side C.C.A, I.C.A and E.C.A, some cardiac and systemic abnormalities (such as heart failure, valvular heart disease, anemia) and also intracranial problems) such as increased ICP, distal ICA stenosis or occlusion) can be predicted and prompted for further evaluation (20).

Vertebral Arteries Evaluation
Important features then can be evaluated during color Doppler study of vertebral arteries including diameter of vessels (to exclude congenital hypoplasia), direction
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of flow (to exclude subclavian steal syndrome) (figure 15), flow disturbance secondary to focal stenosis and finally changes of waveform secondary to stenosis at invisible proximal and intracranial distal portions of vertebral arteries.

**Reporting**
Based on above mentioned different steps, the procedure should be reported finally and any limitations should be emphasized.

**References**
Figure 2. Normal gray scale of CCA in longitudinal plane

Figure 3. Normal gray scale of right CCA, bulb and also origin of ICA and ECA
Figure 4. Magnified longitudinal view through CCA and bulb for measurement of IMT

Figure 5. A calcified plaque at posterior wall of carotid bulb
Figure 6. Severe aliasing of color flow seen at the site of a large atheromatous plaque causing severe stenosis at carotid bulb.

Figure 7. Upper image shows color flow mapping of a heterogeneous, irregular plaque. At the lower image power Doppler study results in well delineation of plaque and residual of patent lumen.
Figure 8. Spectral waveform obtained from upper CCA.

Figure 9. Cervical portion of the vertebral artery seen between transverse processes of cervical spines.
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Figure 10. Cervical portion of the vertebral artery and vein seen between transverse processes of cervical spines, using conventional color (left) and power Doppler (right) modes

<table>
<thead>
<tr>
<th>Hemodynamic (%) Stenosis Diameter</th>
<th>Morphologic</th>
<th>By Surface</th>
</tr>
</thead>
<tbody>
<tr>
<td>H1, mild (&lt;50%)</td>
<td>P1, homogeneous</td>
<td>S1, smooth</td>
</tr>
<tr>
<td>H2, moderate (50%–69%)</td>
<td>P2, heterogeneous</td>
<td>S2, irregular (defect &lt;2 mm)</td>
</tr>
<tr>
<td>H3, severe (70%–95%)</td>
<td></td>
<td>S3, ulcerated (defect &gt;2 mm)</td>
</tr>
<tr>
<td>H4, critical (95%–99%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>H5, occluding (100%)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 1. Classification of Plaques
Figure 11. There is a calcified plaque with smooth surface but a small hypoechoic area at its superior aspect causing about 50% diameter narrowing (H2, P2, S1).

Figure 12. Spectral waveform at the site of ICA origin plaque shows PSV = 88 cm/s and EDV of about 20 cm/s consistent with less than 50% of diameter narrowing.
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Figure 13. Spectral waveform at the site of ICA origin plaque shows PSV=284 cm/s and EDV =114 cm/s consistent with greater than 70\% of diameter narrowing.

Figure 14. Methods of calculating and reporting the degree of stenosis based on NASET and ECST trials
Table 2. Consensus Panel Gray-Scale and Doppler US Criteria for Diagnosis of ICA Stenosis (19)

<table>
<thead>
<tr>
<th>Degree of Stenosis (%)</th>
<th>Primary Parameters</th>
<th>Additional Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ICA PSV (cm/sec)</td>
<td>Plaque Estimate (%)*</td>
</tr>
<tr>
<td>Normal</td>
<td>&lt;125</td>
<td>None</td>
</tr>
<tr>
<td>&lt;50</td>
<td>&lt;125</td>
<td>&lt;50</td>
</tr>
<tr>
<td>50–69</td>
<td>125–230</td>
<td>≥50</td>
</tr>
<tr>
<td>≥70 but less than near occlusion</td>
<td>&gt;230</td>
<td>≥50</td>
</tr>
<tr>
<td>Near occlusion</td>
<td>High, low, or undetectable</td>
<td>Visible</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>Undetectable</td>
<td>Visible, no detectable lumen</td>
</tr>
</tbody>
</table>

* Plaque estimate (diameter reduction) with gray-scale and color Doppler US

Figure 15. Color flow map and spectral waveform show flow toward the transducer but not toward the cranial fossa at vertebral artery, suggestive of subclavian steal syndrome. Note the opposite color of vertebral artery to the carotid artery.
New Modalities and approaches in stroke rehabilitation

Mahmoodi

Introduction
Stroke is the leading cause of disability in the world and is known as one of the most important causes of death. Most of the stroke survivors suffer from disabilities which interfere with their activities of daily living for the rest of their lives. The most important therapeutic approach to decrease disabilities and improve the quality of life after stroke is rehabilitation. Until recently, stroke rehabilitation mostly focused on compensatory techniques to overcome the physical deficits. Also, in most physical therapy and occupational therapy clinics the therapists rely only on a few rehabilitation approaches such as neurodevelopmental techniques, proprioceptive neuromuscular facilitation, and electrical stimulation. There is still a false belief that recovery takes place only during the first 6 to 9 months after stroke. However, the latest neurorehabilitation studies show that the concept of neural plasticity or the ability of the brain to repair works effectively long after the impact of stroke. During the recent years, our understanding of recovery after stroke has changed dramatically. As a result, some new approaches and technologies have emerged to help stroke survivors improve even years after the accident.

In this monograph, we are trying to introduce some of the most recent and scientifically investigated approaches and technologies used in stroke rehabilitation.

Technologies and approaches
1- Intensive task-specific approach
In a series of elegant experiments on primates, Nudo showed that neural plasticity and repair depends on the performance of functional tasks and not simply on the use of an extremity (1-4) In his experiments, monkeys that only performed range-of-motion exercises showed minimal improvement, whereas those that performed multiple repetitions of functional tasks made greater functional gains. Nudo also found that adjacent brain areas adopted the function of the damaged brain area in monkeys that received a full rehabilitation program. Schmidt noted that task specific practice is required for motor learning to occur (5). More specifically, Karni et al. used functional MRI (6) and Classen et al. used transcranial magnetic stimulation (7). Both of them reported a slowly evolving, long term, experience-dependent reorganization of the adult primary motor cortex following daily practice of task-specific motor activities.
Three key factors can be attributed to a successful rehabilitation plan:

- The task must be functional. The learning of a specific skill is required to bring about significant changes in neural connectivity. Neural plasticity and repair therefore depend on the performance of specific tasks rather than just using motor activities.

- The task must be exercised repeatedly. The number of repetitions appears to be crucial in driving plasticity and learning/relearning tasks. There is a critical level of rehabilitation and repetition needed for a patient to see continued improvement and to maintain their functional gains outside of a therapy setting.

- Delays in therapy could result in the development of behaviours that interfere with recovery.

Conclusion for intensive task specific approach: There is strong evidence (level 1a) that intensive task specific training can improve upper limb function and gait in patients with stroke.

2- Non-Invasive Brain Stimulation
Non-invasive brain stimulation is a term to describe methods by which we can stimulate some areas of brain cortex non-invasively. Using different methods of stimulation the activity of a certain cortical area could be increased or decreased. These methods mostly include repetitive Transcranial Magnetic Stimulation (rTMS) and transcranial Direct Current Stimulation (tDCS).

A: repetitive Transcranial Magnetic Stimulation:
rTMS is a novel approach that has been used recently in the fields of neurology, psychiatry and physical medicine and rehabilitation. It uses repetitive pulses of focal magnetic field applied over the skull of the patient and produces alterations in brain function lasting beyond the stimulation time. If the pulses are given with low frequency (i.e. 1 Hz or lower), the function of the stimulated brain cortex will be reduced and if the pulses are given with high frequency (i.e. 5 Hz or higher) the stimulated area will be more active. We can use this features to selectively increase or decrease the function of the brain cortex locally.

One of the mostly recognized applications of rTMS in the field of neurology and rehabilitation medicine is for stroke patients. It is known that immediately after stroke an imbalance between the inhibitory effects of brain hemispheres over each other will appear and the sound hemisphere predominates in inhibiting the function of the lesion side. By understanding this fact, we will have two options to use rTMS in patients with stroke. The first option is using high frequency rTMS over M1 area of the affected side which increases its function and the second option is using low frequency rTMS over M1 area of the contralateral hemisphere.
By using this technique, the function of the non-affected M1 region will be decreased, so its inhibitory effect over the lesion side will be decreased too. Decreasing the inhibition over the affected site will increase its function (8). This effect has been shown interestingly using functional Magnetic Resonance Imaging (fMRI) before and after an rTMS session. A recent meta-analysis by including the results of 18 RCTs and pooling the data from 392 patients reported a clinically significant treatment effect of 0.55 for rTMS (9). Low frequency rTMS over the unaffected hemisphere appeared to be more effective than high frequency protocol (0.69 versus 0.41). Also, the treatment effect for acute, subacute and chronic stages of stroke were 0.79, 0.63 and 0.66 respectively.

Despite the positive effect showed in many RCTs, there are also other investigations that have shown no or minimal effect for this intervention, so overall, the final drawback needs more research.

Conclusion regarding rTMS in stroke:
There is conflicting (level 4) evidence that rTMS improves mobility or upper extremity function following stroke.

B: transcranial Direct Current Stimulation
Electrical brain stimulation, a technique developed many decades ago and then largely forgotten, has re-emerged recently as a promising tool for experimental neuroscientists, physiatrists, clinical neurologists and psychiatrists in their quest to investigate cortical representations of sensorimotor and cognitive functions and to facilitate the treatment of various neuropsychiatric disorders.

tDCS is a newly emerged technique of non-invasive brain stimulation that has been found useful in examining cortical function in healthy subjects and in facilitating treatments of various neurologic disorders. A better understanding of adaptive and maladaptive neuroplasticity and its modulation through non-invasive brain stimulation has opened up experimental treatment options using tDCS for patients recovering from stroke.

The stimulation takes place through applying of 2 saline soaked surface electrodes over the scalp of the areas of interest. There are two major stimulation techniques. In anodal stimulation, the anode will be put over the cortical area which we want to increase its activity (M1 area of the affected side in stroke patients) and in cathodal stimulation, the cathode will be put over the cortical area which we want to decrease its activity (M1 area of the non-affected side in stroke patients). The other electrode will be applied on the contralateral M1 area or the contralateral supra-orbital region. The former montage seems to be superior to the latter (10).

In a meta-analysis conducted recently, the effect of anodal tDCS was investigated (11). The results showed a mild to moderate effect size.
Conclusion regarding tDCS in stroke:
There is strong (level 1a) evidence for the effect of tDCS in chronic stroke. There is moderate (level 1b) evidence that anodal tDCS is more effective than cathodal montage.

3- Virtual Reality Rehabilitation
Virtual reality (VR) or virtual environment is a technology that allows individuals to interact with objects which do not exist in reality. Using this technology, the person will be capable of performing actions which are not available or possible or are dangerous to perform in real life. For example a patient with stroke can jump from a flying plane and navigate through the sky or work in a factory and move heavy objects. The most common forms of virtual environments are conventional computer monitors or projector screens. A computerized virtual environment has opened the doors to an exercise environment where the intensity of practice and positive feedback can be consistently and systematically manipulated and enhanced to create the most appropriate individualized motor learning approach (12). The most important features of the VR for stroke patients are increasing motivation, visual and auditory feedbacks, computerized tracking of the changes in patient’s performance and unlimited types of exercises to be taken. Some VRs are more immersive than the others. For example Head Mounted Displays (HMDs) use a technology to show the virtual environment immediately in front of the person’s eyes, increasing the perception of the being in the new environment. Although VR technologies can be used separately to improve the function in stroke survivors, they can be embedded in other technologies such as robotic devices to enhance their effectiveness.

In a systematic review of VR studies, the authors examined both RCTs and observational investigations. According to RCT results, using VR was associated with significant improvement of 13.7% to 20% in upper limb outcome measures. In the analysis of observational studies, there was a 14.7% improvement in terms of impairment-level measures and 20.1% in motor function(13). A cochrane review including 19 RCTs reported a moderate treatment effect for VR technology (14).

Conclusion regarding VR technology in stroke:
There is strong (level 1a) evidence that VR can improve motor function in the chronic stage of stroke.

4- Robotic Rehabilitation
During the past few years, robots are being used more and more in the field of rehabilitation. Robots can aid in passive movement of the joints to maintain range
of motion and flexibility and to help reduce hypertonia. Robots can also assist in movements when the patient has some voluntary movement but has not enough power to complete the task. In patients who have enough power to do a certain task, robots can resist the movement or induce perturbations in movement trajectory to increase strength or equilibrium. Even though unassisted movement may be most effective technique in patients with mild to moderate impairments, active-assisted movement with robotic devices may be beneficial in more severely impaired patients (15). Major advantages of robotic therapy include the ability to conduct unlimited number of exercises without fatigue, embedding with virtual reality environments, the ability to have fully controlled passive, active-assisted or resisted movements with feedback of the patient’s progress over time and decreasing the need for special therapists in the clinic which decreases the costs over time.

There are also a number of robotic devices to help rehabilitation of lower limb. These devices can be used with or without a sling assembly device to support weight during gait training. The devices can be classified as either an end effector robots which have the patient's feet placed on foot plates and stimulate the stance and swing phases during gait training or an exoskeleton robot in which the patients are outfitted with programmable drives or passive elements moving the hips and knees during gait phases.

A systematic review of upper limb robot-aided therapy on stroke patients included the results of 8 RCTs. It concluded that robotic therapy can improve short and long term shoulder and elbow function more than can be achieved by traditional therapy (16).

A Cochrane review including the results of 23 trials (999 participants) concluded that robotic devices are associated with increased odds of being an independent ambulatory and an increase in walking capacity but not with an increase in walking speed (17).

Conclusion regarding the use of robots in rehabilitation of stroke:
There is strong (level 1a) evidence that sensorimotor training with robot devices improves upper extremity functional outcomes and motor outcomes of the shoulder and elbow but not motor outcomes of the wrist and hand.

There is conflicting (level 4) evidence that robotic devices are superior to conventional gait training in the improvement of functional walking performance.

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Guidelines for the Primary and Secondary Prevention of Stroke

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Abstract
Stroke is a global health problem and a leading cause of adult disability. It is possible to decrease the burden of stroke through control and management of many risk factors. The aim of this paper is to provide recommendations on the prevention of stroke among individuals who have not previously experienced a stroke or transient ischemic attack or among survivors of ischemic stroke or transient ischemic attack. In this brief paper, four most important risk factors are discussed in detail.

Keywords: Stroke; Hypertension; Diabetes Mellitus; Hyperlipidemia; Smoking.

Stroke is a worldwide health problem and the most important cause of disability in adults [1]. Of 35 million deaths due to chronic uncommunicable diseases in 2005, 5.7 million (16.6%) were because of stroke [2]. There are only a few effective treatments for the most threatening forms of stroke. Hence, primary and secondary preventions offer the greatest potentials for reducing the burden of this disease. Primary stroke prevention refers to the treatment of individuals with no history of stroke. Secondary stroke prevention refers to the treatment of individuals who have already had a stroke or transient ischemic attack. There are 3 types of stroke risk factors [3]:

1. Generally Non-modifiable including: Age, Low Birth Weight, Race/Ethnicity and Genetic Factors.
2. Well-documented and Modifiable including: Physical Inactivity, Dyslipidemia, Diet and Nutrition, Hypertension, Obesity and Body Fat Distribution, Diabetes Mellitus, Cigarette Smoking, Atrial Fibrillation, Asymptomatic Carotid Artery Stenosis and Sickle Cell Disease.

Here we focused on the role of most important factors in the second group regarding primary and secondary preventions.
Hypertension is a very important risk factor for both ischemic stroke and ICH and defined as a systolic blood pressure (SBP) $\geq 140$ mmHg or a diastolic blood pressure (DBP) $\geq 90$ mmHg. The relationship between BP and stroke risk is strong, continuous, graded, consistent, independent, predictive, and etiologically significant [5]. AHA/ASA 2014 Recommendations include:

A) Primary Prevention
1. For primary prevention, regular control and appropriate treatment of BP by lifestyle modification and pharmacological therapy is recommended.
2. For patients with prehypertension (systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg), annual BP screening and lifestyle modification are recommended.
3. Reduction of BP is more important in reducing stroke than the choice of specific agent. Patients who have hypertension should be treated with antihypertensive drugs to a target BP of $<140/90$ mmHg. Self-measured BP monitoring is very important in BP control [6].

B) Secondary Prevention
Treatment of hypertension plays an important role in secondary prevention of stroke. The prevalence of HTN among patients with a recent ischemic stroke is $\approx 70\%$ [7, 8, 9]. Treatment of HTN in the first 24 hours is not recommended except for specific situations such as; therapy with tissue-type plasminogen activator (r-tpa), SBP>220 mmHg or DBP >120 mmHg [7]. In the presence of TIA or stroke, Thiazide and Angiotensin-converting enzyme inhibitors (ACEI) are suggested [28]. Here are 2014AHA/ASA recommendations:
1. Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP $\geq 140$ mmHg systolic or $\geq 90$ mmHg diastolic. Initiation of therapy for patients with BP $<140$ mmHg systolic and $<90$ mmHg diastolic is of uncertain benefit.
2. Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days.
3. Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized; but, it is reasonable to achieve a systolic pressure $<140$ mmHg and a diastolic pressure $<90$ mmHg. For patients with a recent lacunar stroke, it might be reasonable to target an SBP of $<130$ mmHg.
4. Several lifestyle modifications have been associated with BP reductions and are a reasonable part of comprehensive antihypertensive therapy include salt restriction, weight loss, consumption of a diet rich in fruits, vegetables and low-fat dairy products, regular aerobic physical activity and limited alcohol consumption.

5. The choice of drug for BP control is uncertain and should be individualized but diuretics or the combination of diuretics and an angiotensin-converting enzyme inhibitor is useful [3].

2- Dyslipidemia
There is an interesting relation between total cholesterol levels and stroke risk in general population: low levels of total cholesterol increase the risk of ICH and high levels of total cholesterol increase the risk of ischemic stroke. So, there is no positive association between total cholesterol level and stroke mortality [10]. Epidemiological studies evaluating the relationship between triglycerides and ischemic stroke have been inconsistent, in part because some have used fasting and others non-fasting levels [6]. Treatment with statins decreases stroke risk in patients with or at high risk of atherosclerosis [11, 12]. The usefulness of statins in ischemic stroke is most likely related to their capacity to reduce progression or to induce regression of atherosclerosis. The usefulness of other lipid-modifying drugs with or without statins in ischemic stroke is unknown [6].

2014 AHA/ASA Recommendations:

A) Primary Prevention
1. In addition to therapeutic lifestyle changes, treatment with an HMG coenzyme-A reductase inhibitor (statin) medication is recommended for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events as recommended in the 2013 “ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [13].

2. Niacin may be considered for patients with low HDL cholesterol or elevated Lp (a), but its efficacy in preventing ischemic stroke in patients with these conditions is not established. Caution should be taken with niacin because it increases the risk of myopathy.

3. Fibric acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in preventing ischemic stroke is not established.

4. Treatment with nonstatin lipid-lowering therapies such as fibric acid derivatives, bile acid sequestrants, niacin and ezetimibe may be considered in
patients who cannot tolerate statins, but their efficacy in preventing stroke is not established [6].

**B) Secondary Prevention**

1. Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level \( \geq 100 \) mg/dL with or without evidence for other clinical atherosclerotic CVD (ASCVD).

2. Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD.

3. Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to 2013 ACC/AHA cholesterol guidelines [16] which include lifestyle modifications, dietary recommendations and medication recommendations [6].

**3-Diabetes Mellitus**

Patients who suffer from diabetes mellitus have 2 problems; an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors especially hypertension and abnormal blood lipids. Diabetes mellitus is an independent risk factor for stroke [14] which increases the risk of stroke more than 2 times. Duration of diabetes mellitus also increases the risk of nonhemorrhagic stroke (by 3%/y of diabetes duration)[14]. In pre-diabetes state, fasting hyperglycemia is associated with stroke [15]. Glycemic control reduces microvascular complications but there remains no evidence that improves glycemic control reducing the risk of incident stroke. Here are the 2014 AHA/ASA recommendations:

**A) Primary Prevention**

1. BP control in accordance with an AHA/ACC/ CDC Advisory 28 to a target of \(<140/90\) mmHg is recommended in patients with type 1 or type 2 diabetes mellitus.

2. Treatment of diabetic adults with a statin, especially those with additional risk factors, is recommended to lower the risk of first stroke.

3. The usefulness of aspirin in primary stroke prevention for patients with diabetes mellitus but lower than 10-year risk of CVD is unclear.
4. Adding a fibrate to a statin in people with diabetes mellitus is not useful for decreasing stroke risk [6].

**B) Secondary Prevention**

No major trials for secondary prevention of stroke have specifically examined interventions for pre-DM or DM. There is no diabetic drug preferable over others for vascular prevention. AHA/ASA 2014 recommendations:

1. After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test.
2. Choice of test and timing should be guided by clinical judgment and recognition. Acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate post event period.
3. The use of existing guidelines from ADA for glycemic control and cardiovascular risk factor management is recommended for patients with an ischemic stroke or TIA who also have DM or pre-DM.
4. Aspirin: 75-162 mg/day: diabetes and CVD history.
5. CVD and aspirin allergy: Clopidogrel 75 mg/day [16].

Antiplatelet therapy in diabetic patients is shown in table below.

![Image](image.png)

4-Cigarette Smoking:
Cigarette smoking increases the risk of ischemic stroke (double) and SAH (2-4 folds increase) [7-12], but data on ICH are inconclusive. Cigarette smoking may potentiate the effects of other stroke risk factors including systolic blood pressure [21] and oral contraceptives. There is a reduction in stroke risk with smoking cessation and with community-wide smoking bans. Passive smoking is a known risk factor for heart disease [22, 23]. Likely, smoking contributes to increased stroke risk through both short-term effects on the risk of thrombus generation in atherosclerotic arteries and long-term effects related to increased atherosclerosis [24]. Smoking as little as a single cigarette increases heart rate, mean BP and cardiac index; it decreases arterial distensibility too [25, 26]. After smoking cessation, the risk of stroke and other cardiovascular events rapidly reduce to a level that approaches, but does not reach that of those who never smoked [23, 26]. Recommendations of 2014 AHA/ASA:

A) Primary Prevention
1. Counseling, in combination with drug therapy using nicotine replacement, bupropion or varenicline is recommended for active smokers to assist quitting smoking.
2. Abstention from cigarette smoking is recommended for patients who have never smoked on the basis of epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH [6].

B) Secondary Prevention
In contrast to extensive data on the association between smoking and risk for first stroke, data on an association with recurrent stroke are sparse. No clinical trials have examined the effectiveness of smoking cessation for secondary prevention of stroke or TIA. Here are 2014 AHA/ASA recommendations:
1. Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit.
2. It is reasonable to advise patients after TIA or ischemic stroke to avoid environmental (passive) tobacco smoke.
3. Counseling, nicotine products and oral smoking cessation medications are effective in helping smokers to quit [3].
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24-Burns DM. Epidemiology of smoking-induced cardiovascular disease.
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An epidemiological study about Stroke subtypes, risk factors and mortality in northwest of Iran

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Background: Stroke is the second leading cause of death and the most important cause of adult disability worldwide. Ischemic stroke, Intracerebral hemorrhage (ICH), and Subarachnoid hemorrhage (SAH) are the most common subtypes of stroke. About 80% of all stroke deaths occur in developing countries. Data on stroke epidemiology have so far been limited in Iran. To fill this gap, this study was focused on stroke demographic data, risk factors, subtypes and mortality.

Methods: A retrospective study was done at Razi hospital, university hospital in the Northwest of Iran, from March 2001 to April 2013. Patients with diagnosis of stroke were enrolled. Demographic data, type of stroke, length of hospitalization, stroke risk factors and hospital mortality were recorded for all the patients.

Results: A total number of 6629 patients enrolled in the present study. Mean age was 67.59±13.8 years in which 3284(49.50%) were male. Final diagnosis of ischemic stroke was made in 87.28% of the patients, as were intracerebral with or without intraventricular hemorrhage (ICH + IVH) and subarachnoid hemorrhage (SAH) in 9.8% and 1.8% of the patients, respectively. Stroke risk factors of the patients were found to be hypertension in 4297(64.8%), diabetes mellitus in1490(22.5%), smoking in 1100(16.6%), Hyperlipidemia in 881(13.3%), atrial fibrillation in 194(2.9%), ischemic heart diseases in17.9% and Family history of CVA in 1345(20.3%). Overall, in hospital mortality was seen to be 136(2.1%).

Conclusions: Most results are comparable with other studies but because Razi is a referral hospital for patients with good general condition and less severe disease, there are some odd results especially in mortality rate and SAH incidence.

Key words: stroke, epidemiology, Iran.
Use of Ultrasound in Acute Ischemic Stroke

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Introduction
Ultrasound is a widely available, noninvasive method having numerous advantages; bedside use, low cost, fast operation and repeatability. In this review, we focus on the diagnostic, prognostic and therapeutic applications in acute stroke. We have to emphasize that the ultrasound investigation is only one part of the complex diagnostic approach in acute stroke; others include:

- Vascular Anamnesis
- Neurological Investigation (with special attention to forebrain or vertebrobasilar stroke symptoms)
- Cranial CT
- Extracranial Ultrasound
- Trans or Intracranial Ultrasound
- CTA or MRA if necessary to complete the diagnosis
- Complex analysis of clinical symptoms, ultrasound and other imaging modalities

Note that the imaging techniques (e.g. MRA, CTA or Ultrasound) are not competing but complementing techniques with different diagnostic strengths.

Extracranial Ultrasound in Acute Stroke
Carotid ultrasound can provide the following information:

IMT (Intima-Media Thickness)
IMT is influenced by age, diabetes, smoking, hypertension, alcohol consumption and can be effectively influenced by pharmacotherapy.

In acute stroke, IMT might be an indicator of general vascular risk including the risk of a second stroke. Prospective studies have demonstrated that pathological IMT values result in a high risk of myocardial infarction and stroke; so, IMT is considered as a marker for future vascular events.

Plaque(s)
The whole visible length of carotids should be investigated as far distally as possible to characterize plaques based on the following criteria:
- Location
Plaques with irregular surface and/or heterogeneous echogenicity are more likely to embolize. Soft plaques present a higher embolic risk than hard plaques. Unfortunately, less than 50% of all plaques can be identified correctly by ultrasound.

**Carotid Stenoses and Occlusions**
Carotid bifurcation is particularly susceptible to the development of atherosclerotic lesions. Unfortunately, plaque calcification or extremely distal bifurcation might influence the visibility of carotid stenosis or occlusion. Stenosis could be estimated by morphological, hemodynamic assessment or both (duplex technique).

The morphological approach measures either the diameter or the area reduction. The grade of stenosis is calculated from the relation of the total vessel diameter or area and the minimal stenosis diameter or area.

Using Duplex technology, we can estimate the carotid stenoses by hemodynamic measurement and analysis of plaque morphology, echogenicity, surface, etc.

Vessel stenosis correlates with increasing flow velocities but this relation is not linear. In high-grade stenosis, flow velocity decreases to normal or below-normal values. Note that the blood flow values remain constant until 75-80% diameter or 90% area reduction.

Stenoses are hemodynamically important only if they cause a reduced blood volume flow and poststenotic pressure drop.

Stroke risk depends on more than the degree of carotid artery narrowing (cardiac diseases, age, sex, hypertension, smoking and plaque structure). Most studies consider carotid stenosis of 60% or greater to be clinically important. The prevalence of 60-99% carotid stenosis is about 1% in persons aged 65 years or older.

In case of a suspected stenosis, not only intrastenotic but also the flow from vessel segments proximal and distal to a stenosis must be analyzed.

If normal flow signals are present before and behind the suspected lesion, significant stenosis can be excluded.

Because of the cross-individual velocity difference, indices have been developed to improve the diagnostic strength of carotid ultrasound.
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The following stenosis criteria are proposed:

- <50% stenoses (peak systolic velocity: <125 cm/s ICA/CCA: <2.0).
- 50-69% stenoses (peak systolic velocity: 125-230 cm/s; ICA<CCA: 2.0-4.0)
- stenoses >70% (peak systolic velocity: >230 cm/s, ICA/CCA: >4).

ICA Stenosis and Occlusion
Mild stenoses (<50%) can be estimated by measurement of area and/or diameter in the cross-sectional and longitudinal image using the B mode and color mode of the ultrasound system. Area measurements in high-grade stenosis are difficult. Diagnosis of severe stenosis is based on hemodynamic parameters (measured by pre-, intra- and poststenotic Doppler spectrum analysis).
Investigation of flow direction in the ophthalmic artery is a simple bedside, ancillary method in suspected ICA stenosis or occlusion (equally severe upper and lower extremity paresis). In case of hemodynamically significant ICA stenosis or occlusion (proximal to the origin of ophthalmic artery), a reversed (extra to intracranial) flow could be detected in the ophthalmic artery.
Occlusion results in a complete absence of color-flow signal, and the diagnosis can be confirmed by ultrasound contrast agents.
Using duplex ultrasound, a proximal ICA occlusion proximal the origin of the ophthalmic artery (no color mode signal and no Doppler flow) can be distinguished from the ICA occlusion distal to the ophthalmic origin (ICA has low flow velocities and higher pulsatility but preserved diastolic velocity).

Extracranial Vertebral and Subclavian Arteries
The origin of vertebral artery (VA) is one of the most common but difficult-to-investigate locations of atherosclerotic stenosis, especially its
Ultrasound Diagnosis of Intracranial Stenosis and Occlusion

Intracranial disease corresponds to approximately 8-10% of acute ischemic strokes depending on gender and race. Diagnosis is frequently reached through arteriography. TCD stands as an ancillary diagnosis tool with good sensitivity and specificity. Transcranial color-coded duplex sonography (TCCD) combines the imaging of intracranial vessels and parenchymal structures. To penetrate the skull, TCCD uses low frequencies (1.75-3.5 MHz), which limit the spatial resolution. The duplex mode of TCCD enables sampling of vessels and Doppler measurements of angle corrected blood-flow velocities. Characteristics of the investigation:

- About 15% of patients cannot be examined by TCCD because of the insufficient acoustic window. Identification rates decline with advancing age.
- The mean velocity analysis is not enough to identify intracranial vessel abnormalities. It must be combined with other parameters such as asymmetry, segmental elevations, spectral analysis and knowledge of extracranial circulation.
- Either flow velocities (frequency-based TCCD) or the integrated power of the reflected signal (power TCCD) can be coded. The p-TCCD does not display information on the flow direction.
- Flow velocities are determined by spectral Doppler sonography using color Doppler image as a guide to the correct positioning of the Doppler sample volume.
- The angle correction should only be applied to velocity measurements when the sample volume can be located in a straight vessel segment of at least 2cm length.
- Flow velocities in the arterial as well as venous systems are higher in women than men and decrease with age; whereas pulsatility index increases.
- Intracranial stenosis: local increase in the peak systolic flow velocities, poststenotic flow disturbances with low frequency and high intensity Doppler signals.
- Intracranial vessel is occluded if the color signal is absent in one segment, while other vessels and parenchymal structures could be visualized correctly. The use
of Levovist increases the sensitivity and specificity. Only 4% of examinations are inconclusive because of insufficient bone windows.

- After application of echo-contrast enhancing (ECE) agents, the diagnostic confidence of TCCD for intracranial vessel occlusion was similar to that of magnetic resonance angiography.
- In an acute stroke study, the ability of duplex ultrasound to diagnose main stem arterial occlusions within the anterior circulation was between 50 and 60% of studied vessels in unenhanced TCCS but reached 80-90% after intravenous contrast administration.
- The diagnostic strength of eTCCD could be a highly specific identification of a normal intracranial arterial status. Therefore, if an experienced sonographer detects no abnormalities using eTCCD in a patient with sufficient bone windows, no more imaging is needed.
- The correctly performed TCD investigation provides valuable information about the vascular status of the ICA too. The presence of collaterals and delayed flow acceleration on TCD usually indicates a hemodynamically significant lesion (>80% ICA stenosis or occlusions). The investigation should start on the presumably non-affected side (roadmap to clinical symptoms). The sonologist looks for a focal velocity rise in a circumscribed vessel segment and differences between the affected and non-affected sides, extending more than 30 cm/s. If a pathologic finding is present, the proximal and distal vessel segments should also be evaluated. Occlusions are characterized by missing color and Doppler flow signals at the site of the occlusion or reduced flow signals in vessel segments proximal to the occlusion.

**MCA Stenosis**
Stenoses of M1-MCA can be graded according to flow velocity, turbulence and asymmetry into mild, moderate and high-grade stenosis. All detectable MCA segments should be insonated.

**MCA Occlusion**
Depending on the location of the occlusion, Doppler spectrum may be completely absent or reduced. In case of a proximal M1-MCA occlusion, no flow signal is seen. In occlusions of the middle part of the MCA, a small orthograde flow with increased pulsatility may be present. In distal M1-MCA occlusion, a reduced flow velocity is present with variable pulsatility depending on the presence of a temporal branch. Distal MCA occlusion, e.g. of a relevant M2-MCA branch or more than one M2 branch, will result in a reduced flow with low velocities and a marked bilateral asymmetry.
ACA Stenosis and Occlusion
The clinical symptoms (contralateral lower leg paresis) can suspect ACA stenosis or occlusion. Altered velocity, the presence of turbulences or missing ACA and ipsilateral increased MCA flow velocities can help the diagnosis of ACA stenosis and occlusion.

Stenosis and Occlusion in Posterior Circulation
Again, the typical clinical symptoms should orient the sonographer (vertigo, nystagmus, hemianopia, double vision, dysphagia, altered consciousness, teraparesis, etc.). Alteration of flow velocities and the turbulence, at least 30 cm/s flow velocity difference between the right and left sides may also be useful. A proximal PCA occlusion can be diagnosed by absent flow signal. Vertebral stenoses can be diagnosed by flow velocity, profile disturbances and pre and poststenotic flow patterns. Flow signals in VA occlusion strongly depend on the site of the occlusion, mainly on their relation to the origin of the PICA (proximal or distal). Occlusions distal to the PICA origin will result in mild-to-moderate flow alterations of the extracranial VA, mainly depending on its own diameter and the former relevance in posterior circulation.

Basilar Artery Stenosis and Occlusion
Transforaminal and transtemporal insonations allow the investigation of the total length of basilar artery. The most distal segment of the basilar artery may be better insonated transtemporally, but the visualization of the distal part of the basilar artery appears to be difficult even using echo-enhancing agents. Occlusions are difficult to assess, and diagnostic certainty depends on the site of the occlusion. A proximal BA occlusion will always result in prestenotic flow alterations of both extracranial vertebral arteries. Therefore, apparently normal and proximal BA velocities are not sufficient to exclude top of the basilar occlusion. However, as this cannot exclude the presence of, for example a fragmented thrombos, ultrasound should always be used together with other diagnostic tools such as CTA, MRA or USA in presumed BA pathology.

Emboli Monitoring and Acute Stroke
TCD identifies microembolic signs (MES) in intracranial circulation. The ultrasound distinguishes signal characteristics through embolic materials,
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solid or gaseous, from erythocyte flow velocity. Potential applications of MES detection include determining the pathophysiology of cerebral ischemia, identifying patients at increased risk for stroke who may benefit from surgical and pharmacological intervention, assessing the effectiveness of novel antiplatelet therapies and perioperative monitoring to prevent intra and postoperative stroke.

The methodology includes simultaneous monitoring of both MCAs for at least 30 min, with fixed transducers in order to reduce movement artifacts. With two possible embolic sources, cardiogenic and carotid plaque, the identification of MES contributes to higher diagnosis accuracy and support for therapy decision making.

At present, monitoring of microembolism is useful for patients with non-defined AIS, which is probably of cardio- or carotid-embolic etiology. Therefore, the use of TCD in acute ischemic stroke allows complementary diagnosis and estimating prognosis.

Simultaneous monitoring for MES in different vessels may help identify active embolic source (cardiac or carotid). Simultaneous monitoring above (i.e. MCA) and below (i.e. common carotid artery) an internal carotid artery (ICA) stenosis is another possible way of differentiating between artery-to-artery and cardiogenic embolism.

The frequency of MES in acute stroke shows a wide range between 10 and 70\% probably due to different therapies, different criteria for MES detection and elapsed time after stroke. Some investigators used single registration and others serial measurements. The incidence of MES was maximal in the first week after stroke.

MES occurrence showed more prevalence in completed stroke than in patients with TIA, in symptomatic than asymptomatic hemispheres and a discrete subcortical or cortical pattern of infarction on computed tomography (CT) compared with a hemodynamic or small-vessel pattern.

Some authors have demonstrated that MES occurs predominantly in patients with large-vessel territory stroke patterns and cases of artery-to-artery or cardiogenic embolism with persisting deficit. In contrast, MES is only occasionally detected in patients with small-vessel infarctions.

In addition, TCD monitoring may help discriminate between different potential sources of embolism (artery-to-artery or cardioembolic strokes). Different types of emboli (cardiac or carotid) have different acoustic properties and ultrasonic characteristics, based on composition and size, which could permit differentiation.

The embolus monitoring is a useful method for testing the efficacy of antiplatelet therapy (Clopidogrel+Aspirin vs. Aspirin).
Diagnostic Brain Perfusion Imaging in Stroke Patients

The availability of new ultrasound contrast agents and the development of contrast-specific imaging modalities have established the application of ultrasound in stroke patients for visualization of brain perfusion deficits. These consist of micro-bubbles composed of a gas that is associated with various types of shells for stabilization. Because of their small size, they can pass through microcirculation. There are interactions between US and microbubbles; at low US energies, UCA microbubbles produce resonance, emitting ultrasound waves at multiples of the insonated fundamental frequency.

The new microbubbles (e.g. Sonovue) generate a nonlinear response at low acoustic power without destruction, thus being particularly suitable for real-time imaging. Harmonic imaging differentiates echoes from microbubbles from those coming from tissue. The insonated tissue responds at the fundamental frequency, while resonating microbubbles cause scattering of multiples of the fundamental frequency i.e. the harmonic frequencies.

Real-Time Visualization of Middle Cerebral Artery Infarction

Perfusion of harmonic imaging after SonoVue bolus injection could be used in patients with acute stroke. At early phase of acute ischemic stroke, bolus imaging after SonoVue injection is useful for analyzing cerebral perfusion deficits at the patient's bedside. The ultrasound imaging data correlate well with the definite area of infarction and outcome after ischemic stroke. The ultrasound perfusion imaging with SonoVue has allowed the measurements not only in ischemic stroke but also in intracerebral hemorrhages due to a characteristic reduction of contrast arrival in the lesion. In spite of continuous effort, perfusion imaging in acute stroke is still at its experimental phase.

Prognostic Value of Ultrasound in Acute Stroke

During last years, ultrasound has become an important non-invasive imaging technique for bedside monitoring of acute stroke therapy and prognosis. By providing valuable information on temporal patterns of recanalization, ultrasound monitoring may assist in the selection of patients for additional pharmacological or interventional treatment. Ultrasound also plays an important prognostic role in acute stroke. A prospective, multicenter and randomized study confirmed that a normal MCA finding is predictive of a good functional outcome in more than two thirds of the subjects. After adjustment for age, neurological deficit on
admission, CT scan results and preexisting risk factors, ultrasound findings remained the only independent predictor of outcomes. The analysis of flow signal changes during thrombolysis acquired by TCD further confirmed the prognostic value of transcranial ultrasound. TIBI grading system (Thrombolysis In Brain Ischemia) has been developed for use in acute stroke:
- Grade 0: absent flow
- Grade 1: minimal flow
- Grade 2: blunted flow
- Grade 3: dampened flow
- Grade 4: stenotic flow
- Grade 5: normal flow
TIBI 0 and 1 refer to proximal occlusions, TIBI 2 and 3 to distal occlusion and TIBI 4 to recanalization. Applying these criteria in acute stroke, the TIBI classification correlates with initial stroke severity, clinical recovery and mortality in patients treated with recombinant tissue plasminogen activator (rt-PA). The grading system can also be used to analyze recanalization patterns. The waveform changes (0 to 5) correlate well with clinical improvements, and a rapid arterial recanalization is associated with better short-term improvement; whereas, slow flow improvement and dampened flow signals are less favorable prognostic signs. Even incomplete or minimal recanalization determined 24h after stroke onset results in more favorable outcome compared with persistent occlusion. The reperfusion is important for prognosis. Both partial and full early reperfusion led to a lesser extent of neurologic deficits irrespective of whether this occurred early or in the 6 to 24-hour interval. Progressive deterioration after stroke due to cerebral edema, thrombus propagation or hemodynamic impairment is closely linked to extra- and intracranial occlusive disease. Transcranial color-coded duplex is also useful for the evaluation of combined IV-intra-arterial (IA) thrombolysis. Patients receiving combined IV-IA thrombolysis show greater improvement in flow signal and higher incidence of complete MCA. Recanalization versus those receiving I.V. thrombolysis, especially when MCA was occluded or had only minimal flow. Patients with distal middle cerebral artery occlusion are twice as likely to have a good long-term outcome as patients with proximal middle cerebral. Patients with no detectable residual flow signals as well as those with terminal internal carotid artery occlusions are least likely to respond early
or long term. Distal MCA occlusions are more likely to recanalize with I.V. rt-PA therapy, terminal ICA occlusions were the least likely to recanalize or have clinical recovery with I.V. rt-PA compared with other occlusion locations.

Alexandrov et al. described the patterns of the speed of clot dissolution during continuous TCD monitoring. Sudden recanalization (abrupt normalization of flow velocity in a few seconds), stepwise recanalization as progressive improvement in flow velocity lasting less than 30 min, and slow recanalization as progressive improvement in flow velocity lasting more than 30 min. Sudden recanalization reflects rapid and complete restoration of flow, while stepwise and slow recanalization indicates proximal clot fragmentation, downstream embolization and continued clot migration. Sudden recanalization was associated with a higher degree of neurological improvement and better long-term outcome than stepwise or slow recanalization.

A tandem internal carotid artery/middle cerebral artery occlusion independently predicted a poor response to thrombolysis in patients with a proximal MCA clot, but not in those with a distal MCA clot.

**Ultrasound Accelerated Thrombolysis and Microbubbles**

Transcranial Doppler can be used not only for diagnostic and prognostic purposes, but also for therapy. The ultrasound enhances enzymatic thrombolysis increasing the transport of t-PA into the thrombus, improving the binding affinity and providing a unique opportunity to detect the recanalization during and after t-PA administration.

Continuous monitoring with 2-MHz TCD in combination with standard I.V. t-P.A therapy results in significantly higher recanalization rate or dramatic recovery than I.V. t-PA therapy without TCD monitoring. The continuous monitoring did not increase the frequency of symptomatic intracranial hemorrhage.

MBs are small, gas-filled microspheres with specific acoustic properties that make them useful as US contrast agents in neurovascular imaging. Administration of MBs may further accelerate the clot-dissolving effect of US by lowering the energy needed for cavitation. Moreover, the administration of MBs has been shown to directly harm the clot surface, induce penetrating, force and shear stress. The bioeffect of US-mediated MB destruction on clot lysis has been demonstrated, even in the absence of thrombolytic drugs.
Recent studies evaluated the effects of administration of MBs on beginning MCA recanalization during systemic thrombolysis and continuous 2-MHz pulsed-wave TCD monitoring. The complete recanalization rate was significantly higher in the t-PA+US+MB group (55%) than t-PA/US (41%) and t-PA (24%) groups with no increase in sICH after systemic thrombolysis. Although recent observations support the usefulness of ultrasound to facilitate thrombolysis, ultrasound-alone treatment should not be substituted for t-PA treatment.

**Conclusion**

Ultrasound has diagnostic, prognostic and therapeutic applications in acute stroke. Both extra- and intracranial vessels can be and should be investigated. Using Duplex ultrasound, we can rapidly estimate IMT thickness and the severity of carotid stenoses or occlusions correspond to approximately 8-10% of acute ischemic strokes. Diagnosis is frequently reached through arteriography, and TCD stands as an ancillary diagnosis tool with good sensitivity and specificity. TCCS combines the imaging of intracranial vessels and parenchymal structures and increases the diagnostic accuracy especially with an echo-contrast agent. TCD also identifies MES in intracranial circulation. Ultrasound also supplies prognostic information in acute strokes with monitoring of vessel recanalization.
Cardiac sources of emboli

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The heart and the aorta are potential sources of embolism to the systemic circulation. 20% of ischemic strokes are cardioembolic and 2/3 of cryptogenic strokes are most likely cardioembolic also more than 50% of strokes in young patients are cardioembolic.

Strokes with sudden onset deficit, in middle or anterior cerebral artery territory or multiple vascular territories are more likely embolic.

Potential Cardiac Sources of Systemic Embolization are:
- Aortic atheroma
- Atrial septal aneurysm
- Intracardiac tumor
- Left atrial/left atrial appendage thrombus
- LA spontaneous echocardiographic contrast
- LV thrombus
- Patent foramen ovale
- Valvular (native/prosthetic) vegetations or thrombus
- Transthoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) have been used for searching cardiac embolic sources and still represent the mainstay for investigation in patients with stroke or TIA.

ATRIAL SEPTUM ABNORMALITIES:
PATENT FORAMEN OVALE AND ATRIAL SEPTAL ANEURYSM
PFO is present in 25% to 30% of normal hearts at autopsy but ASA is infrequently observed in the general population (approximately 1% to 4% of subjects).
PFO and atrial septal aneurysm are more common is patients who have suffered an embolic event, especially when the event is cryptogenic.

Factors That Support a PFO Playing a Role in a Cardioembolic Event are: Clinical event compatible with thromboembolism, simultaneous presence of a venous thrombosis, presence of an atrial septal aneurysm, larger PFO and younger patient age (<40-50 yr).

Treatment strategies for these patients are: Anti platelet therapy, Anti coagulation therapy, Device closure but there is controversy about the best treatment strategy. Several meta analysis about device closure and medical therapy showed that The clinical benefit of PFO closure is minimal and unclear in comparison with the relatively heterogeneous medical therapy. Also no significant difference seen...
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between anti platelet therapy and oral anticoagulation therapy. In conclusion PFO closure was recommended for patients with recurrent cryptogenic stroke despite medical therapy. Aspirin treatment is considered adequate in most patients, replaced by warfarin treatment in case of coexisting deep venous thrombosis or prothrombotic state.

LV THROMBUS
LV thrombus seen in 6.2% of patients with anterior MI, without significant differences according to initial treatment modality. In patients in sinus rhythm with documented LV thrombus, at least 3 months of anticoagulation therapy is recommended.

VALVULAR VEGETATIONS
Neurologic complications occur in 20% to 40% of patients with IE. Staphylococcus aureus is the most common etiologic organism. The frequency of embolic events in IE decreases rapidly after the initiation of effective antimicrobial treatment. A negative TEE has a high negative predictive value for IE, with a range from 86% to 97%.

INTRACARDIC TUMORS
The two most common cardiac tumors are myxoma and papillary fibroelastoma. 50% of all cardiac tumors are myxomas, three of four myxomas originate from the LA, especially the fossa ovalis area of the interatrial septum. Tumor fragmentation, or embolization of superimposed thrombus, is considered a potential embolic mechanism. Large mobile myxomas or those with villous excrescences are more likely to embolize. Surgical resection is recommended in all cases. Papillary fibroelastoma is the most common tumor of cardiac valves, embolic events are often their first clinical manifestation. Aortic valve is the most frequent location, followed by the mitral valve, and LV is the most common extravalvular location. Embolism is thought to occur from superimposed thrombi or fragmentation of the papillary fronds. Surgical resection appears indicated for all symptomatic fibroelastomas; in asymptomatic patients, oral anticoagulation or antiplatelet therapy is usually used for nonmobile tumors; surgical resection should be strongly considered for mobile and larger (more than 1 cm) ones.

AORTIC ATHEROSCLEROTIC PLAQUES
Complex aortic atheroma is both more common in patients who have suffered a first stroke and positively correlated with a higher risk of recurrent stroke. Complex atheroma are those with more than 4 mm thickness, ulcerated or with
superimposed mobile clot. Atherosclerotic plaques more commonly involve the mid or distal aortic arch or descending aorta and are uncommon in the ascending aorta. Plaques with superimposed mobile clot needs anticoagulation therapy but for large, no mobile plaques ASA, ASA and clopidogrel, or warfarin can be used. Also Statins have been shown to reduce the risk of recurrent events in patients with stroke.

**LA THROMBUS**

Risk factors for LA thrombus are atrial fibrillation, LV dysfunction (LVEF<35%), decreased LAA flow velocity (<55cm/s), spontaneous echo contrast (SEC) that increase stroke risk by four-fold and mortality by three-fold. In the presence of LA thrombus anticoagulation therapy is indicated.
Pediatric Stroke

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Definitions
Cerebrovascular diseases compromise neurological health of children, usually by causing stroke. Stroke is defined as a sudden occlusion or rupture of cerebral arteries or veins resulting in focal cerebral damage and clinical neurological deficits. Stroke classification begins with the simple distinction of ischemia from hemorrhage. Ischemic varieties are arterial ischemic stroke (AIS) and cerebral sinovenous thrombosis (CSVT). In AIS, arterial occlusion usually is due to thromboembolism and results in focal infarction within an arterial territory. In CSVT, symptomatic thrombosis of the cerebral veins and/or dural venous sinuses is present, but may or may not result in parenchymal venous infarction. In contrast, strokes due to vascular rupture are termed hemorrhagic stroke and are classified primarily based on their intracranial location. The overlap between ischemic and hemorrhagic strokes can occur in certain circumstances such as the hemorrhagic transformation of an initially bland (no visible blood) ischemic infarct.

In children, fundamental biological differences in comparison with adults create unique issues and challenges in understanding the pathophysiology, risk factors, clinical presentations, diagnosis, treatment and consequences of stroke.

Epidemiology
Hospital administrative data suggest that cerebrovascular disorders are among top ten causes of death in children, with rates highest in the first year of life. Stroke-related mortality in young children may have decreased in the past two decades. A prospective, population-based Canadian registry estimated total ischemic stroke (AIS and CSVT) incidence at 2.2 per 100,000 including 1.8 for AIS and 0.4 for CSVT. Serial calculation of pediatric stroke rates in the decade ending in 1999 demonstrated a near-doubling from 2.8 to 5.4 per 100,000.

At least two factors have increased the number of diagnosed childhood strokes. First, widespread availability of more sensitive diagnostic tests, particularly MRI, has increased. Second, more effective treatments have increased survival in previously lethal pediatric diseases predisposing to stroke, including prematurity, congenital heart disease, sickle cell disease and childhood cancers.

Arterial Ischemic Stroke
AIS often occurs in recognizable patterns within the MCA territory, including:
1. Proximal M1 occlusion (entire MCA infarcted)
2. Distal M1 (basal ganglia spared)
3. Anterior or posterior trunk/M2 occlusion (frontal or parietal/temporal, respectively)
4. Lenticulostriate only (basal ganglia and deep white matter only).

As end-arteries, lenticulostriate lesions lack collaterals, conferring a higher risk of permanent infarction. Despite being small, such lesions also tend to affect critical structures and functional tracts, such as internal capsule. Such specific recognizable patterns also help predict the underlying etiology, with isolated lenticulostriate AIS commonly associated with parainfectious or inflammatory arteriopathy. In population-based studies, such small vessel-distribution infarcts account for 50 percent of childhood AIS. For unknown reasons, AIS more frequently affects left hemisphere.

Additional AIS patterns can be defined within the posterior circulation, involving brainstem, cerebellum, thalamus and occipital or mesial temporal lobes. Patterns include P1 (proximal posterior cerebral artery [PCA]) occlusion, with large-vessel territory infarction in the occipital and mesial temporal lobes and small-vessel infarcts in perforating arterial territories in the thalamus and splenium. Basilar artery thrombosis can be a life-threatening condition, often combining multiple infarcts involving brainstem perforators, cerebellar branches and the PCA. Cervical arteries are a frequent site for arterial dissection, both in the anterior and posterior circulations.

**Clinical Features and Diagnostic Delays and Risk Factors**

Diagnosis of stroke in children is frequently delayed or missed. Diagnostic delays likely reflect a combination of lack of awareness by primary care pediatric physicians, confusing neurological presentations, distracting signs and symptoms leading to erroneous lines of investigation and a complex differential diagnosis. A false-negative rate for initial computed tomography (CT) scanning of 60–80 percent also contributes to missed and delayed diagnosis of childhood AIS.

Acute hemiparesis is the most common presenting focal deficit but may be attributed erroneously to other causes that can mimic stroke (migraine, seizure or Todd's paresis, encephalitis meningitis or demyelination). Additional common focal neurological deficits include diplopia, Hemianopsia, impaired gaze, dysarthria, vertigo, nystagmus, dysphasia (expressive, receptive or mixed), ataxia, hemisensory symptoms and neglect. Seizures at the onset of stroke are also frequent in children compared with adults.

In addition to focal neurological deficits, diffuse or nonfocal neurological signs and symptoms such as headache, confusion, irritability and behavioral changes are
frequent especially in younger children. Neurological deficits can be subtle especially in infants who are unable to manifest language deficits or verbalize subjective complaints. Careful consideration of clinical and imaging information is required to distinguish true stroke from the lengthy list of stroke mimics. Stroke-induced deficits usually begin suddenly and severity is maximal at the onset, aiding differentiation from mimics such as migraine and demyelination. TIA is best defined as “a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms typically lasting less than one hour and without imaging (MRI) evidence of acute infarction”.

Multiple risk factors converge in AIS in more than 50 percent of children, emphasizing the need for thorough investigations. Causes for AIS in children differ significantly from those in adults, in whom atrial fibrillation and atherosclerosis (associated with hypertension, dyslipidemia, smoking and diabetes) predominate. Three main categories of risk factors have emerged as most prominent: arteriopathy, cardiac and prothrombotic/hematological.

**Treatment**

Current treatment of pediatric stroke is informed by three sets of consensus-based guidelines:

1. Chest guidelines
2. American Heart Association guidelines
3. UK guidelines

These guidelines are predominantly concordant for major treatment recommendations, though they differ in certain areas.

**Outcomes and Chronic Management**

Most survivors of childhood stroke suffer neurological morbidity. Moderate to severe neurological deficits or epilepsy occur in over 50 percent of children after AIS. Mortality rates are estimated at 5–13 percent. Risk of adverse outcome may be associated with ages below 12 months, presentation with altered level of consciousness or seizures and infarct location and size. Aggressive multimodal treatment and rehabilitation must target physical, occupational, language, cognitive/behavioral and psychosocial consequences of stroke for both the child and family.

**Cerebral Sinovenous Thrombosis**

CSVT includes thrombosis within the cerebral venous system, whether symptomatic or not. Approximately half of patients will have no visible
parenchymal lesions at diagnosis, while the remainders have venous infarction that often is hemorrhagic. Although CSVT incidence is likely underestimated, epidemiology studies suggest CSVT affects approximately 1 in 100,000 children per year, including neonates and accounts for 1 in 4 cases of childhood ischemic stroke. Similar to AIS, CSVT risk is highest in the neonatal period and in males.

Mechanisms of Thromboembolism
Factors mediating thrombosis in cerebral venous channels differ in some respects from those underlying thrombosis in cerebral arteries. In contrast to AIS, the coagulation cascade and thrombin-rich thrombosis predominate in CSVT, with platelets playing a less significant role. Inherited or acquired coagulation abnormalities, including prothrombotic medications, are important in CSVT pathogenesis.

There is a relative absence of thrombomodulin in the endothelial lining of cerebral sinuses compared with cerebral arteries, theoretically increasing the tendency for thrombosis. Consideration of Virchow's triad is highly relevant in the cerebral venous system, with thrombosis resulting from abnormalities of blood components, blood flow or vessel wall. In many children with CSVT, the exact mechanism of thrombosis is not evident. Dehydration is a frequent and potential risk factor for CSVT, where decreased blood volume and hemoconcentration decrease venous flow rates, favoring thrombus formation and propagation. In septic CSVT, head or neck infection in tissues immediately adjacent to venous channels provokes cerebral venous thrombophlebitis. With mechanical damage or compression of venous structures, venous stasis and vessel wall damage might combine to cause thrombosis. Examples include trauma, neurosurgical procedures, insertion of venous catheters, compressive mass lesions and occipital bone compression in supine young infants.

Clinical Features
Prompt diagnosis of childhood CSVT is clinically challenging but essential to affecting the best possible outcome. Neonates and infants less than 1 year comprise approximately 50 percent of pediatric CSVT patients. As in other varieties of pediatric stroke, clinical features are age-dependent and more difficult to recognize in infants and young children. In contrast to AIS, diffuse neurological signs and seizures are more common than focal deficits. Signs and symptoms also are more likely to develop gradually over many hours, days or even weeks, although symptoms also may begin or worsen abruptly. Common clinical presentations include headache, lethargy, nausea and vomiting, and signs of increased intracranial pressure, including papilledema and sixth nerve palsy. This
syndrome is clinically indistinguishable from idiopathic intracranial hypertension (IIH) and the latter diagnosis should not be made without excluding CSVT. Seizures are more common in CSVT compared to AIS, with estimates ranging from 40 to 90 percent. Young infants tend to present with seizures or diffuse encephalopathy and focal signs are uncommon.

**Risk Factors**
Risk factors are definable in most children and frequently are multiple. CSVT risk factors are age-related. In neonates and young infants, dehydration and perinatal events are common and the proportion without evident risk factors is higher. Head and neck infections are present in nearly one-third of preschool children, while other associations including systemic disease and trauma are clustered in the older age groups.

**Treatment**
Many of the overall approaches to the treatment of child with AIS stroke including urgent supportive and neuroprotective care are applicable in CSVT. Antithrombotic interventions to prevent thrombus propagation and allow intrinsic fibrinolytic systems to work are the mainstay of treatment. Subacute treatment includes treatment of intracranial hypertension. In the long term, attention to secondary prevention is important.

**Hemorrhagic Stroke**
Hemorrhagic stroke (HS) occurs when cerebral blood vessels rupture. These are often abnormal blood vessels (e.g. vascular malformation), although normal vessels can also hemorrhage (e.g. bleeding diatheses). HS is a neurological emergency with a high mortality rate, acutely and secondary to a high recurrence risk. Two major types of HS include intracerebral (i.e. intraparenchymal) hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Relative rates of each location in pediatric HS are compared infrequently but ICH likely accounts for 50–75 percent, while SAH is 25 percent or less. Intraventricular hemorrhage (IVH) is more common in neonates but can occur often via extension of ICH or SAH.

Important differences exist between hemorrhagic and ischemic strokes in children. Although studies vary, the incidence rates of the two are probably comparable overall, estimated at 1–5/100,000 children/year. A specific cause is more likely to be found for hemorrhagic compared to ischemic stroke, though many still remain idiopathic.

In general, etiologies are entirely different, though overlap certainly exists and conditions like moyamoya, SCD, postinfectious and congenital vasculopathies can
predispose to both. In contrast to ischemic stroke, definitive treatment for HS often requires neurosurgical intervention. Compared with AIS, HS is associated with an increased mortality but survivors tend to have better neurological outcomes. Long-term recurrence risk is often high, necessitating close follow-up and curative therapy when possible.

Clinical Features
An instantaneous and severe headache is the hallmark of HS. A thunderclap headache, particularly if accompanied by nausea/vomiting or neurological symptoms, should be considered HS until proven otherwise. Headache with nausea/vomiting is the most consistently reported presentation of HS in children, described in more than 50 percent of cases.
Alterations in level of consciousness and focal neurological deficits also are common, while seizures are initially present in 15–37 percent. However, HS presentations also can be subtle and slowly progressive, described in up to 40–50 percent of cases. In posterior fossa hemorrhage, bulbar signs, ataxia and rapid deterioration to coma are typical. An elevated blood pressure at presentation may be found in up to 45 percent but simply may represent a physiological response.

Risk Factors
A probable cause for HS can be found in 85–90 percent of children. Vascular diseases, both congenital and acquired, as well as intravascular factors, must be considered. Congenital vascular causes predominate and are collectively responsible for more than half of all cases of childhood HS.

Treatment
Management of a child with HS rests on the same principles for ischemic stroke, with a few important distinctions. Evidence to date is minimal and the three pediatric stroke consensus guidelines do not comment on pediatric HS. Neurosurgical intervention is often required in childhood HS, reported in 60–80 percent of cases.
Imaging of Cerebral Venous and Sinus Thrombosis

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Introduction
Cerebral venous and sinus thrombosis (CVST) are often underdiagnosed because they are associated with a wide spectrum of etiologic factors and clinical presentations, and the diagnostic imaging features can be subtle. The correct diagnosis of CVT depends on neurologic imaging. Neuroradiologists play an essential role in patient care by providing early diagnosis through selecting and interpreting imaging studies. Early diagnosis leads to prompt treatment that can be effective in prognosis.

The purpose of this article is to review the approach for radiologic investigation and the pitfalls associated with radiologic evaluation.

Cerebral Sinus Thrombosis
• CT Findings
  Hyperdense dural sinus or cortical vein ("cord sign"), cortical/subcortical ptechial hemorrhages or edema and venous infarct in 50% can be seen.

  • Contrast Enhancement CT
    "Empty delta" sign in 25-30% of cases, enhancing dura surrounding non-enhancing thrombus and "Shaggy," irregular veins (collateral channels) are seen.

  • CT Venography
    CT venogram (CTV) shows thrombus as filling defect(s) in dural sinus.

• MR Findings
  • T1WI
    Acute thrombus usually appears in T1 isointense or hypointense; however, subacute thrombus becomes hyperintense and chronic thrombose usually hypointense.

  • T2WI
    Acute thrombus usually appears in T2 hypointense; however, subacute thrombus becomes hyperintense and chronic thrombose usually hypointense.

It should be noted that in acute phase if thrombus is hypointense, mimic normal sinus can "flow void" on T2WI. On the other hand, chronically occluded, fibrotic sinus eventually appears isointense.
In proton density (PD), imaging is more sensitive than T2W but less sensitive than FLAIR. In FLAIR thrombus appears hyperintense in subacute and chronic phase.

- **T2* GRE**
  Thrombus in GRE appears hypointense, like blooms (blooming effect). Petechial and/or parenchymal hemorrhages appears Hypointense.

- **DWI**
  In DWI, clot in 40% appears hyperintense in occluded vessel; however, DWI/ADC findings in parenchyma are variable and heterogeneous because in CVST we have a mixture of vasogenic and cytotoxic edema; cytotoxic edema may precede vasogenic. Parenchymal abnormalities appear more frequently reversible than in arterial occlusions.

- **TI C+**
  Peripheral enhancement around acute clot is prominent, it should be noted that chronic sinus thrombosis can enhance due to organizing fibrous tissue; therefore, in chronic phase of CVST TI C+ imaging can be confusing and in spite of clot, filling defect due to fibrotic tissue enhancement, is not prominent.

- **MRV**
  Absence of flow in occluded sinus on 2D TOF MRV is the main feature. Frayed or shaggy appearance of venous sinus is prominent. Abnormal collateral channels (e.g. enlarged medullary veins) become prominent. It is better to evaluate standard sequences and source images to exclude artifacts in MRV. Contrast-enhanced MRV (CE-MRV) better demonstrates thrombus, small vein detail and collaterals much faster than 2D TOF.

- **Venous Infarct**
  If there is venous infarct, mass effect with mixed hypo-/hyper-intense signal in adjacent parenchyma is common. However, venous infarct has four characteristic features: usually bilateral, parasagital, in 60% with hemorrhage and is in venous territories not arterial territories.

### Staging, Grading or Classification Criteria for Venous Ischemia
- **Type 1**: No abnormality
- **Type 2**: High signal on T2WI/FLAIR; no enhancement
- **Type 3**: High signal on T2WI/FLAIR; enhancement present
- **Type 4**: Hemorrhage or venous infarction

### Angiographic Findings
  Occlusion of involved sinus is the main finding. However, slow flow in adjacent patent cortical veins and collateral venous drainage are prominent.
Imaging Recommendations for CST
Best imaging tools include:
1- NECT, CECT scans ±CTV as initial screening
2- MRI, MRV (include T2*, DWI, T1 C+)

Protocol Advice
o If CT scan is negative, MRI (including T2*, DWI, T1 C+) with MRV
o If MRV is equivocal, then DSA.

Potential Pitfalls in Image Interpretation
Normal
• Blood in vessels normally slightly hyperdense on NECT scans
• Normally, veins are slightly denser than brain tissue and in some cases it is difficult to say whether it is normal or too dense.
• In these cases, a contrast enhanced scan is necessary to solve this problem.
• In infants, brain is usually less dense than in older children and adults. These result in a relatively high density of the blood in sagittal sinus compared to the brain, which simulates a dense clot sign.

Anatomic Variant
• Congenital hypoplastic/absent transverse sinus (transverse sinus flow gaps 31%, usually non-dominant sinus)
• Right transverse sinus dominant 59%, left dominant in 25%, co-dominant in 16%
• "High- split" tentorium
• Fat in sinus or

"Giant" Arachnoid Granulation
• Round/ovoid filling defect (clot typically long, linear)
• CSF density/signal intensity
• Arachnoid granulations normal in 24% of CECT, 13% of MR
  o Transverse sinus most common location by imaging, L>R
  o SSS most common location for arachnoid granulations on histopath (in lateral lacunae, not well seen by imaging)

False "Empty Delta" Sign
• SDH, subdural empyema

Neoplasm
• Venous infarct can enhance, mimic neoplasm
• Intravascular lymphomatosis (rare)
Cerebral Hemorrhage
• Mimics venous infarct
• Amyloid, contusion and hypertensive

Thrombus Signal Shine-Through at TOF MR Venography (T1 hyperintense thrombus falsely appears as patent flow)
Flow Gaps at TOF MR Venography
Wrong Bolus Timing
Cortical Venous Thrombosis
Definitions
• Superficial cerebral vein thrombotic occlusion with/without associated dural sinus thrombosis (DST)

General Features
• Best diagnostic clue: "Cord sign" on NECT, T2* GRE
• Location: Cortical veins (supra- > infratentorial)
• Size: Varies from small to extensive clot
• Morphology: Linear, cigar-shaped thrombus

CT Findings
CT findings are as sinus thrombosis however,
• If internal cerebral veins (ICV) occlude, thalamiand/or basal ganglia become hypodense
  o Abnormal collateral channels (e.g., enlarged medullary veins)
  o CECT has Limited value in chronic CVT (organizing thrombosis also enhances)

MR Findings
MR findings are as sinus thrombosis however in:
• DWI/ADC imaging findings heterogeneous dependent on presence of ischemia, type of edema, hemorrhage can distinguish cytotoxic from vasogenic edema. Restriction can be seen in clot occluded veins at the time of diagnosis and might be predictive of low rate of vessel recanalization 2 or 3 months later.

• T1 C+ in acute/early subacute clot peripheral enhancement outlines clot can be seen and in late clot, thrombus and fibrous tissue often enhance. However, in venous infarct patchy enhancement is prominent.
• MRV may see abnormal collateral channels (e.g. enlarged medullary veins) but in contrast-enhanced MRV (CE-MRV) faster and better depicts non-enhancing thrombus & small veins than TOF was seen.
• MR Perfusion, T2* Gadolinium perfusion may show extensive venous congestion, but without perfusion deficits may play a role in detecting venous congestion vs. venous infarction in CVT.

Angiographic Findings
• Conventional: More accurate than MRI, particularly for isolated cortical vein thrombosis.

• DSA when imaging findings inconclusive, if clinical suspicion is high or if intervention is planned.

Deep Cerebral Vein Thrombosis (DCVT)
Definitions
• Thrombotic occlusion of deep cerebral veins
• DCVT usually affects both ICVs +/- vein of Galen (V of G), straight sinus (SS)
• More widespread dural sinus thrombosis (DST) and cortical vein occlusion may occur.

Best diagnostic clues include:
- Hyperdense ICV on NECT +/-bithalamic hypodense edema, variable DST
- Location: Clot in ICV +/- V of G, SS, basal veins of Rosenthal
  o Bilateral ICV thrombosis »> unilateral
  o Deep gray nuclei, internal capsule, medullary WM typically affected
  o Variable involvement of midbrain, upper cerebellum (V of G, SS territory)
- Morphology: Cigar shaped, "cord-like"

• TIWI
  o Clot: Early T1 isointense, later hyperintense
  o Most conspicuous sequence if clot is subacute
  o Venous hypertension: Hypointense swelling of thalami, basal ganglia
  o Venous infarct: Hypointense edema, may be hemorrhagic

• T2WI
  o Clot: Often T2 hypointense mimicking flow void ("pseudo flow void"), much later hyperintense

Angiographic Findings
  o Unlike quite variable superficial veins, deep cerebral veins are always present on angiography.
  • In DCVT, occluded ICVs do not opacify.
  • Collateral venous channels (e.g. pterygoid veins) enlarge.
In conclusion, the best diagnostic tool for CST is NECT, CECT scans ±CTV as initial screening and MRI, MRV (including T2*, DWI, T1 C+) and if MRV is equivocal, DSA. For cortical vein thrombosis T2* is the best modality and for deep vein thrombosis hyperdense ICV on NECT and hyperintense T1WI (subacute) +/- bithalamic hypodense edema is the best clue for diagnosis. Venous infarct has four characteristic features: usually bilateral, parasagital, in 60% with hemorrhage and is in venous teriories (not arterial territories).

References
Medical Complications of Stroke

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Medical complications are common in patients who have stroke (Table 1)(1-3). These complications are important because they cause poor outcomes for patients with stroke. They cause mortality, prolonged hospital stay and delay rehabilitation. Death in first week of stroke is due to brain injury of stroke. About 50 percent of causes of death in stroke are related to medical complications. Medical complications such as infections, pulmonary embolism and cardiac disease are cause of death in stroke patients after first week (4-6).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
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<tbody>
<tr>
<td>Falls</td>
<td>25</td>
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<tr>
<td>Urinary Tract Infection</td>
<td>24</td>
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<tr>
<td>Chest Infection</td>
<td>22</td>
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<tr>
<td>Pressure Sore</td>
<td>21</td>
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<tr>
<td>Depression</td>
<td>16</td>
</tr>
<tr>
<td>Shoulder Pain</td>
<td>9</td>
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<tr>
<td>Deep Venous Thrombosis</td>
<td>2</td>
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<tr>
<td>Pulmonary Embolism</td>
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Table 1. Common medical complications in patients with stroke

In one study, at least one complication has been seen in 95 percent of stroke patients. At least one serious complication (defined as lifethreatening, prolonged, leading to hospitalization or death) has been seen in 24 percent(2). The most common serious complications include pneumonia (5 percent), gastrointestinal bleeding (3 percent), congestive heart failure (3 percent), and cardiac arrest (2 percent) (table 2)(2).

<table>
<thead>
<tr>
<th>Complication</th>
<th>Percent</th>
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<tr>
<td>All pneumonias</td>
<td>5</td>
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<tr>
<td>Aspiration pneumonia alone</td>
<td>3</td>
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<tr>
<td>Heart failure</td>
<td>3</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>3</td>
</tr>
<tr>
<td>Cardiac arrest</td>
<td>2</td>
</tr>
<tr>
<td>Angina/MI/cardiac ischemia</td>
<td>1</td>
</tr>
<tr>
<td>Deep venous thrombosis</td>
<td>1</td>
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<tr>
<td>Pulmonary embolism</td>
<td>1</td>
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<tr>
<td>Hypoxia</td>
<td>1</td>
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<tr>
<td>Urinary tract infection</td>
<td>1</td>
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<tr>
<td>Sepsis</td>
<td>1</td>
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<tr>
<td>Cellulitis</td>
<td>1</td>
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<tr>
<td>Peripheral vascular disorder</td>
<td>1</td>
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<tr>
<td>Dyspnea</td>
<td>1</td>
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<tr>
<td>Pulmonary edema</td>
<td>1</td>
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<tr>
<td>Dehydration</td>
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Table 2 Server Medical complications in stroke
Falls
In elderly, approximately 80 to 90 percent of injuries are caused by fall (7, 8). The risk of fall is high in stroke patients. Fall is the most common medical complication in stroke patients. In a study conducted on patients in stroke rehabilitation unit, 39% suffered falls and 24% suffered more than one fall. The rate of injuries was low and only 5% suffered major injuries (9).

Urinary Tract Infection (UTI)
The range of reported risk of in-hospital UTI varies considerably ranging from 3.7 to 65.8 percent (10). Reported risk from a meta-analysis was 10% (1). Depressed consciousness level, stroke severity, increased post-void residual urine volume and diabetes mellitus increased risk of UTI. The risk of UTI in stroke patients were twofold in comparison to general medical population (1, 11).

Pneumonia
Up to one-third of stroke patients suffered from pneumonia. As other infection. Pneumonia increased mortality and morbidly of suffered patients. Between medical complications, pneumonia causes the highest related mortality. Present study often showed than the aspiration is the main cause of pneumonia in stroke. About one-half of stroke patients suffered swallow dysfunction that one-third aspirated (diagnosed by swallow video). Of patients who aspirate, one-third developed pneumonia. Aspiration occurred in one-half of cases silently.

Depression
The prevalence of depression in stroke is at least 17 percent. Stroke severity, physical disability and cognitive impairment increase the risk of depression after stroke. Present data do not support association of depression to lesion of left hemisphere.

VENOUS THROMBOEMBOLISM
Deep vein thrombosis (DVT) is a serious complication in stroke patients because it can cause life-threatening pulmonary embolism (PE). The prevalence of clinically evident DVT is about 5 percent. It may lead to PE in 2 percent. PE, if remained untreated, may cause death in 15 percent of cases (12). DVT may present as early as second (12). Hemiparesis prone the patient for DVT. Additional risk factor include advance age, high score of stroke severity, immobility and atrial fibrillation.

Treatment with anticoagulant, Aspirin or use of intermittent pneumatic compression devices may decrease risk of DVT in Stroke patient (13-15).

Pulmonary embolism (PE)
PE my occurred in 1% of patient with ischemic stroke. It is more common in patient with sever stroke, history of cancer previous PE/DVT or acute DVT. PE is associated with great disability and longer length of hospital stay (16).
Shoulder pain (SP)
Sp is another common complication after stroke. About 30% to 54% of patients developed shoulder pain after stroke with mode to server pain (17, 18). Shoulder subluxation as a cause of SP occurred at early stage of stroke. Slings can prevent subluxation. Injection of corticosteroid does not improve pain and range of motion of shoulder joint in hemiplegic patients while botulinum toxin combined with physical therapy may reduce shoulder pain (19).

Pressure sore
In a community based cross-sectional study this type of sore was detected in 16.8% of responders, more common in male (59%) then Female (41%). The majority of the participants (70.4%) Developed sore on sacral area (20). Prevalence of decubitus sore was


Headache in Cerebrovascular Diseases

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Headache issue in cerebrovascular diseases could be divided into 3 types:
1. Headaches during cerebrovascular events or as the main symptoms of a cerebral vascular event
2. Headaches as a warning or presenting symptoms of cerebrovascular events
3. Migraine headache as a predisposing factor for ischemic stroke

Headaches during Cerebrovascular Events
Based on different studies, headaches are common during acute ischemic infarcts and intracranial hemorrhages. Such headaches are not usually throbbing, often localized and frequently ipsilateral to the infarct or presumed arterial occlusion. They are occasionally severe. Of special interest is the relatively high frequency of headache in posterior cerebral artery territory infarctions.

In a quite large study on 2196 patients experiencing ischemic stroke or transient ischemic attack within a multicenter hospital-based stroke registry, 588 (27%) patients experienced headache at stroke onset. In a multivariate analysis, headache at stroke onset was positively associated with female sex, history of migraine, younger age, cerebellar stroke (but not with other brain stem locations) and blood pressure values on admission <120 mmHg systolic and <70 mmHg diastolic. It showed no significant association with stroke severity measured by the modified Rankin Scale on days 5th to 7th after the event, presumed etiology, or time of the day. Headache was bilateral in the majority of the patients (n=363; 61%). One hundred and five patients (18%) experienced left-sided and 129 (21%) from right-sided headache. In those patients with hemispheric stroke and unilateral headache, headache was significantly more often on the side of the lesion (65% ipsilateral)(1).

In another recent study on 1411 stroke patients, headaches were recorded in 18.2% of them i.e. three times more frequent in ICH patients. One month mortality was significantly higher in ICH patients with headache. Patients with headache were younger and had higher frequency of decreased consciousness and lower frequency of aphasia. Severity of the stroke was not different among patients with or without headache (2).

Multiple secondary headaches could be accompanied by increased risk of stroke. In this category, headache is the most prominent symptom of Giant cell arteritis and
CADASIL (Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts) syndrome. Headache is also a common symptom of cerebral venous sinus thrombosis that is usually prolonged and may be accompanied by ischemic or hemorrhagic infarcts. Besides, patients with lateral sinus thrombosis may present with an Idiopathic intracranial hypertension like syndrome. So, in all patients with prolonged headache or evidence of raised intracranial pressure, even without evidence of neurological deficit, dural venous sinus thrombosis should be among differential diagnosis.

**Headache as a Warning or Presenting Symptom of Cerebrovascular Events**

The most grave cerebrovascular event, subarachnoid hemorrhage usually starts with a sudden severe headache, but headache as a warning symptom, could be a useful symptom to prevent a catastrophic event, if physicians do pay attention to it. We studied warning symptoms of SAH in a cross-sectional study. Interestingly, 64% of our patients with SAH experienced a severe unfamiliar headache during the days before aneurysmal rupture (3).

Another important but rare vascular event is Cerebral Reversible Vasoconstriction Syndrome (CRVS) which mostly presents itself through a thunderclap headache that may be repeated during a few weeks. It may be accompanied by ischemic infarcts, Cortical SAH or parenchymal hemorrhage. The event may be spontaneous, but in up to 60% of cases, it is secondary to other causes such as; vasoactive substances (stimulants), blood products and the post-partum state. Calcium channel antagonists are recommended for treatment. As RCVS occurs in a broad range of clinical situations, it needs more awareness among physicians (4).

**Migraine Headache as a Predisposing Factor for Ischemic Stroke**

Recent meta-analyses confirmed the relationship between migraine and cerebrovascular accidents, which are documented for ischemic stroke and migraine with aura (MA) that is stronger in smokers and females who use oral contraceptives. Migraineurs also showed an increased risk of hemorrhagic stroke. Moreover, there is an increased frequency of possible ischemic lesions in the white matter of migraine sufferers that is more prominent in the posterior circulation territory and is more frequent in patients with high attack frequency. It seems that the prevalence of Patent Foramen Ovale (PFO) is higher in migraineurs, but the relationship between migraine and PFO is controversial and PFO closure is not suggested for migraine prevention. Some data suggested increased frequency of cervical artery dissections in migraineurs. But further data are needed to confirm the pathophysiological tendency for artery dissection in migraine sufferers (5).
Although the relation between migraine with aura (MA) and tendency to have risk factors for cerebrovascular events is confirmed by several studies (5-6), this relationship in patients with migraine without aura (MO) is a matter of debate. We compared the risk factors of cardiovascular disease in 614 individuals (347 patients suffering from migraine without aura and 267 healthy controls). Migraineurs had higher DBP (P=0.01), lower FBS (P≤0.001), higher total cholesterol (P=0.006) and LDL (P=0.006) and higher BMI (P=0.02) (Table 1). HTN, hyperglycemia, dyslipidemia, obesity and age were the potential confounders in the multivariate logistic regression analysis. After adjusting for confounding factors, HTN was the only variable related to MO (OR adj = 1.9, p= 0.029). In line with previous observations, our study showed MO to be associated with a higher prevalence of HTN in the Iranian population (7).

Conclusion
Headache is a symptom that could accompany a cerebrovascular event, a warning sign of a severe vascular accident or a predisposing factor for ischemic stroke. So, headache in different situations needs more attention.

References

Questions
1- A 34 year-old lady presented with a sudden severe headache that increased to peak severity in a minute and continued for three hours prior to admission. She had experienced the same headache for about 5 days prior to admission. In her history, she...
had had nasal congestion because of allergy during the days prior to the headache and had used usual drugs for that. Neurological and systemic examinations and brain CT scan are normal on admission. What is the most possible impression?

A- CVT
B- SAH
C- Meningitis
D- CRVS

Answer: D, She may use Psudoephedrin predisposing her to CRVS. First exam and imaging might be normal.

2- A patient with frequent migraine attacks is referred to you. She has a history of PFO. What is your recommendation to reduce the frequency of her migraine attacks?

A- Surgery if PFO is large
B- Surgery even if PFO is not large
C- Surgery if her attacks are resistant to drug therapy
D- Other options of treatment rather than PFO surgery

Answer: D, At the time, surgery is not recommended for PFO as a treatment of migraine.
Stroke: Just a Chemistry

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Abstract
Stroke is a significant health issue with its neuropathological mechanisms requiring better understanding. Within the course of ischemic stroke, obstruction of a major brain artery results in an abrupt blood flow limitation below a critical threshold and focal ischemic brain insult arises. Chemical shift imaging using magnetic resonance spectroscopy and more advanced imaging methods has recently provided some novel insights into the chemistry of stroke. Given the fact that stroke disturbs the normal brain chemistry, assessing and perhaps targeting the metabolic pathways ought to be a practical and useful approach to better understand the neurobiochemical aspects of stroke. This perspective paper focuses on the evolving dimensions of neurochemical research in stroke.

Keywords: Stroke, Neurochemistry, Ions, Chemical shift imaging, Neuropathophysiology

Key basic insights into the pathophysiology of stroke
Well-supported theories and evolving evidence have spotlighted the significance of neurochemical changes following stroke. The diminished oxygen and glucose delivery disrupts the ATP build-up and the resultant energy failure triggers ischemia-induced and neuroinflammatory phenomena such as acidosis, production of reactive oxygen species, apoptosis, necrosis and eventually neuronal cell death. The disturbance in metabolic pathways and events such as excessive extracellular glutamate release, increased anaerobic glycolysis and disconcertion in glutamate–glutamine cycle are shown to play important roles in protein synthesis turnover and brain ischemic injury (1-4).

Following ischemic stroke, depending on the duration and severity of the ischemic insult, rapid necrotic cell death or expression of apoptotic genes may occur. While depletion of energy stores is recognized as the primary pathologic mechanism in stroke, a considerable body of evidence suggests that excitatory amino acids (EAAs) potentially contribute to ischemic injury. EAAs, including glutamate, are found in almost 30% of synapses in the central nervous system (5). EAAs are known to take part in various cognitive and neurological functions such as memory, sensation, movement, and synaptic plasticity. Meanwhile, they can exert pathologic effects as well. Early neuroscience research demonstrated EAA-
mediated toxicity when administered in the arcuate nucleus of the hypothalamus and further studies confirmed that increased extracellular glutamate and other EAAs induce a notable rise in cytosolic calcium concentrations (6, 7). Such an increase in intracellular calcium is lethal to primary neuronal cultures and the direct link between extracellular calcium stimulation and induced cell death in neurons when exposed to glutamate highlights the importance of calcium entry in the process of excitotoxicity (8).

In fact, the increased intraneuronal calcium in response to extracellular EAAs in vitro has resulted from opening of N-methyl-D-aspartate (NMDA)-gated ion channel. As such, NMDA antagonists would compete with glutamate and other EAAs for the receptor and prevents calcium entry into the neurons thus hinder glutamate-induced cell death. In addition to glutamate, glycine is also required to open the NMDA calcium channels, hence antagonists which bind to glycine site on the NMDA receptor counteract excitotoxicity in vitro (9, 10). Many of the key molecular events in programmed cell death have now been determined. Just as calcium entry into the neuron is a key step in excitotoxicity, the release of cytochrome c from the mitochondria is a key event in initiating apoptosis in many cell types. Cytosolic cytochrome c complexes with APAF-1 and procaspase 9. As a result, procaspase 9 is cleaved into its active form, caspase 9. Caspase 9 then cleaves and activates other caspases, including caspase 3. The molecular mechanisms by which programmed cell death is initiated are numerous and complex. Programmed cell death may be activated via cell surface receptors, including the Fas receptor and tumor necrosis factor- alpha (TNF-a). Activation of these receptors triggers activation of caspase 8, which in turn cleaves the bcl-2 family protein (9, 10). A schematic outline of such molecular mechanisms is illustrated if Figure 1.
In line with the above, compelling in vivo evidence has postulated that NMDA-mediated excitotoxicity contributes to injury from cerebral ischemia. An abrupt substantial increase in extracellular amino acids concentration has been monitored by microdialysis in animal models of acute cerebral ischemia. Despite the lack of efficacy of NMDA antagonists in global ischemia models, many studies have shown that they reduce infarct volume in both permanent and temporary middle cerebral artery occlusion (MCAo) models in rodents. In addition, when translation of a gene which encodes a subunit of the NMDA receptor is blocked via intraventricular injection of antisense oligonucleotides, the infarct volume in rat model of MCAo is notably decreased (9, 11).

The cascade of neurochemical reactions in stroke
Many calcium-dependent or -induced enzymes such as phospholipase A2, nitric oxide synthase, Calpain 1, and cyclooxygenase regulate the process of
excitotoxicity (Figure 1). Calpain 1 is a calcium-activated protease specifically linked to glutamate receptors in the hippocampus. This enzyme contributes to the conversion of xanthine dehydrogenase to xanthine oxidase. The latter metabolizes xanthine to its reactive oxygen species, superoxide. Likewise, calcium activates the phospholipase A2 which facilitates the release of arachidonic acid from injured cell membranes. The above stream of chemical events collectively result in the oxidant injury following stroke (12-16).

Neurons which have not faced immediate necrosis in stroke often die within subsequent days and weeks. These cells might survive when we know about, and intervene, their cascade of chemical reactions leading to their death. Upon hemorrhagic stroke, the breakdown of hemoglobin from the blood cells flooding into the brain tissue may increase the tissue iron. Recent imaging investigations have employed SSRL’s XRF imaging beam lines (Stanford Synchrotron Radiation Lightsource) to examine the possible role of iron in distorting the required fine chemical balance serving brain cells survival. While other imaging methods suggest that the tissue iron concentration is raised in the lesioned hemisphere of the brain, XRF imaging has shown that iron is much accumulated in the perihematoma region. Referring to the above evidence, Iron chelators were recently tested as adjunct stroke therapy in experimental models. Documented by quantitative XRF mapping, although a ferric iron chelator resulted in diminished
iron levels in the brain, it failed to recover the stroke-related disabilities in the experimental rodent model (17-19).

**Investigating the stroke damage markers**

Ischemic stroke occurs secondary to narrowing of the brain vessels or an entrapped clot in them. This limits the blood flow through a vessel and disturbs normal brain chemistry. Although it is well known that specific neurons in the brain are more susceptible to ischemia, the chemistry behind their vulnerability is yet to be better defined. Integrating the XRF mapping and sulfur K-edge X-ray absorption spectroscopy (XAS) along with traditional biochemical and histological methods has recently been shown to offer a deep understanding on the neurochemical image of ischemic stroke as well as the underlying biochemical pathways by which treatments tend to reduce the expected damage. Applying the beam lines 10-2 and 2-3 in SSRL’s XRF imaging method in healthy rats’ brain and stroke models at various time points, the distributions of ions such as Zn, K, Cl, and Ca were determined before and after gentle brain cooling which is considered as a promising stroke therapy (17, 18, 20).

In the same vein, neurobiochemical markers in stroke patients have attracted much attention over the recent decade (21, 22). The cellular activation and disintegration which occurs after cell injury in the central nervous system leads to the release of proteins which belong to specific cell types. These include neuron-specific enolase (NSE), glial fibrillary astrocytic protein (GFAP), myelin basic protein (MBP) and the calcium-binding protein S100B. These damage markers can be measured both in cerebrospinal fluid (CSF) and blood. The poor relation between CSF and serum levels of these damage markers are often not strong and this prevents us from making comment about the surrogacy of brain markers in the blood. Therefore, since CSF concentrations more accurately represent cerebral pathological changes, brain damage markers in ischemic stroke seem to be better measured in the CSF in future studies (23-25).

The unique biochemical background of the above damage markers roots in their differences in cellular and subcellular origins. Due to the paucity of the data on these damage markers in the literature, studies need to investigate the CSF levels of these markers namely MBP, GFAP, S100B, and NSE in the course of acute ischemic stroke. Based on the relation between these damage markers with the baseline stroke severity, location, long-term outcome, new avenues for targeted therapy of stroke can possibly be drawn in the future (26-30).

**Metabolic imaging and lesion chemistry in stroke**

As discussed earlier, metabolic analysis tend to be a useful approach for understanding the biochemical aspects of stroke. Magnetic resonance
spectroscopy (MRS) is a chemical shift imaging method which is proven as beneficial tool to investigate the in vivo metabolic changes in ischemic stroke. Some in vivo investigations have demonstrated altered levels of lactate, creatine, N-Acetyl Aspartate (NAA) and choline in cerebral ischemia (31, 32). Nevertheless, unfavorable sensitivity and resolution often limits the relevance of the detectable and assignable metabolites from MRS in stroke. On the other hand, high-resolution nuclear magnetic resonance (NMR) spectroscopy serves as a better alternative to capture more metabolic information owing to the its capacity in simultaneously detecting a wide range of metabolites. Evaluating the correlation of such changes with physiological and genetic alterations in the brain upon stroke would shed light to the key role of chemistry in the pathophysiology of stroke (33-35).

Some approaches such as principal component analysis (PCA) and orthogonal partial least squares discriminant analysis (OPLS-DA) are among widely used multivariate data analysis methods [17-19] which are used to explore metabolic alterations in relation to a given biological disturbance. The above approach is known to be the technical basis for so-called metabonomics. In research setup, metabonomics encompass high-resolution NMR or mass spectrometry (MS) analyses to help draw the metabolic map of samples such as blood or CSF. This approach has been used as a successful tool to diagnose the condition, understand pathophysiology, identify biomarkers, and explore mechanistic aspects of toxicity (36-38).

NMR and high performance liquid chromatography (HPLC) has recently been used to detect metabolic alteration in ischemic condition. Based on some recent reports, cerebral ischemia resulted in increased level of adenosine, inosine and hypoxanthine at 4, 6 and 8 hours after the occlusion in extracellular fluid of striatum, respectively (39-41).

In addition, acetate, glutamine/aspartate were increased and decreased the ischemic tissue 6 hours after occlusion, respectively. Similarly NMR-based studies demonstrated that focal ischemia leads to a decrease in aspartate, glutamate, NAA and total creatine levels 24 hours after the occlusion. Despite the overall quality of such investigations, these works appear fragmented in terms of the metabolisms and the holistic metabolic responses of cerebral tissues to focal brain ischemia (42).

**Future directions**

Future studies in the field need to define the metabolic features associated with stroke. Comprehensive insights on the metabolic analysis would provide a clearer view about the biochemical aspects of stroke; the perspective which offers future potentials for targeted therapies.
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Intracranial stenosis accounts for 10% of all strokes. Its natural history is variable. It may progress, regress or remain stable during follow-up. The natural history depends on the location of stenosis and the extent of intracranial atherosclerosis. Patients with more than 70% stenosis are at more risk of developing a stroke in follow-up. Moreover, the possibility of progression of stenosis in lesions of middle cerebral artery, anterior cerebral artery and posterior cerebral artery are more than intracranial internal carotid artery. The risk of annual stroke in symptomatic intracranial stenotic group is significantly more than patients with extracranial stenosis. Recurrent annual stroke rates are estimated at 4–12% per year with atherosclerosis of the intracranial anterior circulation and 2.5–15% per year with lesions of the posterior (vertebrobasilar) circulation.

In general, intracranial atherosclerosis occurs in the setting of widespread atherosclerosis. Asians, blacks and Hispanics are more likely to have intracranial atherosclerosis than whites. Although ICAS is more prevalent in Asians than in Westerners, the reason for racial-ethnic differences is unknown. Possible explanations include inherited susceptibility to intracranial vessel atherosclerosis, acquired differences in risk factor prevalence and differential responses to the same risk factors. Because both Moyamoya disease (MMD) and ICAS are more prevalent in Asians than in Westerners, the increased prevalence of ICAS may, in part, be caused by adult-onset MMD that is misclassified as ICAS.

Moyamoya disease (MMD) is a unique cerebrovascular disease characterized by progressive stenosis of the distal internal carotid artery (ICA) and a hazy network of basal collaterals called Moyamoya vessels. It was known that MMD mostly occurs in children in Asia, and the hemorrhage rate is higher among adults than children. However, recent epidemiologic studies of Asians and Westerners revealed that patients with MMD are older and more often ischemic or asymptomatic than previous studies indicated.

One regional, all-inclusive data set of newly registered patients with MMD in Hokkaido (Japan, 2002 to 2006) showed that the percentage of patients less than 10 years of age at onset was 15% (compared to 48% in previous studies), and the highest peak was observed at 45–49 years. The data also revealed that the
percentage of cases with ischemia increased to 57.4%. Only 21% (previously 42%) of adult MMD patients were hemorrhagic. Risk factor control, aggressive medical management (including Statins) and stent placement (in selected patients) are important for preventing stroke in patients with ICAS. The pathophysiology of MMD is still unknown, and no medication can stop or reverse its progression. Several case series consistently showed that the role of stenting in MMD is highly questionable and is associated with a high rate of symptomatic re-stenosis/occlusion. Revascularization surgery remains the mainstay of treatment for MMD, whereas recent guidelines do not recommend bypass surgery for ICAS. Therefore, differentiation of MMD from ICAS is important for treating patients with intracranial occlusive disease.

It is also female predominance. Besides sex, race and ethnicity, risk factors associated with intracranial atherosclerosis include hypercholesterolemia, diabetes mellitus, cigarette smoking and hypertension.

Three modalities of treatment considered for intracranial atherosclerotic disease include; medical therapy with Aspirin vs. Warfarin, endovascular revascularization with angioplasty and stent, and extracranial-intracranial bypass surgery. WASID (Warfarin Aspirin Symptomatic Intracranial Disease) trial demonstrated that Aspirin was as effective as and safer than Warfarin for preventing stroke in patients with symptomatic intracranial stenosis. However, neither therapy was particularly effective, especially in patients with more severe stenosis (70%-99%) and recent symptoms.

As shown by Warfarin–Aspirin symptomatic intracranial disease (WASID) study, the risk of recurrent ischemic stroke was still high in patients with intracranial artery stenosis even after Aspirin therapy and standard treatment of vascular risk factors. The overall rate of any stroke or death in 1 year was 22% in WASID for patients with 50–99% stenosis which can cause disability in nearly half of these patients. In particular, for patients with a high degree of stenosis (≥70–99%), the ischemic stroke recurrence rate in 1 year was 18%.

The Warfarin-Aspirin Recurrent Stroke Study (WARSS) and Warfarin-Aspirin Symptomatic Intracranial Disease Study (WASID) trials showed the poor effectiveness of medical management of IAS. This is one of the reasons why transluminal angioplasty and vascular endoprothesis arise as useful therapeutic tools.

The first randomized trial to evaluate endovascular therapy for intracranial stenosis was SAMMPARIS (Stenting and Aggressive Medical Management for Preventing Recurrent Ischemic Stroke) trial. Enrollment in SAMMPARIS was stopped early because of the higher-than-expected rate of periprocedural stroke in
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stenting group (14.7% in 30 days including 10.2% ischemic stroke and 4.5% hemorrhagic stroke).

Criticisms of SAMMPARIS soon followed. One particular concern involved technical aspects of the self-expanding stent used in this trial which required an over-the-wire exchange technique after balloon angioplasty, the balloon is removed over long exchanged wire and the stent advanced subsequently and deployed. In contrast, a balloon mounted stent requires crossing the lesion and a single time for simultaneous angioplasty and stent deployment. The stent system used in SAMMPARIS trial may theoretically increase the risk of hemorrhagic stroke from wire perforation during the exchange or ischemic stroke from crossing the lesion after angioplasty for stent deployment. So, some authors have suggested these periprocedural risks could be lowered by delivering and deploying a balloon-mounted stent in a single-step procedure that leaves less residual stenosis. Consequently, the first randomized trial to use balloon-mounted intracranial stent VISSIT (Vitesse Intracranial Stent Study for Ischemic Stroke Therapy) which had similar eligibility criteria to SAMMPARIS including some sites in China and Europe was done but enrollment was stopped early after only 112 patients were randomized because of higher- than-expected rate of stroke in stenting group. The periprocedural stroke rate in VASSIT was 25.8% in 30 days (17.2%, ischemic stroke and 8.6% hemorrhagic stroke).

The SAMMPRIS trial suggested that aggressive treatment was superior to endovascular stenting in patients with severe symptomatic intracranial atherosclerotic stenosis (ICAS) due to high complication rates in patients in the stenting group. Given that 12.2% patients failed aggressive medical therapy in the SAMMPRIS study, it is imperative to perform a multicenter prospective registry study of stenting for patients with ICAS in China. This study aims to evaluate the safety and efficacy of endovascular stenting for patients with symptomatic intracranial artery stenosis and poor collaterals in China and to identify the characteristics of the population that would benefit the most from endovascular stenting in Chinese patients and reported the morbi-mortality about 11.5% which was similar to the last series published.

Based on these trials, there are some recommendations by AHA for the treatment of ICAS as follows:

- For patients with a stroke or TIA due to 50% to 99% stenosis of a major intracranial artery, Aspirin is recommended as preferred to Warfarin (Class I; Level of Evidence B).
- Endovascular revascularization by intravascular balloon angioplasty and/or stenting may be considered for patients with symptomatic severe
intracranial stenoses (70% luminal narrowing) despite optimal medical therapy (Class IIb, Level of Evidence C).
- For patients with stroke or TIA due to 70% to 99% stenosis of a major intracranial artery, extracranial-intracranial bypass surgery is not recommended (Class III; Level of Evidence B).

Due to intracranial artery morphology which has thin media without robust adventitia, nearly absent external elastic lamina and vasa vasorum any interventional procedure to overcome the stenosis has own special risks. So, case selection is an important aspect for treatment strategy in these groups of arterial stenotic disease.

So, for determining the efficacy of endovascular treatment, two important factors should be considered:
1. Patient’s related factor
2. Endovascular feasibility

Regarding the first issue, endovascular treatment is recommended only for patients with more than 70% stenosis of major intracranial vessels and refractory to medical therapy, previous stroke or TIA, neurologic symptoms referable to the target lesion, presence of symptoms during the 6 months prior to treatment and minimum vessel diameter of 2 mm.

**Endovascular feasibility depends on a few factors including stenotic lesion character which is classified by Mori into three types:**
1. Type A: <5mm in concentric or moderately eccentric, smooth stenosis
2. Type B: 5mm to 10mm in length, extremely eccentric or angulated (>45°), or irregular stenosis, or total occlusion (<3 months old)
3. Type C: >10mm in length, extremely angulated (>90°) stenosis, or total occlusion (>3 months old), or lesion with a number of neovascultures all around.

**Other important factors considering endovascular treatment are vascular access which also has its own classification:**
- Type I: mild-to-moderate tortuosity and smooth access
- Type II: severe tortuosity and/or irregular arterial wall
- Type III: excessively severe tortuosity

So, patient selection according to above criteria is very important in endovascular cerebral revascularization with stent and angioplasty.
Accepted procedure consists of percutaneous transluminal balloon angioplasty with gateway balloon and deployment of wingspan stent which is self-expandable
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stent with low radial force. Balloon should be 0.5-1mm smaller than vessel diameter and stent should be 0.5-1mm larger. Cautions should be taken during balloon angioplasty due to vessel dissection that may occur in 20%, acute occlusion, acute vessel recoil and post residual stenosis. So, for better outcome, deployment of stent is advisable which has some advantages including avoiding plaque dislodgement, avoiding intimal dissection, avoiding elastic vessel recoil, avoiding plaque re-growth and avoiding late re-stenosis. Recently, cerebral revascularization with balloon expandable stents is also tried in many cases with good results. This includes using stents that are equal to or slightly less than diameter of the adjacent distal normal vessel. The length of stent should be slightly more (1-2mm) than the length of lesion. The balloon is then inflated gradually at 6 to 9 atm depending on the type of stent and its location. After technical success was achieved, defined as ≤20% of residual stenosis, the balloon is withdrawn and the micro-guide wire is left in the original site for a 30-minute observation until general anesthesia is discontinued. After ensuring angiographical patency and evaluating the National Institutes of Health Stroke Scale (NIHSS) score, the micro-guide wire and guiding catheter will be withdrawn. Residual stenosis at the end of procedure defined as more than 20% stenosis is due to balloon sub-expansion and elastic recoil. Early detection of complication could be life-saving. These complications include: Ischemic stroke, intracerebral hemorrhage, hyperperfusion syndrome, snow plow effect and re-stenosis.

Timing of ischemic complication could lead us to determining the cause and mechanism of this type of complication. Acute intra-operative strokes that manifest immediately after stent placement may be the result of a “snow plowing” effect, thromboembolism, acute occlusion of perforator ostia by stent struts or in situ thrombus. Early delayed strokes that develop within the first few days after stent placement may be related to in-stent thrombus, occlusion of perforator ostia or thromboembolism. Late delayed strokes (≥2 weeks after stent placement) may be related to all of the above factors in addition to another potential mechanism caused by intimal hyperplasia within and around perforator ostia.
Cerebrovascular accident poses a great burden on population of different age, sex and ethnicity (1, 2). Hypertension is one of the most important risk factors of stroke and the major cause of hemorrhagic cerebrovascular accident (CVA) (3, 4). Treatment of hypertension remains one of the most effective primary preventive strategies which should be tailored both logically and systematically (5). On the other hand, handling hypertension in a patient with recent or old CVA and secondary prevention of recurrence of the disease is of the same importance. In this brief review, we have tried to cover main questions that may arise in management of hypertension both before and after occurrence of cerebrovascular accident.

Treatment of Hypertension as Primary Prevention of Stroke

By definition, levels of blood pressure above 140/90 mm Hg are considered as hypertension. Prehypertension –i.e. levels above 120/80 but below 140/90- is also associated with increased risk of stroke (6). Interestingly, isolated systolic hypertension –i.e. systolic blood pressure above 140 mm Hg and diastolic blood pressure blow 90 mm Hg- is linked with increased risk of stroke in the population aged above 50 years (7, 8).

Measuring blood pressure accurately is one of the greatest concerns of clinicians. So far, ambulatory or home blood pressure monitoring has proved more reliable than office blood pressure measurements (9).

Lifestyle modification is the initial treatment step offered to all hypertensive patients. These modifications generally include: adoption of a healthy diet, avoidance of tobacco and alcohol, weight reduction and maintenance of ideal body weight, regular physical activity and dietary sodium restriction to less than 100 mmol/day (10). Adherence to all or most of these modifications may not be possible for all hypertensive patients. Repeated counselling sessions may help the patients with acceptance and compliance.

Different classes of antihypertensive medications can be used for treating hypertension. These include: diuretics, angiotensin converting enzyme inhibitors (ACEI) and aldosterone receptor blockers (ARB), calcium channel blockers, beta-adrenergic receptor blockers, alpha-adrenergic receptor blockers, central alpha agonists and vasodilators. Choosing an appropriate class of drug depends on careful evaluation of patients' condition and cardiovascular risk factors.
According to recommendations of the Eighth Joint National Committee (JNC 8), first choice of antihypertensive medication should be made among these classes: thiazide diuretic, angiotensin converting enzyme inhibitors, angiotensin receptor blockers or calcium channel blockers. The committee did not recommend use of alpha and beta-adrenergic blockers as first line antihypertensive therapy as these classes have been linked to higher incidence of death from cardiovascular events (10). Beta-adrenergic blockers do not effectively protect against stroke; they were found to be associated with higher incidence of stroke (11).

Although for primary prevention of stroke, it is important to lower blood pressure with any class of hypertensive medications that would be effective, some classes are of have priority in special populations. In adult patients suffering from chronic kidney disease including diabetic nephropathy and proteinuria, ACEI or ARB should be the first choice. These classes improve kidney function and reduce proteinuria in such patients. Moreover, they can be added to diuretics to improve their antihypertensive efficacy when needed.

In older age group –i.e. 75 years and older- ACEI, ARB, calcium channel blockers or thiazide diuretics can be used as first choice. However, diuretics and calcium channel blockers would result in less variable blood pressure levels in this age group (10).

For patients with severe hypertension –i.e. levels above 160/100 mm Hg- initial treatment should begin with two drugs. For others, if blood pressure goal cannot be reached within a month of initiating first choice and a moderate dose of first drug is administered, one may add a second drug. A third choice may be added if problems with control of blood pressure still persist. The most reasonable choice would be a diuretic, an ACEI or ARB and a calcium channel blocker, in this condition. Care must be taken not to use ACEI and ARB classes together.

**Goals of antihypertensive Therapy**

In adult general population younger than 60, the goal of antihypertensive therapy is reduction of blood pressure to a level below 140/90 mm Hg. Same goal is recommended for all age groups with cardiovascular disease, stroke or multiple risk factors. The body of evidence supports lowering blood pressure to reach levels below 150/90 mm Hg in general population aged 60 years and older to prevent stroke (10).

For patients with isolated systolic hypertension, medical treatment should be initiated if systolic blood pressure is above 160 mm Hg regardless of age. For those with systolic blood pressure levels between 140-159 mm Hg, treatment should be individualized and considered in those patients with other risk factors e.g. diabetes or smoking (12).
Treatment of Hypertension as Secondary Prevention of Stroke

Many patients with acute stroke will experience elevations in blood pressure in first 24 hours after the cerebrovascular event. These hypertensive emergencies will be discussed in three clinical situations:

*Acute ischemic stroke*: if blood pressure rises to a level above 220/120 mm Hg, reduction of mean arterial pressure by 10-15% would be desirable within an hour.

*Acute ischemic stroke and thrombolytic therapy indicated*: if blood pressure is above 185/110 mm Hg, reduction of mean arterial pressure by 10-15% would be desirable within an hour.

*Cerebral hemorrhage*: if systolic blood pressure is above 180 mm Hg or mean arterial pressure is above 130 mm Hg, decreasing blood pressure to levels less than these within an hour is recommended (13).

Intravenous Labetalol is the drug of choice in these acute conditions. Nicardipine and Nitroprusside can also be used alternatively. Strict monitoring of blood pressure is recommended while handling these emergency conditions as rapid or more fall in blood pressure results in adverse cerebral outcomes.

After first few days of stroke (first 24 to 72 hours) oral antihypertensive medications can be safely started if there is no other contraindication (13). For prevention of recurrent stroke, beta-adrenergic blockers are not effective and ACEI and ARB drugs are of low efficacy in secondary prevention of stroke unless used with a diuretic (12).

Blood pressure goals for prevention of recurrent stroke are not well established. Currently, same blood pressure goals as primary prevention are well accepted (12, 13).

Multiple Choice Questions:

1. Consider a 63 year old patient with diabetes and hypertension. He does not smoke and does only receive medications for diabetes. What is your first choice of antihypertensive drug?
   a) Amlodipine   b)Valsartan   c)Metoprolol   d)Furosemide
   correct answer: b

2. Which drug is not recommended for controlling hypertension in acute stroke?
   a) Nitroprusside   b)Nicardipine   c)Labetalol   d)Losartan
   correct answer: d

3. A 50 year old woman has been admitted in intensive care unit with acute non-traumatic intracerebral hemorrhage of 8 hours duration. Currently her blood pressure is 210/135 mm Hg. How would you manage hypertension in this case?
   a) immediately decrease systolic blood pressure to less than 160 mm Hg
b) decrease systolic blood pressure to less than 180 mm Hg within one hour

c) immediately decrease mean arterial blood pressure by 15%

d) decrease mean arterial blood pressure by 20% within one hour

correct answer: b

References


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Endovascular Treatment of Extracranial Carotid Artery Disease: A retrospective study of 7 year experience at northwest of Iran

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Purpose: Extracranial carotid artery disease accounts for approximately 25% of ischemic strokes. Carotid artery angioplasty and stenting (CAS) has steadily developed for stroke prevention. We present our results of 7 years of experience in angioplasty and stenting of extracranial carotid artery stenosis with embolic protection devices.

Materials and Methods: Between 2009 to July 2015, 651 patients with symptomatic carotid stenosis of at least 50%, and asymptomatic at least 70% stenosis by angiography underwent CAS in our clinic. Clinical files of patients were reviewed based on age, clinical symptoms, occurrence of stroke, myocardial infarction (MI), death from any cause during a 30-day peri-procedural period, post-procedural ipsilateral stroke within follow-up period and rate of restenosis.

Results: There were 300 female and 351 male with mean age 76 years (ranging from 42-94 yr). 599 patients (92%) had symptomatic stenosis and 52 patients (8%) were asymptomatic. The rate of stroke, MI and death during peri-procedural period was 1.8% (n=12), 1.38% (n=9), and 1.68% (n=11) respectively. Initial follow-up studies were obtained in 98% (n=638) at first month and 73% (n=475) beyond 30 days with a mean of 26 months (ranging from 1-45 month). Rate of hemodynamically significant restenosis at 6, 12, 18, and 24 months was 0%, 0.6% (n=4), 1.2% (n=8), 1.5% (n=10) and 1.8% (n=12) by color Doppler ultrasound. Post-procedural ipsilateral stroke within follow-up period occurred at 2.3% (n=15).

Conclusion: CAS is continually developing into a safer and more efficacious therapy for extracranial carotid artery stenosis. The use of CAS while optimizing current medical treatments, will provide the greatest likelihood of minimizing poor patient outcomes.
The Effect of ketogenic diet on stroke

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Ischemic stroke is a leading cause of death and disability in the world. Many mechanisms contribute in cell death in ischemic stroke. Ketogenic diet which has been successfully used in the drug-resistant epilepsy has been shown to be effective in many other neurologic disorders. The mechanisms underlying of its effects are not well studied, but it seems that its neuroprotective ability is mediated at least through alleviation of excitotoxicity, oxidative stress and apoptosis events. On the basis of these mechanisms, it is postulated that ketogenic diet could provide benefits to treatment of cerebral ischemic injuries.

Aim of this study is to evaluate ketogenic diet neuroprotective effect on ischemic stroke

**Methodology:** 24 male rats with weight of 200-240 grams in 3 groups, control, sham and main groups (8 rats in each group) were selected. This study was experimental and interventional type. These rats have been teaching tests of step, beam, and cylinder. In the end of 3th day they have been examined at first blood level of ketones registered. Then ketogenic diet that with carbohydrate to fat and protein ratio was 4/1 with MCT oil was used in the main group. Ten days this diet to be continued. And ketones levels were assessed (in 2th, 7th and 10th days). Stroke was induced with ET-left intrastriatal. The tests (step, beam and cylinder) were performed in 3 groups and the results have been compared and analyzed with SPSS FOR WINDOWS, Tukeys’s test in ANOVA software.

Results: Motor function was tested in rats by beam and cylinder test and step adjusting. In ketogenic diet group it was shown that motor function was better meaningfully after stroke than the other two groups.
Can mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) syndrome begin in adulthood, without significant previous history?

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Abstract:

Introduction: Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS) is a mitochondrial metabolic disease with multisystem involvement which can cause stroke-like episodes and status epilepticus.

Case Report: A 48 years old female with history of early fatigueability, migraine-type headaches and bilateral sensory-neural hearing loss presented with two episodes of serial seizures. On admission she were affected by Wernicke aphasia and then right hemiparesis. Investigations showed elevated arterial lactate and ragged red fibers on muscle biopsy.

Conclusion: Several cases of adult-onset MELAS syndrome were reported. This syndrome should be considered in patients with stroke-like events in adults without cerebrovascular risk factors and difficult-to-treat seizures.

Key words: MELAS syndrome, stroke-like episode, status epilepticus, adult
Assessment of admission platelet level and age, in responsiveness to Aspirin in ischemic stroke patients; one year follow up.

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Introduction: Stroke is seated in the first rank of leading cause disability worldwide. Aspirin inhibit the platelet aggregation and were used as secondary preventing in ischemic stroke. The aim of present study is evaluating possible impact of patient platelet level; age and sex on aspirin efficacy for preventing recurrent stroke or TIA.

Materials and Method: A retrospective cohort study conducted on the patient with ischemic stroke of TIA whom admitted in Rasul-e-Akram Hospital of Tehran, Iran, during 2013. All data including demographic variables and clinical profile on admission and discharge time, have been recorded in a checklist for each patient. After three months to one year of admission, all patients have been called by expert for follow-up about the symptoms of renewed TIA or stroke and other problems. The exclusion criteria were previous consumption of antiplatelet before stroke event, discharge with prescription of other anticoagulants except alone aspirin, and lack of follow-up data.

Finally four balanced age group composing under 55, 55-70, 70-80, and over 80 years were defined. For analysis, SPSS edition 16th statistical software and the C5 decision tree is used.

Results: From 231 patients diagnosed as ischemic stroke, 122 patients (88%) met the criteria. On follow up, 2.60% reported renew Stroke, 4.60% renew TIA and 6.49% admitted to hospital due to vascular diseases. In 4 age groups, mean ± SD of admission platelet level were 226.255±60.5, 228.39±79.8, 202.17±68.3 and 199.55±67.4 respectively. Base on C5 decision tree, Aspirin had no significant effect on patients over 80 years with platelet below 155/mm³ (p<0.001 according to Cochran–Mantel–Haenszel test). This result was not banded to patient’s gender.

Conclusion: on follow up of the patients with ischemic stroke or TIA, we found that Aspirin had no significant effect on patients over 80 years with platelet below 155/mm³. For substitution of aspirin with another medication in these patients, more studies are required.
Patient characteristics of posterior reversible encephalopathy in Isfahan, Iran

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Introduction: Posterior reversible encephalopathy syndrome (PRES) is a neurotoxic procedure resulting from endothelial dysfunction associated with several etiologies including systemic infection, transplantation, pregnancy, autoimmune diseases, and malignancy/chemotherapy. A diagnosis of PRES should be considered in the setting of acute neurological symptoms in patients with renal failure, blood pressure fluctuations, use of cytotoxic drugs, autoimmune disorders, or eclampsia. Typical imaging findings of PRES consist of vasogenic edema predominantly involving peripheral white matter within parieto-occipital and posterior frontal regions. In severe forms, PRES might cause substantial morbidity and even mortality, most often as a result of acute haemorrhage or massive posterior fossa oedema causing obstructive hydrocephalus or brainstem compression.

Methods: All PRES patients who referred to neurologic ward of Alzahra and Kashani hospitals from February to July 2015 included in this cross-sectional study. Patient’s demographic data gathered at first and their risk factors, symptoms and MRI findings evaluated and registered by a neurologist.

Result: Totally 19 PRES patients registered. 5 patients were male and 14 ones were women. Their mean age was 35.27 ± 14.56 years. Their prevalence of risk factors were hypertension (31.6%), eclampsia (21%), Systemic Lupus Erythematous (31.6%), chronic renal failure (49.3%). The most symptom was chronic headaches and serial seizures (63.2%). The most prevalent MRI finding was parieto-occipital lesions (52.6%).

Conclusion: Although our knowledge of this syndrome has grown, a lot remains to be learned. Pathophysiological studies are needed to unravel the mechanisms leading to endothelial dysfunction and increased blood–brain barrier permeability.

Keywords: Risk factor, posterior reversible encephalopathy, Isfahan.
The effect of task-oriented exercises on balance in stroke patients

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Abstract

Background: One of the most common disability after stroke is impaired balance; therefore improving balance for everyday activities through rehabilitation treatment is essential. There are various treatment approaches for rehabilitation of stroke patients. Task-oriented practice as a new approach improves balance, movement and coordination. The aim of the present study was to evaluate the effect of task-oriented practice on balance in stroke patients.

Methods: Ten stroke patients participated in this study. They were treated during twelve-sessions of task-oriented exercises. Functional balance was investigated using the Berg Balance Scale and Static balance was evaluated by a Zebris platform pedobarograph tool in this study. The subjects were tested barefoot during bilateral leg stance conditions with open eyes. The outcome measurements included measurement of the center of pressure path line length and confidence ellipse area before and after the treatment.

Results: In double leg stance, data analysis revealed that the COP path line length, confidence ellipse area and Berg Balance Scale all showed a significant improvement after task-oriented training in the stroke subjects (P ≤ 0.01).

Conclusion: Task-oriented training can establish a significant improvement in postural sway parameters and functional balance in stroke patients.

Key words: Stroke, Hemiplegia, Postural Balance, Rehabilitation
Cost-Effectiveness Analysis of the Unfractionated Heparin versus Low Molecular Weight Heparin in Hospitalized Patients with Stroke due to Atrial Fibrillation in Iran

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Abstract

Introduction: Patients with Atrial Fibrillation (AF) make a unique group of strokes. Unfractionated Heparin (UFH) and Low Molecular Weight Heparin (LMWH) are among medications used by physicians for preventing blood coagulation. The present study was done aiming at analyzing the cost-effectiveness of LMWH versus UFH in hospitalized patients with stroke due to AF from Iranian population perspectives.

Title and Structure: In this study, decision tree model was used. Data on costs were collected through interviews with patients with stroke due to AF and their companions, using data collection forms including the medical direct costs, non-medical direct costs, and indirect costs three months after the injection of medications. Effectiveness criterion was prevention of new stroke recurrence. Therefore, results of this study were expressed as cost per new stroke prevention. Finally, a one-way and probabilistic sensitivity analysis was conducted to examine the strength of the results.

Results: Our analysis results showed the effectiveness of preventing a new stroke by LMWH more than UFH. Also, UFH medical direct costs, non-medical direct costs and also indirect cost were more than LMWH. Cost-effectiveness ratio was estimated 150, 201, 26$ per effectiveness.

Conclusion: The results of the cost–effectiveness analysis of LMWH versus UFH showed that LMWH is a dominant strategy for patients with stroke due to AF from Iranian population perspective.

Keywords: Cost-effectiveness analysis, Stroke, Low molecular weight heparin, Unfractionated Heparin.
Effects of Edaravone on Ischemic Stroke induced by MCAO in male rats

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Background: A novel free radical scavenger, edaravone, has been demonstrated to exert a neuroprotective effect and improve outcomes in acute ischemic stroke, but there have been few clinical studies regarding its long term use. Therefore, the aim of this study was to evaluate edaravone effects on behavioral and histological assessments of induced stroke in male rats.

Methods: 14 adult male Sprague Dawley rats were subjected to middle cerebral artery occlusion (MCAO) for 1 hour. The control group received saline whereas treatment group received 3 mg/kg twice daily edaravone for 14 days. We evaluated the behavioral recovery of rats with using neurological deficit score (NDS) and pole tests 2 hours after surgery and then daily. After fixation, the rat brains were serially and coronally sectioned and stained with cresyl violet. The volume of the brain and infarction area was evaluated by using stereological methods.

Results: The pole test showed that edaravone significantly decreased both time to turn and descending time in comparison with control group. These parameters also significantly decreased in day 14 in comparison to day 1. Evaluation of NDS test showed non-significant decrease in both group with time, however, this decrease was more obvious in edaravone treated rats. Histological and stereological evaluation showed no difference between the total volume of brain. However, edaravone significantly decreased infarction percentage in comparison to control group (P <0.001).

Conclusion: Edaravone decreased size of infarction and improved behavioral evaluation of stroke-induced in rats and could be suggested for using with other prescriptions.

Key word: stroke; edaravone; MCAO; brain ischemia;
Demographic and Technical Risk Factors of 30-Day Stroke, Myocardial Infarction, and/or Death in Standard- and High-Risk Patients Who Underwent Carotid Angioplasty and Stenting

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Abstract

Background: Carotid angioplasty and stenting (CAS) is an accepted treatment to prevent stroke in patients with carotid artery stenosis. The purpose of this study is to identify risk factors for major complications after CAS.

Materials and Methods: This is a prospective study that was conducted at Shiraz University of Medical Sciences in southern Iran from March 2011 to June 2014. Consecutive patients undergoing CAS were enrolled. Both standard- and high-risk patients for endarterectomy were enrolled. Demographic data, atherosclerotic risk factors, site of stenosis, degree of stenosis, and data regarding technical factors were recorded. Thirty-day stroke, myocardial infarction, and/or death were considered as the composite primary outcomes of the study.

Results: A total of 251 patients were recruited (mean age: 71.1 ± 9.6 years; male: 65.3%). Of these, 178 (70.9%) were symptomatic, 73 (29.1%) were diabetic, 129 (51.4%) were hyperlipidemic, 165 (65.7%) were hypertensive, and 62 (24.7%) patients were smokers. CAS was performed for left internal carotid artery (ICA) in 113 (45.4%) patients. Fourteen (5.6%) patients had sequential bilateral stenting. Mean stenosis of operated ICA was 80.2 ± 13.8%. An embolic protection device was used in 203 (96.2%) patients. Pre- and postdilation were performed in 39 (18.5%) and 182 (86.3%) patients, respectively. Composite outcomes were observed in 3.6% of patients (3.2% stroke, 0% myocardial infarction, and 1.2% death). Left-sided lesions and the presence of diabetes mellitus were significantly associated with poor short-term outcome (p = 0.025 and p = 0.020, respectively).

Conclusion: There was a higher risk of short-term major complications in diabetic patients and for left carotid artery intervention.

Key Words: Stroke, Carotid artery angioplasty and stenting, Outcome, Cerebrovascular disease
Study of the Efficacy, Safety and Tolerability of Low Molecular Weight Heparin vs. Unfractionated Heparin as Bridging Therapy in Patients with Embolic Stroke due to Atrial Fibrillation

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Abstract

Background: Ischemic stroke due to atrial fibrillation (AF) needs rapid treatment with unfractionated heparin (UFH) to prevent recurrent stroke but data on administration of low molecular weight heparin (LMWH) instead of UFH are limited. We compared LMWH and UFH, focusing on safety, efficacy, and tolerability in ischemic stroke due to AF.

Method: This study was a randomized single-blind clinical trial in patients with acute ischemic stroke due to AF who were eligible for receiving warfarin and randomly treated with weight-based LMWH subcutaneously every 12 hour, or continuous intravenous UFH and followed for 3 months. The primary efficacy endpoints were occurrence of new ischemic stroke, myocardial infarction and death. The primary safety endpoints were CNS and non-CNS hemorrhages (safety-related outcome). Secondary endpoints were time to achieve therapeutic level of INR (international normalized ratio) as efficacy-related outcome and heparin side effects (other than bleeding) as safety-related outcome.

Results: In 74 patients, mortality rate was 2.7% in hospital course and 13.5% after 3 months in LMWH group vs. 8.1% and 21.6% in UFH group, respectively. New embolic stroke was seen in 5.4% of patients receiving UFH but not in LMWH group. Hemorrhagic transformation was seen in 8.1% in LMWH group vs 13.5% in UFH group which had a strong association with mortality rate in hospital course (p-value: 0.007). Both groups had similar incidence of non-CNS hemorrhage. Patients receiving LMWH achieved INR level after 5.3+/2.6 days compared with 6.1+/2.3 days in UFH group.

Conclusion: Our study shows that subcutaneous LMWH twice daily has the same efficacy and safety compared with UFH in this group of patients and can be used with more convenient route of administration compared with intravenous UFH.

Keywords: Ischemic Stroke, Atrial Fibrillation, Bridging Therapy, Low Molecular Weight Heparin, Unfractionated Heparin
Psychogenic pseudostroke, warning to use of thrombolytic (rtPA)

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Psychogenic pseudostroke (PS) is when acute symptoms are suggestive of a stroke but in reality, of psychogenic origin. Little information exists on psychogenic pseudostroke (PS) epidemiology, demographics, and psychopathology of PS is scare, in an area of wide spread thrombolytic use, neurologist need guidance on how to approach these encumbrances. All three forms of psychogenic symptoms (malingering, factitious and functional symptoms), can manifest as PS. Malingering is simply fabricating or exaggerating symptoms for the purpose of secondary gain, A factitious stroke is when individual is feigning a stroke to receive attention or sympathy from health care providers or family members. The individual is feigning a stroke to receive attention or sympathy from health care providers or family members. The individual in both cases is fully aware of deceptive scheme and the disingenuousness of his or her malady functional neurologic symptom (formely, conversion) is an unconscious state where on individual, with or without a defined reason, present with acute neurologic deficit that is deemed to be nonorganic, and be expression of an underlying psychological conflict or need, for appropriate therapy, especially if the patient truly suffers from an underlying psychopathology, a correct differentiation between these three may be necessary. The majority of PS cases present with some degree of motor weakness. PS is much more common than the medical community admits. The reason for rarity of epidemiological data and exact incidence of PS are under reporting and over reporting of PS. In a study of stroke mimicks involving 355 patients, no data on psychogenic stroke-like symptoms were provided. This is another example of under reporting where the existence of PS as stroke mimicker is ignored, purpose fully or unintentionally.

Diagnosis:
History and physical examination: PS is a diagnosis of exclusion that requires concurrence of physical exam and diagnostic testing. Redflages suggesting PS are: Previous history of psychogenic symptoms, history of psychiatric disorders, presence of emotional triggers, symptoms triggered or ameliorated by placebo, a long history of recurrent TIAs despite no clear mechanism and adequate stroke prevention therapy. These elements help to the diagnosis but physical exam and diagnostic testing are completed.
The most important features of psychogenic are inconsistency of the examination absence of objective signs, distractibility and La belle Indifference. caution must be taken with patients having hemineglect, Hoover sign is the most sensitive and specific maneuver in delineating psychogenic weakness. Adductor sign use to synergic contraction, Babinski trunk-thigh and Give Way or collapsing weakness are another tests, Astasia-Abesia, dramatic gait, hypoesthesia of non anatomical distribution and splitting of vibratory sensation are useful and must validate with diagnostic studies like EEG, MRI, MRA and MRV

**Management of PS:** Diagnosis and management of PS are difficult factors that influence diagnosis (or misdiagnosis) and management of PS may be legal, ethical moral or financial: The first step is discussion with the patient and the family, some physicians express of PS boldly and some by witty explanations and some on obscure diagnosis such as mini stroke. If PS is suspected a confirmatory MRI is an indispensable strategy, the symptoms of a true stroke may be exaggerated by the patients because of psychogenic factors, matters become more complicated when the DWI reveals incidental brain infarct, The biggest dilemma in diagnosis and management of PS is prescription of rtPA. when the diagnosis of PS is equivocal but leans toward PS, the risk of intracerebral hemorrhage may afflict the neurologist, a team of neurologists, psychiatrists, psychologists and social-workers can prevent recurrent psychogenic episodes that carry a high cost.

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Stroke mimics and chameleons. study of 400 cases and review of articles

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Introduction: There are several subtypes of stroke and also some non vascular disorders may have clinical pictures that appear identical to strokes, unusual clinical pictures that may result from stroke that names is stroke chameleons, strokes that take on the appearance of something else, misclassified stroke used to described patient s initially thought to have stroke but later after advanced neuromaging techniques move into diagnostic stroke subtypes. The mimics include both processes, occurring within the CNS and systemic events. Distinguishing these non cerebrovascular stroke mimics from stroke is important in this area of interventional stroke therapies like rtPA with potential adverse effects.

Background and studies: A prospective study review 800 consecutive patient admitted to the emergency department, found that in the initial diagnosis of stroke incorrect in 13% of patients. The most common misdiagnosis resulted from unwitnessed seizures with the postictal state being misdiagnosed as stroke in 5%, most of these patients had postictal confusion and transient focal neurological signs including hemiparesis, monoparesis, ophthalmoparosis or hemisensory deficits. 1% of patients admitted with a diagnosis of acute stroke have CNS tumors. There was a small patients with a misdiagnosis of stroke that had radical nerve palsy, vertigo, encephalitis, hepatic encephalopathy, and other medical condition including cardiac failure, at consecutive patients presenting to an emergency department over a two year period to determine on initial diagnosis of stroke and discriminate between stroke and stroke like pictures, the definition of stroke was the sudden onset of a focal deficit by history or physical examination lasting more than one hour. The initial diagnosis was made before computed tomographic study of 400 patients initially diagnosed as stroke, 19% were found to have mimics. The majority of the mimics were unrecognized seizures with postictal deficits (17%, of mimics) systemic infections (17%) brain tumor (15%) and toxic metabolic disturbances (13%). Other diagnosis were vertigo, trauma, subdural hematoma, and syncope. Analysis showed that decreased level of consciousness, and normal age movements increased the odds of a stroke mimic being present while abnormal visual fields. Initial diastolic blood pressure greater than 90mm Hg, arterial fibrillation, and history of angina decreased the odds of mimic being present.
Kothari reviewed admission diagnosis of stroke for over four hundred patients, of the patients misclassified at admission as having ischemic stroke or TIA, final diagnosis included paresthesia or numbness of unknown cause, seizure, complicated migraine, peripheral neuropathy, cranial nerve neuropathy and psychogenic paralysis.

The incidence of stroke mimics upon the time that the acute stroke syndrome is assessed, when initial assessment was made after history and physical examination alone, stroke mimic was present in 19% of cases, when the assignment of stroke syndrome was made after routine laboratory work and CT scanning the incidence of stroke mimic was 4% and with employed MRI, the incidence mimics dropped to 1-2%.

**Conclusion**: The clinician recall that ischemic stroke does have uncommon manifestations. Acute stroke should be considered in neurologic syndromes where abrupt onset of symptoms, particularly, patients with cerebrovascular risk factors.

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Use of Virtual reality to improve balance in patients after stroke

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Introduction: Balance deficits are frequently seen in patients after stroke. The less of balance in most cases results in a fall and consequently seen in patients after stroke. Reduced balance control is a major obstacle to achieving independence in activities of daily living after stroke. Balance control is complex and multifactorial. Different rehabilitation approaches like physiotherapy and force platform therapy, aim to improve balance after stroke. Virtual reality as a novel technology is rapidly becoming a popular intervention for improving balance. Virtual reality has been defined as the use of interactive simulations created with computer hardware and software to present users with opportunities to engage in environments that appear and feel similar to real-world objects and events. Virtual reality offers augmented feedback about performance with visual, vestibular, and somatosensory input, enables individualized repetitive practice of balance control, and stimulates both motor and cognitive process simultaneously. Virtual reality technology is an ideal tool to improve balance. For investigated about effectiveness of virtual reality for balance improvement in patients after stroke, and offer future guide for virtual reality use after stroke, in 2015 zhen li et al to evaluate the effectiveness of virtual reality interventions for improving balance in people after stroke done Systematic review and meta-analysis.

Methods: Sixteen studies involving 428 participants were included. Only randomized controlled studies testing the effects of virtual reality interventions on balance after stroke were included. Studies comparing two or more exercise interventions. The effectiveness of virtual reality exercise interventions for balance versus usual care was assessed, a score of 3 or above meant a good study criteria included.

Outcome measures: The primary outcomes included objective balance measure scales and tests. The secondary outcomes included Force Platform Indicators.

Results: Sixteen randomized controlled studies were included in the review. Four studies included patients with acute/subacute stroke and twelve targeted patients with chronic stroke. The majority of studies compared the virtual reality intervention with a comparable alternative intervention. Results indicate that virtual reality had a statistically significant effect on Berg Balance Scale score.
Conclusions: This meta-analysis indicated that stroke patients who received virtual reality rehabilitation had significant improvements in the Berg Balance Scale and the Timed Up and Go Test than those who did not. Virtual reality therapies are advantageous to conventional therapies in part because of the ability to provide the intensive repetition of meaningful task related activities. Thus virtual reality to improve balance after stroke.
Effect of a care plan based on roys adaptation model biological dimension on stroke patients physiologic adaptation level

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Introduction: Cerebrovascular stroke is a disastrous even which is associated with multiple somatic, functiona, psychological, social and economical consequences, and result in decreased quality of life. After a short while usually sufferers utilize different methods to cope with these difficulties and return to normal life. The goal of this study is to evaluate the physiologic reconditioning of patients by the biological care program.

Methods & materials: 50 patients who previously suffered from stroke and admitted due to that in Isfahan university hospitals were randomly enrolled in the control and case groups of this RCT. Biological care program based on Roys adaption model was initiated. The patients were followed for a month. Patients rehabilitation was evaluated by pre and post intervention questionnaire based on Roys adaption mode. The data were analyzes by 18th edition of SPSS by Chi-Square, independent – T and paired T-tests.

Findings: There was a significant statistical improvement in the mean physiologic adaption scores of the case group over the control groups after the intervention (P<0.001).

Conclusion: We conclude that utilization of the Roys adaption model will increase the physiological adaption rates in stroke patients and could be employed to promote the physiologic adoption in these patients.

Key words: Cerebrovascualr stroke, adaption, care program, Roys adaption model.
Functional Motor Neuron Subtypes Generated from neurosphere drived adipose tissue, a promising protocol for Stroke Recovery

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Introduction: No treatment currently exists to restore lost neurological function after stroke. A growing number of studies highlight the potential of stem cell transplantation as a novel therapeutic approach for stroke. In the current study, showed that RA +GDNF+BDNF a key differentiation factor allowed cultured adipose drived stem cells (ADSCs) to form motor neuron like cells with characteristics corresponding to form functional connections with muscle fibers. Our study provides a new fundamental basis for autologous cell replacement therapy to treat stroke and neurodegenerative disorders.

Material & Method: Rat visceral fat was enzymatically digested to yield rapidly proliferating fibroblast-like cells (ADSCs), a proportion of which expressed the mesenchymal stem cell marker. Cells induced with amixture of motoneuron factors (RA,SHH,GDNF,BDNF) adopted a morphology similar to motoneuron cells. This cells evaluated by Immunocytochemical staining and RT-PCR ; also, the cells of functionality indicated with ability innervated myotubes and release of synaptic vesicles using FM1-43 and flou4.

Result & Conclusion: the treated cells with motoneuron factors expressed markers, HB9,Islet1,oligo2 indicative of differentiation. When co-cultured with C2C12(myotube cells), These cells were established synaptic contacts with muscle like cells and these cells increased in number and neuritis. These results indicate adipose tissue contains a pool of regenerative stem cells which can be differentiated to a motoneuron cell phenotype and functional may be of benefit for treatment of stroke and neurodegenerative disorders.

Key Word: adipose drived stem cells (ADSCs), FM1-43, C2C12
Acute stroke management, thrombolysis, stroke care units, Neurocritical care

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Stroke, Myocardial infarction (MI), pulmonary thromboembolism, deep venous thrombosis and several other pathologies with coagulation as their core event, are now important medical priorities. Stroke and MI are the leading causes of mortality and disability worldwide. The lifesaving treatment for these pathologies is called thrombolysis which is now prescribed by plasminogen activators. To aid this treatment and further knowledge of the mentioned pathologies, various investigations have been conducted for modeling and simulation of coagulation and thrombolysis. This paper is a review of the introduced mathematical equations and simulations for coagulation and thrombolysis.

Medical and computational methods was searched in the databases of PubMed/Medline, science direct, Scopus and google scholar.

Navier-Stokes and continuity equation has been utilized in the coagulation and thrombolysis modeling. Reaction equations of coagulative factors and their kinetic constants were extracted and are presented in the review. Physical and chemical properties of reactants including diffusion coefficient were collected as well.

Methods of mathematical calculations and engineering simulations would be discussed in detail.

Modeling and simulation of coagulation and thrombolysis are in their primary development especially thrombolysis which few studies have been focused on. Their completion requires multidisciplinary brainstorming and research among clinicians, biomedical scientists, mathematicians and simulation engineers; and there is still a long way to go.
Assessment of erythropoietin pretreatment effect on tissue water content after brain ischemia induction in male wistar rat by middle cerebral artery occlusion

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Introduction: One of the major complications of cerebral ischemia is the water content enhancement in brain tissues that increases mortality. Recently, therapeutic strategies focused on preconditioning mechanisms including drug preconditioning. Erythropoietin is a glycoprotein hormone that several studies have shown its anti-inflammatory and antioxidant effects on brain and may be effective on brain edema reduction.

Methods: Male wistar rats were divided into 5 groups of 6 in each: sham, control and three treatment groups with a dose of 1,000 IU / kg EPO injected IP at 0.5, 48 and 96 hours before of stroke induction by the middle cerebral artery occlusion model. After pretreatment with EPO, animals were exposed to the middle brain artery occlusion for 60 minutes and then 24 hours after reperfusion, the brain water content, neurological defects and differentiation of blood cells were studied.

Results: Brain water content decreased in the group with a precondition of 5.0 hours before the stroke induction but the value increased in the preconditioning groups of 48 and 96 hours before the stroke induction which it was significant in the 48-hours group. The results of neurological defects were related to brain water content.

Conclusion: Erythropoietin effects on the brain edema was variable and depended on the dose. In the 48-hours treatment group, damage increased which may be as a result of an increased thrombosis risk.

key words: Erythropoietin; Pretreatment; Brain ischemia; Brain water content; Middle cerebral artery occlusion
The Role of Obesity and Leptin Hormone in Stroke Patients

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Introduction: stroke is the second most common cause of death and the leading cause of serious, long term disability world wide. Many epidemiological studies have considered the impact anthropometric measurements and plasma level of leptin on the risk of chronic disease, including stroke. In the present study we investigate the correlation between these values and stroke.

Method: we conducted a population-based case-control study. A total number of 54 cases and 30 control were matched with age, sex, race ethnicity and risk factors. Plasma level of leptin and anthropometric measurements including Body mass index (BMI), Triceps skin fold (TSF) and waist-hip ratio (WHR) were identified in cases and controls.

Result: In this study the frequency of ischemic stroke (n=44) was 78%, hemorrhagic stroke (n=10) 18%. The prevalence of obesity defined by BMI, was slightly lower among cases than controls (p<0.05). There was a significant relation between leptin and TSF index and it was significantly more in cases with higher TSF (p<0.05). Plasma leptin in ischemic stroke patients was significantly lower compared to control group (p<0.05), average leptin in hemorrhagic stroke is significantly higher but there was no significant association between control group and hemorrhagic stroke patients.

Conclusion: current study demonstrated, average BMI and plasma leptin in CVA patients is significantly lower than control group. Also it was determined that there is a significant relation between plasm leptin and TSF index which is due to more impact of subdermal adipose tissue on current plasma leptin.

Key words: leptin, obesity, stroke
Stress ulcer prophylaxis in cerebrovascular accident patients: a retrospective evaluation of current study in a neurology ward

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Abstract

Background: Stress ulcer prophylaxis in the digestive tract of hospitalized patients is very important. In this study, we evaluated the appropriateness of stress ulcer prophylaxis, in cerebrovascular accident (CVA) patients, in the neurology ward of two general hospitals.

Methods: This is a multi-center medication use evaluation (MUE) study conducted during 8 months in neurology ward of two hospitals affiliated to Shiraz University of Medical Sciences, Iran (one teaching and one non-teaching hospital). Appropriateness of stress ulcer prophylaxis was evaluated according to the American Society of Health-System Pharmacists (ASHP) guideline.

Results: 126 of the 134 CVA patients has been received acid-suppressive therapy. Only 20 patients out of 134 patients (14.9%) had an indication for stress ulcer prophylaxis. Among 20 patients just 17 of them received AST. 114 out of 134 patients (85.0%) were not indicated for stress ulcer prophylaxis; however, 109 patients (81.3%) has been received AST. The excess cost for inappropriate use of AST medications were estimated about 76,222,600 Rials.

Conclusion: Our results suggest that stress ulcer prophylaxis do not accomplish according to the ASHP guideline indications, in the CVA patients of these two hospitals. This study highlighted the need for establishment of clinical practice guidelines for the use of SUP in both teaching and non teaching hospitals in Iran.

Key words: stress ulcer prophylaxis, gastrointestinal bleeding, ASHP guideline, CVA.
Functional electrical stimulation along with rehabilitation measures in the improvement of dysphagia in stroke

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Background: Dysphagia, which is a common snag following stroke, can be life-threatening and thus novel therapeutic techniques such as functional electrical stimulation (FES), improving such a problem, would be of crucial importance. Therefore, the present study was designed to assess the combination therapy of functional electrical stimulation and traditional techniques to achieve oral feeding and decrease discharges with NG tubes.

Material and methods: In the present study, 112 stroke patients with dysphagia were selected and evaluated by 3-ounce water swallow test and the results were recorded in the Northwestern Dysphagia Patient Check Sheet. Daily Electrotherapy with 4 electrodes placed on suprahyoid and infrahyoid muscles with a current with standard frequency, duration, and time was carried out. Thereafter, swallowing maneuvers and manipulation with modification of food texture were done and patients were weekly monitored for 5 weeks.

Results: Patients with ischemic and hemorrhagic strokes presenting with dysphagia accounted for 70% and 30%, respectively. Forty one percent, 54%, 40%, 47%, and 26% of the patients achieved oral feeding from first to fifth week, respectively.

Conclusion: Taking into account of the high prevalence of dysphagia in stroke patients, novel interventions such as FES coinciding with traditional rehabilitation measures may decrease the problem and hasten oral feeding.

Keywords: Stroke, Dysphagia, Functional electrical stimulation
Comparison of serum lipid level in ischemic and hemorrhagic stroke

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Background: Although serum lipids are an independent risk factor for arteriosclerosis, the relation between serum lipids and CVA has not been clarified.

Objective: This study aimed to compare the serum lipid profile in patients with ischemic and hemorrhagic CVA.

Methods: This is a descriptive project included 80 patients of hemorrhagic and 80 of ischemic stroke on the first day after hospital admission at hospital intorbatyedaryeh (Iran) over a period of 1 year from April 2011 to April 2013. Exclusion criteria were smoking, overt diabetes, cardiovascular disease, and patients on antihypertensive and lipid lowering drugs. Types of stroke investigated by CT scanning and serum lipids level (Ch, Th, TG, HDL, LDL) were measured in the morning of night fasting on the first day after admission. Analysis of data was done by student t-test.

Findings: Total cholesterol level was 180 ± 6.26 and 187 ± 5.9 and HDL-Ch level was 64.8± 2.56 and 56.2± 204 in patients with hemorrhagic and ischemic CVA respectively (p< 0.05). On comparing the other lipid levels between cerebral hemorrhage and ischemia no significant difference was observed.

Conclusion: We come in conclusion that higher HDL-Ch and lower total cholesterol levels are associated with hemorrhagic stroke. This verifies the protective role of atherosclerosis effect of cholesterol on preventing of hemorrhagic stroke.

Keywords: Cerebral Infarction, Cerebral Ischemia, Arteriosclerosis, Lipids, Serum
Survey Of Various Post Stroke Pain Syndromes and the Related Risk Factors

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INTRODUCTION: Stroke is the most common cause of disability among neurologic.
Post stroke pain is a common and often neglected complication with prevalence several studies ranging from 18.6% to 49%.
Different types of pain occurs following stroke that including central, nociceptive, spastic, headache, and others. It is also important to Differentiate between various causes of pain because of their clinical pictures, risk factors and treatments.

Objective: To evaluate the relative frequency of post stroke pain syndromes and respective related risk factors.

Materials and methods: In this cross-sectional descriptive study 125 consecutive patients with stroke during the last 3 months, who visited in spring 2012 at the neurology clinic of nohomday Hospital for their routine follow up, were interviewed and examined for the presence and classification of post stroke pains. Demographic data and stroke characteristics were also registered. Collected data were analyzed using spss 16 software version.

Results: Among the 125 patients 45 (36.5%) complained about post stroke pain.
The most common types of pain were spastic pains and headaches (12.9% and 11.1%, respectively) and the most common locations of pain were upper limbs, and head (18.5% and 11.3%, respectively). Nociceptive and central pains were significantly more common in deep gray nuclei and internal capsule infarcts (p=0.002 and p=0.001, respectively) and headache was more common in brainstem Infarcts (p=0.002). There were no associations between other types of pain and location of lesion.

Conclusion: Post stroke pain is a common complication of stroke. As pain syndromes adversely affect the quality of life, and are potentially treatable, it is important to consider the occurrence of pain in all stroke patients in any outpatient visit. Pattern of correlated risk factors such as location of the lesion can help predict certain types of post stroke pain syndromes.

Key word: Pain / Stroke
Severity of aphasia in Persian speaking CVA aphasic patients as it relates to the site of lesion

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Background: Aphasia is one of the most common and disabling impairments of stroke which brings about many communicative limitations for the patients.

Methods: 30 Persian speaking CVA individuals with different lesion sites were recruited in the current study. The lesion site of the participants was determined in consultation with neurologist and MRI images as cortical and subcortical. The cortical group were categorized as anterior, posterior and anterior-posterior. The severity of aphasia of each patient was measured based on AQ (Aphasia Quotient) taken from the Persian version of Western Aphasia Battery (Nipour, 2014) used as a validated clinical linguistic measuring tool. Based on AQ results, the patients were classified into four groups of severity as mild, moderate, severe and very severe.

Results: 4 patients (13.4%) had severe aphasia, 4 other (13.4%) had moderate aphasia and the rest 22 patients (73.2%) had mild aphasia. 18 patients(60%) had LH lesions and 12 patients(40%) had RH lesions.

Conclusion: The Mean AQ of patients with anterior, posterior, and anterior-posterior lesions was 74.3, 85.7 and 83.3 respectively which reveals that the anterior group had a lower AQ and a more severity of aphasia as compared with the Mean of patients whose lesions were identified in posterior or anterior-posterior areas. The severity of aphasia in patients with cortical lesions was significantly higher than the patients with sub-cortical lesions.(P=0.031). No specific relationship was seen between the existence of lesion in either the left or right hemisphere with the severity of aphasia.

Key Words: Severity of Aphasia, Post stroke Lesion Site, Aphasia Quotient
Post stroke dementia and its putative risk factors:  
A hospital-based study

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Abstract

Introduction: Dementia is common after stroke and has a considerable impact on mortality, rehabilitation and quality of life. There are some published articles regarding post stroke dementia but there are many controversies surrounding this topic. Our aim was to identify the prevalence of post stroke dementia 3 months after stroke and evaluation of some its putative risk factors in Iranian population.

Method: In this cross-sectional study, 151 patients with acute stroke were evaluated. The diagnosis was confirmed by physical examination and neuroimaging. Three months after the stroke, all patients were visited again. The diagnosis of post stroke dementia was made according to the criteria in the DSM-IV. Demographic data were collected using a questionnaire and data about lesion location and kind of stroke were obtained according to neuroimaging. To analyze the data, descriptive statistics, and chi-square test were used.

Results: In our study, 47% patients were male and the rest were female. Thirty five (23.2%) of patients had post stroke dementia (PSD) after 3 months. 70.6 % of patients were 60 years old or more. 88.7% of patients had ischemic infarction and the rest had hemorrhagic stroke. The most frequent lesion locations were temporal, frontal and parietal lobes respectively. There was no significant statistical difference between PSD and sex, age, educational status, lesion location and kind of stroke. 

Conclusion: Our results show that a significant portion of patients with stroke are prone to PSD. The risk of dementia occurring after a stroke does not seem to be influenced by the stroke type.

Key words: Dementia, Stroke, Risk factor
Extra-cranial carotid artery stenosis in patients with ischemic stroke, a hospital-based study in Shiraz, Iran

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Abstract:
Background: Stroke is one of the most important causes of mortality and morbidity in the world and about 15% of strokes are due to large vessels involvements such as extra-cranial carotid artery disease. It is possible to decline the risk of stroke due to carotid artery stenosis by surgical or non-surgical investigation. The aim of this study was to assess the extra-cranial carotid artery in patients with ischemic stroke by color Doppler ultrasonography (CDS).

Methods and materials: This cross-sectional study was done to determine the prevalence of carotid artery stenosis in the ischemic stroke patients from August 2011 to January 2012 at Namazee hospital, Shiraz, Iran. The data were gathered by completing data sheets and review of the patient’s charts. Two hundred patients with diagnosis of ischemic stroke were enrolled in this study. The stenosis of carotid artery was evaluated with CDS. The demographic data and those obtained from carotid CDS were gathered and then statistical analysis was performed using Chi-square, and Logistic Regression test.

Results: Among a total of 200 stroke patients, 93 (47%) were male and 107 (53%) were female. The prevalence of severe stenosis (>70%), moderate stenosis (50% to 70%) and mild stenosis (<50%) was 2.5%, 23.9% and 26%, respectively. The prevalence of stenosis was 23%, 21% and 27.4% in the age group <50 years, 50-70 years, and >70 years, respectively. There was no significant relationship between stenosis and diabetes (p=0.83), ischemic heart disease (p=0.30), hyperlipidemia (p=0.91) and hypertension (p=0.17) but there was a significant relationship between age and stenosis (P=0.02)

Conclusion: The prevalence of extra-cranial carotid stenosis in Iran is higher than that of most Asian studies but it is close to western countries’ reports.

Keywords: Stroke, Carotid artery, stenosis, Ultrasonography, Doppler
Cerebral venous thrombosis in Ramadan: an epidemiological approach

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Introduction: In this study we tried to evaluate any relation between combination of OCP administration and fasting in Ramadan month and CVST in Namazi Hospital, Shiraz, Iran between January 2009 and January 2015.

Patients and method: All patients who were admitted in Namazi Hospital between January 2009 to January 2015 with CVA and CVST were included in this retrospective study. We divided the patients according to lunar month of admission, we also investigated any history of OCP administration in female patients, and Revealed data was evaluated with SPSS version 16 under supervision of statistical specialist.

Results: overall 13094 patients with CVA and 332 patients with CVST were admitted in this duration. From these 942 patients with CVA and 38 patients with CVST were admitted in Ramadan month, from 20 female with CVST, 13 (65%) patients had definite history of OCP administration. comparing to the other lunar month incidence of CVST were significantly higher in Ramadan month.(p value = 0.003)

Conclusion: Both OCP administration and fasting are considered as CVST risk factors, in this study we showed that combination of these two important risk factors in Ramadan month can increase the risk of CVST significantly.

Key words: Cerebral venous thrombosis, Fasting, Oral contraceptive.
The role of the herbal medicine in stroke

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Abstract

Background: The lack of effective and widely applicable pharmacological treatments for ischemic stroke patients may explain a growing interest in traditional medicines, for which extensive observation and anecdotal experience has accumulated over the past thousand years. In recent years, several reviews have been published on the effect and potential benefits of traditional Eastern medicine in stroke. It has been suggested that some herbal medicines may improve microcirculation in the stroke, so the purpose of this study was investigation the role of herbal in stroke.

Methods: Using predetermined criteria and keywords we searched PubMed, CINAHL, Scopus and etc. for human and animal studies that measured at least one domain of cognition or herbal treatment intervention. Titles, abstracts and manuscripts were screened by three researchers and data consolidated into spreadsheets.

Results: A total of 263 titles were returned from the literature search, 15 articles were included in the final review. Our research results show that cultural beliefs in some Eastern countries or attributable to belief that some adverse effects (eg, diarrhea) are part of the normal response to herbal treatment; uncertainty and multicomponent structure of active ingredients and other chemical compounds of herbal medicines that can be considered as complex interventions of varying dosages and interactions, especially in the context of differences in treatment concepts between Western and traditional medicines; timing, dosage and duration of the interventions.

Conclusion: The potential of herbal drugs as defined therapeutic agents is undermined by the difficulty in standardization, pharmacodynamics and pharmacokinetics of these multi-component mixtures and also the lack of enough experimental data. Therefore, the potential of herbals in the treatment of stroke needs to be further explored.

Keywords: stroke, herbal medicine, drug
Sneddon's syndrome presented at first with Hemorrhagic stroke: A case report

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Abstract:
Sneddon's syndrome is characterized by chronic, progressive arteriopathy that causes ischemic stroke and skin lesions. It seems that thrombotic or embolic process in vessels may have role in Sneddon's syndrome. Skin manifestations include deep blue skin lesions with irregular margins called livedo reticularis and livedo racemosa. Neurological symptoms are always due to with ischemic event of cerebrovascular system, however, in spite of ischemic event, hemorrhagic cerebral accidents are unusual in this syndrome. Our case was an apparent normal woman with negative past medical history who developed hemorrhagic stroke at first and after a few days to new skin lesions (livedo reticularis). In the follow-up she was diagnosed with sneddon's syndrome.

Keywords: Sneddon's syndrome, Hemorrhagic stroke, livedo reticularis
Cerebrospinal fluid Interpretation in Subarachnoid hemorrhage: Pearls & Pitfalls

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Background
Subarachnoid hemorrhage (SAH) is a serious condition in the differential diagnosis of thunderclap headaches. If the noncontrast CT scan could not disclose SAH in a suspected patient, lumbar puncture (LP) should be performed to evaluate the CSF for the presence of red blood cells and xanthochromia. LP has false negative and false positive results.

Methods & Materials
During investigation for SAH, CSF must be analyzed as viewpoint of opening pressure, Cells with differentiation, centrifuged, Heme destruction products, Glucose, Protein and Gram stain. In certain cases it is possible to assess CSF for D-dimer assay, Adenosine deaminase (ADA), Lactate/pyruvate ratio, Fibrin/fibrinogen degradation products (FDP’s), total protein, and plasminogen, CSF interleukin-6 and CSF leukotriene C4.

Results
In SAH, CSF may be negative for early Lumbar puncture (until 12 hours after symptom onset), late lumbar puncture (after 2-4 weeks) and another technical errors, like CSF exposed to spring daylight or transport by pneumatic tube. On the other hands, it may show false positive in traumatic taps, RBCs lysis and liberated oxyhaemoglobin (due to delay in examination), Infectious and Inflammatory conditions, Intra cerebral hemorrhage, Subdural and epidural hematoma and Infarct, as well as other causes like Jaundice, Hypercarotenemia, Melanin, Rifampin therapy and Clots in other locations. Newborn CSF is often xanthochromic. It is necessary to differentiate traumatic tap from true SAH.

Conclusion
Interpretation of CSF analysis to diagnose SAH requires considering time interval from event, iatrogenic pitfalls, Physical examination, Infectious and inflammatory diseases, history of some medical conditions and laboratory technical remarks.

Key Words: Subarachnoid hemorrhage, Lumbar puncture, Cerebrospinal fluid

References
Guidelines for the Primary and Secondary Prevention of Stroke

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Abstract
Stroke is a global health problem and a leading cause of adult disability. It is possible to decrease the burden of stroke through control and management of many risk factors. The aim of this paper is to provide recommendations on the prevention of stroke among individuals who have not previously experienced a stroke or transient ischemic attack or among survivors of ischemic stroke or transient ischemic attack. In this brief paper, four most important risk factors are discussed in detail.

Keywords: Stroke; Hypertension; Diabetes Mellitus; Hyperlipidemia; Smoking.

Stroke is a worldwide health problem and the most important cause of disability in adults [1]. Of 35 million deaths due to chronic uncommunicable diseases in 2005, 5.7 million (16.6%) were because of stroke [2]. There are only a few effective treatments for the most threatening forms of stroke. Hence, primary and secondary preventions offer the greatest potentials for reducing the burden of this disease. Primary stroke prevention refers to the treatment of individuals with no history of stroke. Secondary stroke prevention refers to the treatment of individuals who have already had a stroke or transient ischemic attack. There are 3 types of stroke risk factors [3]:

1. **Generally Non-modifiable** including: Age, Low Birth Weight, Race/Ethnicity and Genetic Factors.
2. **Well-documented and Modifiable** including: Physical Inactivity, Dyslipidemia, Diet and Nutrition, Hypertension, Obesity and Body Fat Distribution, Diabetes Mellitus, Cigarette Smoking, Atrial Fibrillation, Asymptomatic Carotid Artery Stenosis and Sickle Cell Disease.
3. **Less Well-Documented or Potentially Modifiable Risk Factors** including: Migraine, Metabolic Syndrome, Alcohol Consumption, Drug Abuse, Sleep-Disordered Breathing, Hyperhomocysteinemia, Hypercoagulability, Inflammation and Infection.

Here we focused on the role of most important factors in the second group regarding primary and secondary preventions.
1-Hypertension
Hypertension is a very important risk factor for both ischemic stroke and ICH and defined as a systolic blood pressure (SBP) $\geq$ 140 mmHg or a diastolic blood pressure (DBP) $\geq$ 90 mmHg. The relationship between BP and stroke risk is strong, continuous, graded, consistent, independent, predictive, and etiologically significant [5]. AHA/ASA 2014 Recommendations include:

A) Primary Prevention
1. For primary prevention, regular control and appropriate treatment of BP by lifestyle modification and pharmacological therapy is recommended.
2. For patients with prehypertension (systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg), annual BP screening and lifestyle modification are recommended.
3. Reduction of BP is more important in reducing stroke than the choice of specific agent. Patients who have hypertension should be treated with antihypertensive drugs to a target BP of $<140/90$ mmHg. Self-measured BP monitoring is very important in BP control [6].

B) Secondary Prevention
Treatment of hypertension plays an important role in secondary prevention of stroke. The prevalence of HTN among patients with a recent ischemic stroke is $\approx 70\%$ [7, 8, 9]. Treatment of HTN in the first 24 hours is not recommended except for specific situations such as; therapy with tissue-type plasminogen activator (r-tpa), SBP $>220$ mmHg or DBP $>120$ mmHg [7]. In the presence of TIA or stroke, Thiazide and Angiotensin-converting enzyme inhibitors (ACEI) are suggested [28]. Here are 2014AHA/ASA recommendations:

1. Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP $\geq 140$ mmHg systolic or $\geq 90$ mmHg diastolic. Initiation of therapy for patients with BP $<140$ mmHg systolic and $<90$ mmHg diastolic is of uncertain benefit.
2. Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days.
3. Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized; but, it is reasonable to achieve a systolic pressure $<140$ mmHg and a diastolic pressure $<90$ mmHg. For patients with a recent lacunar stroke, it might be reasonable to target an SBP of $<130$ mmHg.
4. Several lifestyle modifications have been associated with BP reductions and are a reasonable part of comprehensive antihypertensive therapy include salt restriction, weight loss, consumption of a diet rich in fruits, vegetables and low-fat dairy products, regular aerobic physical activity and limited alcohol consumption.

5. The choice of drug for BP control is uncertain and should be individualized but diuretics or the combination of diuretics and an angiotensin-converting enzyme inhibitor is useful [3].

2. Dyslipidemia
There is an interesting relation between total cholesterol levels and stroke risk in general population: low levels of total cholesterol increase the risk of ICH and high levels of total cholesterol increase the risk of ischemic stroke. So, there is no positive association between total cholesterol level and stroke mortality [10]. Epidemiological studies evaluating the relationship between triglycerides and ischemic stroke have been inconsistent, in part because some have used fasting and others non-fasting levels [6]. Treatment with statins decreases stroke risk in patients with or at high risk of atherosclerosis [11, 12]. The usefulness of statins in ischemic stroke is most likely related to their capacity to reduce progression or to induce regression of atherosclerosis. The usefulness of other lipid-modifying drugs with or without statins in ischemic stroke is unknown [6].

2014 AHA/ASA Recommendations:

A) Primary Prevention
1. In addition to therapeutic lifestyle changes, treatment with an HMG coenzyme-A reductase inhibitor (statin) medication is recommended for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events as recommended in the 2013 “ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [13].
2. Niacin may be considered for patients with low HDL cholesterol or elevated Lp (a), but its efficacy in preventing ischemic stroke in patients with these conditions is not established. Caution should be taken with niacin because it increases the risk of myopathy.
3. Fibric acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in preventing ischemic stroke is not established.
4. Treatment with nonstatin lipid-lowering therapies such as fibric acid derivatives, bile acid sequestrants, niacin and ezetimibe may be considered in
patients who cannot tolerate statins, but their efficacy in preventing stroke is not established [6].

**B) Secondary Prevention**

1. Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL with or without evidence for other clinical atherosclerotic CVD (ASCVD).
2. Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and no evidence for other clinical ASCVD.
3. Patients with ischemic stroke or TIA and other comorbid ASCVD should be otherwise managed according to 2013 ACC/AHA cholesterol guidelines [16] which include lifestyle modifications, dietary recommendations and medication recommendations [6].

### 3-Diabetes Mellitus

Patients who suffer from diabetes mellitus have 2 problems; an increased susceptibility to atherosclerosis and an increased prevalence of atherogenic risk factors especially hypertension and abnormal blood lipids. Diabetes mellitus is an independent risk factor for stroke [14] which increases the risk of stroke more than 2 times. Duration of diabetes mellitus also increases the risk of nonhemorrhagic stroke (by 3%/y of diabetes duration)[14]. In pre-diabetes state, fasting hyperglycemia is associated with stroke [15]. Glycemic control reduces microvascular complications but there remains no evidence that improves glycemic control reducing the risk of incident stroke. Here are the 2014 AHA/ASA recommendations:

**A) Primary Prevention**

1. BP control in accordance with an AHA/ACC/ CDC Advisory 28 to a target of <140/90 mmHg is recommended in patients with type 1 or type 2 diabetes mellitus.
2. Treatment of diabetic adults with a statin, especially those with additional risk factors, is recommended to lower the risk of first stroke.
3. The usefulness of aspirin in primary stroke prevention for patients with diabetes mellitus but lower than 10-year risk of CVD is unclear.
4. Adding a fibrate to a statin in people with diabetes mellitus is not useful for decreasing stroke risk [6].
B) Secondary Prevention
No major trials for secondary prevention of stroke have specifically examined interventions for pre-DM or DM. There is no diabetic drug preferable over others for vascular prevention. AHA/ASA 2014 recommendations:

1. After a TIA or ischemic stroke, all patients should probably be screened for DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test.
2. Choice of test and timing should be guided by clinical judgment and recognition. Acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate post event period.
3. The use of existing guidelines from ADA for glycemic control and cardiovascular risk factor management is recommended for patients with an ischemic stroke or TIA who also have DM or pre-DM.
4. Aspirin: 75-162 mg/day: diabetes and CVD history.
5. CVD and aspirin allergy: Clopidogrel 75 mg/day [16].

Antiplatelet therapy in diabetic patients is shown in table below.

<table>
<thead>
<tr>
<th>Antiplatelet Therapy Recommendations</th>
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<tr>
<td><strong>Aspirin:</strong> Primary prevention</td>
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<tr>
<td>75-162 mg/day: type 1 and type 2 diabetes at increased CVD risk (10-yr risk &gt;10%)*</td>
</tr>
<tr>
<td>Low-risk patients (10-yr risk &lt;5%):† not recommended; potential for bleeds likely offsets potential benefits</td>
</tr>
<tr>
<td>Men &lt;50 yrs, women &lt;60 yrs with multiple other risk factors (10-yr risk 5%-10%): use clinical judgment</td>
</tr>
<tr>
<td><strong>Aspirin:</strong> Secondary prevention</td>
</tr>
<tr>
<td>75-162 mg/day: diabetes and CVD history</td>
</tr>
<tr>
<td><strong>CVD and aspirin allergy</strong></td>
</tr>
<tr>
<td>Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td><strong>Dual antiplatelet therapy</strong></td>
</tr>
<tr>
<td>Reasonable for ≤1 year after ACS</td>
</tr>
</tbody>
</table>

*Includes most men aged >50 yrs or women aged >60 yrs with ≥1 add'l major risk factor: family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria
†Men aged <50 yrs and women aged ≥60 yrs with no major additional CVD risk factors
ACS= acute coronary syndrome, CVD=cardiovascular disease

4-Cigarette Smoking:
Cigarette smoking increases the risk of ischemic stroke (double) and SAH (2-4 folds increase) [7-12], but data on ICH are inconclusive. Cigarette smoking may potentiate the effects of other stroke risk factors including systolic blood pressure [21] and oral contraceptives. There is a reduction in stroke risk with smoking cessation and with community-wide smoking bans. Passive smoking is a known risk factor for heart disease [22, 23]. Likely, smoking contributes to increased stroke risk through both short-term effects on the risk of thrombus generation in atherosclerotic arteries and long-term effects related to increased atherosclerosis [24]. Smoking as little as a single cigarette increases heart rate, mean BP and cardiac index; it decreases arterial distensibility too [25, 26]. After smoking cessation, the risk of stroke and other cardiovascular events rapidly reduce to a level that approaches, but does not reach that of those who never smoked [23, 26]. Recommendations of 2014 AHA/ASA:

A) Primary Prevention
1. Counseling, in combination with drug therapy using nicotine replacement, bupropion or varenicline is recommended for active smokers to assist quitting smoking.
2. Abstention from cigarette smoking is recommended for patients who have never smoked on the basis of epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH [6].

B) Secondary Prevention
In contrast to extensive data on the association between smoking and risk for first stroke, data on an association with recurrent stroke are sparse. No clinical trials have examined the effectiveness of smoking cessation for secondary prevention of stroke or TIA. Here are 2014 AHA/ASA recommendations:
1. Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit.
2. It is reasonable to advise patients after TIA or ischemic stroke to avoid environmental (passive) tobacco smoke.
3. Counseling, nicotine products and oral smoking cessation medications are effective in helping smokers to quit [3].

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16- 2015 American Diabetes Association (ADA) Diabetes Guidelines


Dry Needling Hypertonia spasticity (DNHS): Novel Method for spasticity treatment

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Dry needling as a complementary tool in the treatment of CNS injury patients, as it can provide the achievement certain effects than other techniques not a priori seem achievable. Dry needling treatment was also applied in neurological patients for pain treatment with good results, although the application technique no different from those usually performed to treating myofacial pain origin. Dry needling (DN) is a relatively new technique used by physical therapists to treat myofascial trigger points (MTrPs) and a variety of pain syndromes (Dunning et al., 2014; Vulfsons, Ratmanksy, & Kalichman, 2012; Casanueva et al., 2014; Osborne, & Gatt, 2010; Tough, White, Cummings, Richards, & Campbell, 2009; Dommerholdt, del Moral, Gröbl, 2006). It is an intervention that uses a thin monofilament needle, without the use of injection, to penetrate into the muscle to stimulate underlying neural, muscular and connective tissues for the purpose of pain management and functional improvement (Dunning et al., 2014). Dry needling of MTrPs has been used in neurological conditions to treat: hemiparetic shoulder pain after stroke (DiLorenzo et al., 2004); adult patients with incomplete spinal cord injuries who have spastic hypertonia (Fresno, Mediavilla, & Mayoral, 2004); and a child with spastic tetraplegia and spasticity (Gallego, & del Moral, 2007). Case study the effect of dry needling in post stroke spasticity(Ansari et al2015);and(Jaime Salom-Moreno et al2014). Spasticity is a neural phenomenon resulting from imbalance between inhibitory and excitatory fibers due to an upper motor neuron lesion (Shean, 2002).

Both mechanical and neurophysiologic mechanisms are associated with DN.
The admission frequency of patients with cerebral stroke and venous sinus thrombosis during the month of Ramadan in comparison to other 11 non-fasting months in Bushehr Medical University Hospital: A 4.5-year hospital-based study

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Abstract

Introduction: One of the 10 ancillaries of the faith of Islam is fasting during the month of Ramadan, which is one lunar month in duration. Muslims neither eat nor drink anything from dawn until sunset. The objective of this study was to investigate whether Ramadan fasting has any effect on the admission frequency of cerebrovascular diseases, including ischemic stroke and venous sinus thrombosis.

Methods: This is a retrospective and cross-sectional study that was done in Bushehr Medical University Hospital, one of the most important referral hospitals in Bushehr province. The admission data of 4.5 years were taken from patient’s files in the archive of the hospital and put into a questionnaire. Then, the data were analyzed with SPSS version 22 to determine any patterns over the Ramadan periods.

Results: A total of 2143 admitted patients were included in this study over 4.5 years, from March 21st, 2009 to September 23rd, 2013; 1338 (55.7%) were
males. Overall, 2124 patients were hospitalized due to stroke; 1171 (55.2%) were males. 19 patients were admitted due to sinus venous thrombosis; 4 (21.11%) were males. The number of patients with during the month of Ramadan in comparison to other months did not show a significant difference (p= 0.312). But number of hospitalized patients due to stroke was higher than other months.

**Conclusion:** Our study showed higher number of admission of patients due to SVT but not stroke during the month of Ramadan as compared with other months. However, it is in consistency with other studies, but further evaluations are required to verify these preliminary results

**Keywords:** Ramadan fasting, cerebral stroke, venous sinus thrombosis

**Introduction**

One of the 10 ancillaries of the faith of Islam, the religion professed by over one billion people, is fasting during the month of Ramadan. Muslims neither eat nor drink anything from dawn to sunset(1). The time of observance differs each year because it follows the lunar calendar. The fasting period from dawn to sunset varies with geographical site and season. In the summer months and northern latitudes, the fast can last up to 18 hours or more. Muslims observing the fast must not only abstain from eating and drinking, but also from taking oral medications, smoking, as well as receiving intravenous fluids and nutrients(2-5). Except for patients who are under treatment and need medications or intravenous fluids. During the Ramadan fasting, Muslims eat two meals a day; one before dawn and the other shortly after sunset (6). This change of meal schedule is accompanied by changes in sleeping habits (shortened sleeping period) (7)(1). The medication schedule during the day is also changed due to fasting, which may have an effect on patients(1,8). Ramadan fasting is a great opportunity for scientific research due to its peculiar nature(9). Despite the fact that it concerns the Muslim community of more than one billion people, the effects of fasting on humans have not been adequately investigated(6,10-11).

Stroke is one of the major causes of death and disability in most developed countries (12-14). It's more frequent in men other than women (15-17) Fasting during Ramadan is essentially a radical change in lifestyle for the period of one lunar month that may affect patients with stroke (18-20).

Akhen et al found no negative or positive effects of Ramadan fasting on stroke frequency (18). Maghzi and colleges showed that physiological and biochemical changes that occur during fasting in Ramadan are not a risk factor for stroke and do not affect the short-term survival of patients (21). Berner et al also demonstrated that no significant difference was found in the number of hospitalizations for stroke while fasting during the month of Ramadan when
compared to the non-fasting months (8). El-Mitwalli et al showed Ramadan fasting has no effects on stroke frequency, type, and severity. The duration of fasting has no effect on either frequency or type of stroke (10).
Saadatnia et al reported that fasting increases frequency of sinus thrombosis, while these findings are inconsistent with other reported studies on arterial stroke(12). Saidee et al clearly showed the higher incidence of CVT in Ramadan, but they could not detect any risk factors in this group except OC consumption (22).
Thirst and hunger and also other alteration in routine lifestyle during Ramadan might influence the pattern and frequency of cerebrovascular diseases.
The objective of this study was to investigate whether fasting during Ramadan has any effect on the frequency of hospitalization of patients with stroke and venous sinus thrombosis (SVT) in Bushehr Port, which is located in the southwestern of Iran and has a hot weather.

Materials and methods
This is a retrospective and cross-sectional study that was done in neurology department of Bushehr Medical University Hospital, one of the most important referral hospitals in Bushehr province; most neurology patients are referred to this center from other hospitals.
This project spanned about 4.5 years of records evaluating frequency of hospitalization of patients with two neurological diseases (2009-2013) (stroke and SVT) during Ramadan in compare to other months of the year.
Ischemic Stroke was defined as acute neurologic deficit following blood supply disturbance lasting >24 h (unless interrupted by surgery or death) following blood supply disturbance, with no apparent nonvascular cause.
Sinus venous thrombosis (SVT) was diagnosed based on the clinical manifestation and MRI and MRV findings. Also, Patients were investigated for thrombosis risk factors including family history of venous thrombosis, hyper coagulopathy state, collagen vascular disorders, infectious disorders, complicated otitis, malignancy, past history of trauma, drug abuse and history of short and long-term consumption of OC and the type of OC based on the estradiol component.
Relevant data were taken from patient files in the archive of the hospital and put in a questionnaire that consisted of: age and sex of the patient; year of admission; season of admission; and month of admission (Ramadan or other months).
We included patients with age range of 20-90 who were admitted due to stroke or SVT (which diagnosed by a neurologist) in the Persian Gulf university hospital of Bushehr province. Patients whose final diagnosis changed to anything other than stroke and SVT were excluded.
The study complied with the Declaration of Helsinki. It was sanctioned by the Institutional Ethics Committee of Bushehr University of Medical Sciences.
Statistical analysis
All data were expressed as the mean ± SD, with ranges given when suitable. Continuous variables were compared by using the unpaired T-test, and categorical variables were compared using the chi-square analysis. A P value of less than 0.05 was considered to be statistically significant. The SPSS for Windows software package version 22 (SPSS Inc., Chicago, Illinois) was used for the statistical analysis.

Results
A total of 2143 admitted patients were registered to this study over 4.5 years, from March 21st, 2009 to September 23rd, 2013; 1338 (55.7%) were male. Overall, 2124 patients were hospitalized due to stroke; 1171 (55.2%) were male. 19 patients were admitted due to sinus venous thrombosis; 4 (21.11%) were male. Demographic features of patients have been shown in table 1.

<table>
<thead>
<tr>
<th>Cerebrovascular diseases</th>
<th>Parameters</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Ramadan</td>
<td>Other months</td>
</tr>
<tr>
<td>Stroke</td>
<td>Number</td>
<td>103</td>
<td>1069</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>63.23</td>
<td>65.50</td>
</tr>
<tr>
<td>SVT</td>
<td>Number</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Age</td>
<td>31</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 1. Demographic parameters

Stroke
The mean age of patients was 65.67 years overall; 65.5 for men and 66.13 for women. The mean number of hospitalized patients per each lunar month due to stroke was 40.24 cases. The highest average rate of admission was recorded in the fourth month, in winter, and also the ninth month (Ramadan), in summer (Figure 1).

Figure 1. Mean number of admissions due to stroke in Ramadan is not significantly higher than other lunar months.
Mean of stroke per month in all months other than Ramadan were not significantly higher than mean of stroke in Ramadan. (P value =0.312).

**Venous sinus thrombosis**

During these 4.5 years, there were only 19 cases of SVT admitted to our hospital. The mean age of the patients was 38.47 years, overall; 35.25 for men and 39.33 for women. Most SVT cases were administered during the ninth month, Ramadan, while during some other months; no SVT case was seen (Table 2).

<table>
<thead>
<tr>
<th>Month</th>
<th>Number of patients with SVT</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>6</td>
</tr>
<tr>
<td>10</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>2</td>
</tr>
<tr>
<td>12</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 2. The number of hospitalized patients due to venous sinus thrombosis in each lunar month.

Number of patients with SVT during Ramadan was 8 out of 19 cases. As the small number of SVT cases during these 4.5 years of study, it’s better not to use a statistical analysis. However it seems that it is almost as much as other months combined 8:11.

**Discussion**

The current investigation depicted more hospitalization of patients with SVT in the month of Ramadan as compared with the other 11 non-fasting months. But number of hospitalized patients with stroke during Ramadan was not significantly more than other months.

The hospitalizations due to SVT during Ramadan could be due to the change in lifestyle of patients, including not drinking and eating, change in sleep habits, and the increased rate of using oral contraceptives in females during Ramadan. However it seems these changes did not affect hospitalization of patients due to stroke during Ramadan.

There are a few studies that evaluated cerebrovascular diseases during Ramadan compare to other months of the year. Most of them showed no significant difference between the month of Ramadan and other months in hospitalization of
patients with stroke. As Chitsaz et al., who conducted a study from 2006 to 2007, when Ramadans coincided with the summer and autumn seasons, showed fasting as not associated with stroke (14). Benner et al., who conducted a study from 1991 to 2003, when Ramadan coincided with the autumn and winter seasons, did not show a significant difference in stroke rates between the Ramadan fasting month and other non-fasting months (8).

In contrast, some studies showed hospitalization due to SVT during Ramadan was significantly higher than other months. A study that was performed in three neurological centers from 2001 to 2006 in Isfahan City aimed to assess whether Ramadan fasting would change the frequency of cerebral venous and sinus thrombosis as compared to other months. They demonstrated a significantly increased rate of cerebral venous sinus thrombosis events in Ramadan when compared to other months. Eventually, they concluded that these issues may not be a concern for healthy people while fasting, but vulnerable persons, such as those with hypercoagulable states and women who use oral contraceptive pills (OCP), may be at increased risk (20).

In our study, it is indicated in Figure 1 that the rate of stroke in cold months was increased; this is probably due to higher risk of infectious diseases that can make patients prone to a stroke. Later, in warmer months of the year, the number of cases of stroke descending proceeding. But, while summer months typically have this descending period for stroke cases, the number of stroke cases increased when Ramadan occurred in the summer in our study. In Shawwal (and also dhu al-qhada and dhu al-hijjah), the lunar month right after Ramadan, the number of stroke cases reached the lowest number of all other months. Turin et al. has been shown that Stroke incidence was highest in the spring, followed closely by the winter (23) which was similar to other study in Japan, where stroke incidence was found to be higher during the winter and spring (24). Based on these documents, hospitalization due to stroke in Ramadan, which was in summer during our project, expect to decrease, but in contrast, it increased. A decrease pattern of hospitalization due to stroke during 3 months after Ramadan seems to be due to decline of stroke incidence during summer.

Akhan et al. evaluated all patients with stroke admitted to any hospital in the Isparta Province between 1991 and 1995. The stroke rate of Isparta has been found to be 137 per 100,000 for people older than 25 years of age. There were no noticeable differences between the age and sex distribution of patients and the admission frequency of patient with stroke strokes. The study also depicted that fasting during Ramadan has no effect on stroke rate in the Isparta Province (18).

In addition, Omoúlu et al. assessed hospitalized patients due to ischemic stroke and intracerebral hemorrhage in the neurology department and the in-hospital
clinical course; mortality rates of the patients with stroke were evaluated. The most frequently encountered type of stroke was ischemic. The ratios of hemorrhagic and ischemic strokes had no significant differences between the periods before Ramadan, during Ramadan, and after Ramadan. The ratio of hemorrhagic stroke diminished in hypertensive patients during.

As hundreds of millions of people may participate in Ramadan fasting each year, additional scientific research on the different aspects of medicine during this fasting period is required. Physicians who work in Islamic countries and those taking care of Muslims in different corners of the world should keep in mind the physiological changes experienced during Ramadan, and the influence of Ramadan fasting on different neurological issues and medications. It is also recommended that medical practitioners communicate with their local scholars before Ramadan starts to remind Muslims that certain people are exempt from fasting, and those who plan to fast should consult their physicians before doing so.

This study suffered from a shortage of cerebrovascular risk factors in patients who were admitted during the study in all months, as well as lack of interaction with participating patients. The next limitation arises from the nature of methodology, in which some patient records over this long retrospective project did not have complete data. Therefore, further research requires a larger number of patients split into more categories based on risk factors to find the individuals who may need closer inspection regarding participation in Ramadan fasting.

**Conclusion**

The study showed higher number of admission of patients due to SVT but not stroke during the month of Ramadan as compared with the other 11 months, which is in consistency with other studies, but further evaluations are required to verify these preliminary results.

**Acknowledgement:** The research deputy of Bushehr University of medical sciences granted this research project.

**Conflict of interest:** The authors have no conflict of interest to declare.

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Efficacy of Citalopram on Ischemic Stroke Functional Outcome: A Randomized Clinical Trial

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This clinical trial conform to consort statement.

Abstract:

Background and Purpose: Stroke is one of the main causes of death and disability in the adult population and recovery from it is considered by many researchers. The aim of the present study was to evaluate the efficacy of citalopram on 3-month functional outcome of non-depressed acute ischemic stroke (AIS) patients.

Methods: In a randomized, placebo controlled clinical trial, 144 patients with AIS were studied for 3 months. In one group, the patients received oral citalopram 20 mg (once daily) and in the other group, they received placebo. All patients received standard care including physiotherapy. Patients with depression were excluded from the study. Primary outcome was set to a 50% reduction in the 3-month National Institutes of Health stroke scale (NIHSS) compared to the baseline scores.

Clinical Trial Registration-URL: http://www.irct.ir; Unique identifier: IRCT201203192150N2.

Results: Of 144 eligible patients, 123 with mean age of 66.39 (62 in citalopram group and 61 in placebo group) were considered for the final analysis. The primary outcome of the study was obtained in 61 patients (98.3%) of citalopram group and 34 patients (68%) of placebo group (p<0.000) with the risk ratio and number needed to treat of 10.6 (CI: 1.6-71.8) and 1.8 (CI: 1.4-2.4), respectively. No major adverse events were found in either group.

Conclusions: Citalopram is a safe and tolerable medication in patients with AIS and could improve functional outcome in these patients.

Key Words: Acute ischemic stroke; randomized clinical trial; functional outcome; citalopram; selective serotonin-reuptake inhibitors; Stroke rehabilitation.
Guidelines for the Primary and Secondary Prevention of Stroke

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Abstract
Stroke is a global health problem and a leading cause of adult disability. It is possible to decrease the burden of stroke through control and management of many risk factors. The aim of this paper is to provide recommendations on the prevention of stroke among individuals who have not previously experienced a stroke or transient ischemic attack or among survivors of ischemic stroke or transient ischemic attack. In this brief paper, four most important risk factors are discussed in detail.

Stroke is a worldwide health problem and the most important cause of disability in adults [1]. Of 35 million deaths due to chronic uncommunicable diseases in 2005, 5.7 million (16.6%) were because of stroke [2]. There are only a few effective treatments for the most threatening forms of stroke. Hence, primary and secondary preventions offer the greatest potentials for reducing the burden of this disease. Primary stroke prevention refers to the treatment of individuals with no history of stroke. Secondary stroke prevention refers to the treatment of individuals who have already had a stroke or transient ischemic attack. There are 3 types of stroke risk factors [3]:
4. Generally Non-modifiable including: Age, Low Birth Weight, Race/Ethnicity and Genetic Factors.
5. Well-documented and Modifiable including: Physical Inactivity, Dyslipidemia, Diet and Nutrition, Hypertension, Obesity and Body Fat Distribution, Diabetes Mellitus, Cigarette Smoking, Atrial Fibrillation, Asymptomatic Carotid Artery Stenosis and Sickle Cell Disease.
Here we focused on the role of most important factors in the second group regarding primary and secondary preventions.

1-Hypertension
Hypertension is a very important risk factor for both ischemic stroke and ICH and defined as a systolic blood pressure (SBP) ≥140 mmHg or a diastolic blood
pressure (DBP) $\geq 90$ mmHg. The relationship between BP and stroke risk is strong, continuous, graded, consistent, independent, predictive, and etiologically significant [5]. AHA/ASA 2014 Recommendations include:

**A) Primary Prevention**

4. For primary prevention, regular control and appropriate treatment of BP by lifestyle modification and pharmacological therapy is recommended.

5. For patients with prehypertension (systolic blood pressure of 120–139 mmHg or diastolic blood pressure of 80–89 mmHg), annual BP screening and lifestyle modification are recommended.

6. Reduction of BP is more important in reducing stroke than the choice of specific agent. Patients who have hypertension should be treated with antihypertensive drugs to a target BP of $<140/90$ mmHg. Self-measured BP monitoring is very important in BP control [6].

**C) Secondary Prevention**

Treatment of hypertension plays an important role in secondary prevention of stroke. The prevalence of HTN among patients with a recent ischemic stroke is $\approx 70\%$ [7, 8, 9]. Treatment of HTN in the first 24 hours is not recommended except for specific situations such as; therapy with tissue-type plasminogen activator (r-tpa), SBP $>220$ mmHg or DBP $>120$ mmHg [7]. In the presence of TIA or stroke, Thiazide and Angiotensin-converting enzyme inhibitors (ACEI) are suggested [28]. Here are 2014AHA/ASA recommendations:

6. Initiation of BP therapy is indicated for previously untreated patients with ischemic stroke or TIA who, after the first several days, have an established BP $\geq 140$ mmHg systolic or $\geq 90$ mmHg diastolic. Initiation of therapy for patients with BP $<140$ mmHg systolic and $<90$ mmHg diastolic is of uncertain benefit.

7. Resumption of BP therapy is indicated for previously treated patients with known hypertension for both prevention of recurrent stroke and prevention of other vascular events in those who have had an ischemic stroke or TIA and are beyond the first several days.

8. Goals for target BP level or reduction from pretreatment baseline are uncertain and should be individualized; but, it is reasonable to achieve a systolic pressure $<140$ mmHg and a diastolic pressure $<90$ mmHg. For patients with a recent lacunar stroke, it might be reasonable to target an SBP of $<130$ mmHg.

9. Several lifestyle modifications have been associated with BP reductions and are a reasonable part of comprehensive antihypertensive therapy include salt restriction, weight loss, consumption of a diet rich in fruits, vegetables and low-fat dairy products, regular aerobic physical activity and limited alcohol consumption.
10. The choice of drug for BP control is uncertain and should be individualized but diuretics or the combination of diuretics and an angiotensin-converting enzyme inhibitor is useful [3].

2- Dyslipidemia
There is an interesting relation between total cholesterol levels and stroke risk in general population: low levels of total cholesterol increase the risk of ICH and high levels of total cholesterol increase the risk of ischemic stroke. So, there is no positive association between total cholesterol level and stroke mortality [10]. Epidemiological studies evaluating the relationship between triglycerides and ischemic stroke have been inconsistent, in part because some have used fasting and others non-fasting levels [6]. Treatment with statins decreases stroke risk in patients with or at high risk of atherosclerosis [11, 12]. The usefulness of statins in ischemic stroke is most likely related to their capacity to reduce progression or to induce regression of atherosclerosis. The usefulness of other lipid-modifying drugs with or without statins in ischemic stroke is unknown [6].

2014 AHA/ASA Recommendations:

C) Primary Prevention
5. In addition to therapeutic lifestyle changes, treatment with an HMG coenzyme-A reductase inhibitor (statin) medication is recommended for the primary prevention of ischemic stroke in patients estimated to have a high 10-year risk for cardiovascular events as recommended in the 2013 “ACC/AHA Guideline on the Treatment of Blood Cholesterol to Reduce Atherosclerotic Cardiovascular Risk in Adults [13].
6. Niacin may be considered for patients with low HDL cholesterol or elevated Lp (a), but its efficacy in preventing ischemic stroke in patients with these conditions is not established. Caution should be taken with niacin because it increases the risk of myopathy.
7. Fibric acid derivatives may be considered for patients with hypertriglyceridemia, but their efficacy in preventing ischemic stroke is not established.
8. Treatment with nonstatin lipid-lowering therapies such as fibric acid derivatives, bile acid sequestrants, niacin and ezetimibe may be considered in patients who cannot tolerate statins, but their efficacy in preventing stroke is not established [6].

D) Secondary Prevention
4. Statin therapy with intensive lipid-lowering effects is recommended to reduce the risk of stroke and cardiovascular events among patients with ischemic stroke
or TIA presumed to be of atherosclerotic origin and an LDL-C level ≥100 mg/dL
with or without evidence for other clinical atherosclerotic CVD (ASCVD).
5. Statin therapy with intensive lipid-lowering effects is recommended to reduce
the risk of stroke and cardiovascular events among patients with ischemic stroke
or TIA presumed to be of atherosclerotic origin, an LDL-C level <100 mg/dL, and
no evidence for other clinical ASCVD.
6. Patients with ischemic stroke or TIA and other comorbid ASCVD should be
otherwise managed according to 2013 ACC/AHA cholesterol guidelines [16] which
include lifestyle modifications, dietary recommendations and medication
recommendations [6].

3- Diabetes Mellitus
Patients who suffer from diabetes mellitus have 2 problems; an increased
susceptibility to atherosclerosis and an increased prevalence of atherogenic risk
factors especially hypertension and abnormal blood lipids. Diabetes mellitus is an
independent risk factor for stroke [14] which increases the risk of stroke more
than 2 times. Duration of diabetes mellitus also increases the risk of nonhemorrhagic stroke (by 3%/y of diabetes duration)[14]. In pre-diabetes state,
fasting hyperglycemia is associated with stroke [15]. Glycemic control reduces
microvascular complications but there remains no evidence that improves
glycemic control reducing the risk of incident stroke. Here are the 2014 AHA/ASA
recommendations:

C) Primary Prevention
5. BP control in accordance with an AHA/ACC/ CDC Advisory 28 to a target of
<140/90 mmHg is recommended in patients with type 1 or type 2 diabetes
mellitus.
6. Treatment of diabetic adults with a statin, especially those with additional risk
factors, is recommended to lower the risk of first stroke.
7. The usefulness of aspirin in primary stroke prevention for patients with
diabetes mellitus but lower than 10-year risk of CVD is unclear.
8. Adding a fibrate to a statin in people with diabetes mellitus is not useful for
decreasing stroke risk [6].

D) Secondary Prevention
No major trials for secondary prevention of stroke have specifically examined
interventions for pre-DM or DM. There is no diabetic drug preferable over others
for vascular prevention. AHA/ASA 2014 recommendations:
6. After a TIA or ischemic stroke, all patients should probably be screened for
DM with testing of fasting plasma glucose, HbA1c, or an oral glucose tolerance test.
7. Choice of test and timing should be guided by clinical judgment and recognition. Acute illness may temporarily perturb measures of plasma glucose. In general, HbA1c may be more accurate than other screening tests in the immediate post event period.

8. The use of existing guidelines from ADA for glycemic control and cardiovascular risk factor management is recommended for patients with an ischemic stroke or TIA who also have DM or pre-DM.


10. CVD and aspirin allergy: Clopidogrel 75 mg/day [16].

Antiplatelet therapy in diabetic patients is shown in table below.

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**Antiplatelet Therapy Recommendations**

<table>
<thead>
<tr>
<th>Aspirin: Primary prevention</th>
<th>75-162 mg/day: type 1 and type 2 diabetes at increased CVD risk (10-yr risk &gt;10%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low-risk patients (10-yr risk &lt;5%):† not recommended; potential for bleeds likely offsets potential benefits</td>
<td></td>
</tr>
<tr>
<td>Men &lt;50 yrs, women &lt;60 yrs with multiple other risk factors (10-yr risk 5%-10%): use clinical judgment</td>
<td></td>
</tr>
<tr>
<td>Aspirin: Secondary prevention</td>
<td>75-162 mg/day: diabetes and CVD history</td>
</tr>
<tr>
<td>CVD and aspirin allergy</td>
<td>Clopidogrel 75 mg/day</td>
</tr>
<tr>
<td>Dual antiplatelet therapy</td>
<td>Reasonable for ≤1 year after ACS</td>
</tr>
</tbody>
</table>

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*Includes most men aged ≤50 yrs or women aged ≥60 yrs with ≥1 add’l major risk factor: family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria
†Men aged ≤50 yrs and women aged ≥60 yrs with no major additional CVD risk factors
ACS=acute coronary syndrome, CVD=cardiovascular disease


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**4-Cigarette Smoking:**

Cigarette smoking increases the risk of ischemic stroke (double) and SAH (2-4 folds increase) [7-12], but data on ICH are inconclusive. Cigarette smoking may potentiate the effects of other stroke risk factors including systolic blood pressure [21] and oral contraceptives. There is a reduction in stroke risk with smoking
cessation and with community-wide smoking bans. Passive smoking is a known risk factor for heart disease [22, 23]. Likely, smoking contributes to increased stroke risk through both short-term effects on the risk of thrombus generation in atherosclerotic arteries and long-term effects related to increased atherosclerosis [24]. Smoking as little as a single cigarette increases heart rate, mean BP and cardiac index; it decreases arterial distensibility too [25, 26]. After smoking cessation, the risk of stroke and other cardiovascular events rapidly reduce to a level that approaches, but does not reach that of those who never smoked [23, 26].

Recommendations of 2014 AHA/ASA:

C) Primary Prevention
3. Counseling, in combination with drug therapy using nicotine replacement, bupropion or varenicline is recommended for active smokers to assist quitting smoking.
4. Abstention from cigarette smoking is recommended for patients who have never smoked on the basis of epidemiological studies showing a consistent and overwhelming relationship between smoking and both ischemic stroke and SAH [6].

D) Secondary Prevention
In contrast to extensive data on the association between smoking and risk for first stroke, data on an association with recurrent stroke are sparse. No clinical trials have examined the effectiveness of smoking cessation for secondary prevention of stroke or TIA. Here are 2014 AHA/ASA recommendations:
4. Healthcare providers should strongly advise every patient with stroke or TIA who has smoked in the past year to quit.
5. It is reasonable to advise patients after TIA or ischemic stroke to avoid environmental (passive) tobacco smoke.
6. Counseling, nicotine products and oral smoking cessation medications are effective in helping smokers to quit [3].

Keywords: Stroke; Hypertension; Diabetes Mellitus; Hyperlipidemia; Smoking

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Effect of Nigella sativa extract on volume of middle cerebral artery occlusion induced ischemia in the male rats and the model to study stroke

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Introduction: Stroke still remains as a major cause of morbidity and mortality throughout the world. Now a day, there are some synthetic drugs to alleviate adverse effect of ischemia. In addition there are several herbal extracts have being studied for their neuroprotective effects in such condition. Nigella sativa is a natural based composition that has been used in many diseases for some centuries especially in traditional medicine. Therefore the potential neuroprotective effect of Nigella sativa has been considered in this animal based study.

Materials & Methods: The main goal of the present study was to investigate the effect of Nigella sativa extract (1ml/kg, po) for 30 continues days on and its neuroprotective effect in cerebral ischemia induced by middle cerebral artery occlusion (MCAO) model. In the mentioned model the middle cerebral artery was occluded for 1 h followed by 24 h of reperfusion one day after the termination of gavage protocol.

Results: The pretreated rats showed a significant improvement in neurological score and infarction volume compared to the control (distilled water) group, (One-way ANOVA, P<0.05).

Conclusion: It can conclude that the Nigella sativa extract reduce the amount of cerebral injury and infarction volume. So, it could propose as an effective herbal agent to improve neurological aspects of MCAO induced-ischemia.

Keywords: Stroke, Nigella sativa, neuroprotective
Effect of Fluoxetine on Motor Improvement in Ischemic Stroke Patients; a double blind clinical trial study

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Abstract

Background: Ischemic stroke is one of the most frequent reasons of adult disability. Newly, few trials have represented that fluoxetine might meliorate functional recovery after stroke, even in people who are not depressed. Our purpose of this study was evaluation of effectiveness of fluoxetine in rehabilitation of patients after stroke.

Materials and Methods: Patients who admitted for stroke participated in a double-blind, randomized, clinical trial study with fluoxetine (20mg once per day, orally), and placebo. They were examined for alterations in depressive mood, evaluated by the Hamilton Depression Rating Scale (HDRS), and changes in motor impairment, assessed by the Barthel Index (BI). All patients had physiotherapy. Assessments of patients were done in days 0, 45, and 90 with BI and HDRS scales according to their functional treatment response.

Findings: 172 patients were randomly assigned to fluoxetine (n=86) or placebo (n=86), and 150 were included in the analysis (75 in the fluoxetine group and 75 in the placebo group). Differences of BI between fluoxetine and placebo groups between days 0 to 45, between days 45 to 90, and between days 0 to 90 had significant statistical differences (p<0.001). Also for HDRS changes in fluoxetine group had significant statistical differences (p<0.001). On the other hand changes in placebo group had no statistical differences.

Conclusions: Early prescription of fluoxetine has significant effect on motor improvement after ischemic stroke.

Key Words: Rehabilitation, Cerebrovascular Stroke, Placebo Effect, Fluoxetine.
Safety and efficacy of intravenous tissue Plasminogen Activator (IV-tPA) in acute ischemic stroke patients, Update on Tabriz Thrombolytic Therapy on Acute Ischemic Stroke (T3AIS) project


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BACKGROUND: Intravenous tissue plasminogen activator (IV-tPA) has been proven to reduce mortality and morbidity after stroke if given within golden hours of symptoms onset. At this study our aimed is to assess feasibility, safety and efficacy of thrombolysis at our center.

METHODS: Prospectively, over a 4 year period, all patients who were treated with IV-tPA were recruited. Inclusion and exclusion criteria were almost based on American Heart Association (AHA) guideline for stroke. Outcome were measured based on MRS and National Institutes of Health Stroke Scale (NIHSS) changes between admission and after 3 months follow up. Any hemorrhagic complications including symptomatic or non-symptomatic, intra or extra cranial were recorded for safety assessment. In addition, prospectively, in-hospital stroke time targets during the diagnostic process preceding thrombolysis were recorded. The results are presented as median and interquartile range.

RESULTS: During the study period, a total of 142 patients were treated with IV-tPA. Median age was 66 (55-73) years; Median baseline NIHSS score was 14 (10-18). Thrombolysis was started at an average time of 144 (120-166) minutes after symptom onset. Nine non symptomatic (6.9%) and 5 (3.8%) symptomatic cerebral hemorrhages occurred. There were two urinary bleeding and one case of angioedema. At three months, favorable Outcome (MRS 0 or 2) was seen in 44.6%. The mortality rate (MRS 6) was 26.4% (32/121). The median door-to-CT time was 20 (11-27) minutes and the door-to-needle time was 55(40-71) minutes.

CONCLUSIONS: Intravenous thrombolysis with IV-tPA for acute ischemic stroke patients was safe and feasible in our center.

Key Words: Stroke; Thrombolysis; time factors; door-to-needle time
Functional electrical stimulation along with rehabilitation measures in the improvement of dysphagia in stroke

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Background: Dysphagia, which is a common snag following stroke, can be life-threatening and thus novel therapeutic techniques such as functional electrical stimulation (FES), improving such a problem, would be of crucial importance. Therefore, the present study was designed to assess the combination therapy of functional electrical stimulation and traditional techniques to achieve oral feeding and decrease discharges with NG tubes.

Material and methods: In the present study, 112 stroke patients with dysphagia were selected and evaluated by 3-ounce water swallow test and the results were recorded in the Northwestern Dysphagia Patient Check Sheet. Daily Electrotherapy with 4 electrodes placed on suprathyroid and infrahyoid muscles with a current with standard frequency, duration, and time was carried out. Thereafter, swallowing maneuvers and manipulation with modification of food texture were done and patients were weekly monitored for 5 weeks.

Results: Patients with ischemic and hemorrhagic strokes presenting with dysphagia accounted for 70% and 30%, respectively. Forty one percent, 54%, 40%, 47%, and 26% of the patients achieved oral feeding from first to fifth week, respectively.

Conclusion: Taking into account of the high prevalence of dysphagia in stroke patients, novel interventions such as FES coinciding with traditional rehabilitation measures may decrease the problem and hasten oral feeding.

Keywords: Stroke, Dysphagia, Functional electrical stimulation
Therapeutic Effects of Oral Dimethyl-fumarate on Stroke Induced by Middle Cerebral Artery Occlusion: An Animal Experimental Study

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Abstract

Introduction: The fumaric acid esters have been used for the treatment of multiple sclerosis and many other neurological diseases. We investigated the therapeutic effects of dimethyl fumarate on pathological and functional recovery of rats with middle cerebral artery (MCA) occlusion.

Methods: 21 Sprague-Dawley male rats weighing 275–300 g were randomized into 3 groups: in the sham group (n=7) the neck was opened but neither MCA was occluded nor any drug was administered. The control group (n=7) were treated with gavage of methocel (vehicle) for 14 days after MCA occlusion. In the DMF-treated group (n=8) treatment was done with 15 mg/kg body weight DMF (diluted in methocel) twice a day for 14 days after MCA occlusion. Temporary occlusion of the right MCA was performed by intraluminal thread in the DMF-treated and control groups. Neurological dysfunction score, Pole test (time to turn and time to descend), adhesive removal test (time to sense and time to remove), were performed before surgery, and on post-operative days 1, 3, 5, 7, 10 and 14. After the final behavior test, animals’ brains were perfused and removed. Brains frozeed and sectioned serially and coronally using a cryostat. The infract size and brain volume were estimated by stereology method.

Results: Percent of infarct area was significantly lower in DMF-treated animals compared to control and sham groups (P<0.0001). Among behavioral tests, DMF-treated group showed better function in NDS on days 7 (P=0.041) and 10 (P=0.046), but not in pole and adhesive removal tests. There was no significant correlation between behavioral tests and histological results.

Conclusion: Dimethylfumarate could be beneficial as a potential neuroprotective agent in the treatment of stroke.

Keywords: Stroke, Cerebrovascular accident, Dimethyl fumarate, Middle cerebral artery occlusion, Neuroprotection
Intracranial dissections: therapeutic approach

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2. Assistant Professor of Neurology, Zabol University of Medical Sciences, Zabol, Iran.

Abstract
Intracranial dissections (ICDs) have only been reported in small case series. Cervicocephalic dissections (CCDs) are responsible for 5-20% of ischemic strokes in individuals younger than 45 years. ICDs account for approximately 10 percent of CCDs with death rates approach 70% or higher compared to extra cranial carotid and vertebral dissections (5-10% mortality rate). In ICD, different pathologic involvement of vessel wall leads to formation of intramural hematomas and narrowing of the vessel lumen. Most ischemic symptoms (85-95%) are caused by emboli from the site of the dissection, while the remainder is due to vessel narrowing with hemodynamic insufficiency (5-15%) or a combination of both. The most frequent presenting complaints with cervicocephalic dissections are ischemic symptoms that include transient ischemic attack (TIA) or stroke (cerebrovascular accident) with pain complaint in the second place. Trauma, arteriopathies, systemic infections, hypertension, migraine, elevated homocysteine levels, alcohol and oral contraceptive use are identified causes of CCD. Since most ischemic strokes caused by dissections are likely to be due to emboli originating from a thrombus at the site of dissection, many experts recommend anticoagulation for the first 3-6 months. Patients presenting within 3-4 1/2 hours of stroke symptom onset may be considered for treatment with intravenous tissue plasminogen activator. The role of thrombolysis in patients with acute infarction secondary to dissection is unproven. In most patients, the vessel wall is fully healed after 3-6 months; thus, patients may be switched to aspirin. Alternatively, all therapy may be discontinued.

Keywords: Intracranial dissection; carotid; vertebral; thrombolysis
Prognostic value of HbA1c in ischemic stroke patients

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Background: Diabetes is a well-known risk factor for ischemic stroke. Prognostic value of HbA1c in ischemic stroke patients has been in attention in recent year. The aim of this study was to evaluate prognostic value of HbA1c serum level on morbidity and mortality in ischemic stroke patients.

Methods: This is a cross sectional study on 150 patients with acute ischemic stroke, confirmed with neuroimaging. HbA1c during the first 24 hours of admission were assessed. Subsequently, the patients were categorized in two groups in term of diabetics and followed to assess for morbidity (by NIHSS score) and mortality in one and three months follow up. The data were analyzed statistically using t-test and logistic regression.

Results: Mean NIHSS score in one month post stroke in patients with normal and abnormal HbA1c was 5/44±0/53 and 6/36±0/84.(p=0/43) respectively. Mean NIHSS score in three months post stroke in patients with normal and abnormal HbA1c was 4/71±0/52 and 6/25±0/97 respectively.(p=0/19) Mean NIHSS score in one month post stroke in diabetic and non diabetic patients was 5/86±0/72 and 5/53±0/57 respectively.(p=0/75) Mean NIHSS score in three months post stroke in diabetic and non diabetic patients was 5/55±0/76 and 4/79±0/53 respectively. (p=0/47) In diabetic and non diabetic patients mortality rate was correlated with age (p=0/02 6) and (p=0.018).
In non diabetic patients mortality rate was correlated with HbA1c (p=0/002)

Conclusion: HbA1c may be a predictive factor in non diabetic patients with ischemic stroke.

Key words: HbA1c, Stroke, Prognosis
Role of Omega3 in stroke prevention

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Fatty acids (FAs), the components of phospholipids in organelle and cellular membranes, play important biological roles by maintaining or processing membrane protein function or fluidity. In addition, FAs modulate vascular inflammation, a key mechanism of atherosclerosis, cerebral small vessel pathologies, and stroke, by altering intracellular signal transduction or controlling lipid mediators. Omega 3 decrease expression of receptors for chemoattractants on blood inflammatory cells and prohibit migration of neutrophils or monocytes. Therefore, omega 3 may protect from atherosclerotic changes.

Several clinical studies have emphasized the role of FAs in the risk or occurrence of stroke or cardiovascular disease. High-dose ω3-PUFAs has been reported to have beneficial effects on cardiac or sudden death. High levels of plasma ω3-PUFAs can decrease the risk of myocardial infarction. In terms of stroke, low levels of circulating ω3-PUFAs in the blood is a risk factor for ischemic and hemorrhagic stroke. A decreased proportion of linoleic acid is also associated with ischemic stroke.

Compared to normal controls, stroke patients with moderate-to-severe intracranial arterial stenosis or occlusion had decreased levels of DHA. On the other hand, a recent meta-analysis revealed that the evidence for the beneficial effects of ω3-PUFAs is insufficient in adults with peripheral arterial disease associated with poor cardiovascular outcome.

Some study results demonstrate that ω3-PUFA levels correlate with stroke severity at admission and functional outcomes at 3 months. ω3-PUFAs may be considered potential blood biomarkers for prognosis of acute non-cardiogenic ischemic stroke patients.
MECHANICAL THROMBECTOMY IN STROKE,
The initial experience in Mashhad University of Medical Sciences

Mohammad Reza Sobhani MD, Human Baharvahdat MD FACS, Payam Sasannezhad MD, Kavian Ghandehari MD FLSP RCPC

Introduction: Although intravenous thrombolysis is an approved treatment for ischemic stroke, here we present our first experience of mechanical thrombectomy in Mashhad University of Medical Sciences.

Materials and Methods: In this study, the patients with suspected ischemic stroke were enrolled according to following inclusion criteria: modified NIHSS: 4-20, ASPECT >8, the window time between onset of symptoms and treatment less than 6 hours or small ischemia evidence in FLAIR.

Results: Five patients were included in the study from February 2015 to April 2015. Main MCA (M1) occlusion in 4 cases. BA occlusion in 1 case. Mean age was 58/4 years, with range of 28-79 years. Mean pre operation modified NIHSS: 12/8. Mean hours between onset of symptoms and treatment: 5/6 hours.

In one patient, IA thrombolysis and mechanical thrombectomy is carried out. In two patients Eric retrieval stent was used and in three cases Solitaire was used. Mechanical revascularization achieved completely in 4 patients and incomplete in 1 patient. Mean postoperation NIHSS after 72 hours: 7/8. Survival rate: 80%. One death is due to hyperkalemia.

Conclusion: Early mechanical thrombectomy of main intracranial arteries could result in good outcomes in most cases of ischemic stroke.

Keywords: Ischemic stroke, thrombectomy, mashhad university of medical sciences
Care of patients with stroke who are treated R-TPA were injection

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Stroke ward of Namazi Hospital Shiraz University of Medical Sciences

In patients with acute stroke symptoms (under 3 hours) to visit the hospital emergency team now and for the patient's bedside glucometry TPA was then inserted intravenous lines and sampling for laboratory analysis needed to do. Tests required by emergency medicine physicians, that immediately for (, NA, K BUN, CBC, BS, PT, PTT, INR).

The patient immediately transferred to the CT scan and CT scan without contrast is the brain. If you scan the patient during transfer and while it is based on observation of the patient is not a contraindication for injection and the scan will not be a contraindication to thrombolytic therapy, the patient injection site (part of the brain angiography) will be transferred. A second vein located at the site of injection to the patient and placed under continuous cardiorespiratory monitoring. After filling out the forms MRS, NIHSS and acquit written consent of relatives and patients in the absence of contraindications to testing, to inject a doctor on call will be contacted and if the corresponding master, injection starts immediately.

Reception time to do a brain scan should be less than 25 minutes and reception time until the start of infusion should be no less than 60 minutes.

**Contraindicated in patients candidate to receive r-TPA:**
- Any recent surgery > 14 days
- serious head trauma Intera Cranial
- MI recent surgery or previous stroke within 3 months
- past history of ICH
- uncontrolled hypertension at the time of treatment (BP >185/110)
- seizure at the start of stroke
- Internal bleeding active (> 21 days)
- Neuoplasm inside the skull,
- AV malformation
- Aneurysm
- patient on anticoagulation with 15 PT> or 1.7 INR>
- plt less than 100,000 / mm
- heparin within 48 hours prior to the stroke, PTT, up to 40 seconds at the time of admission
- 1.p> 7 days or perforation of the artery recently created
- subarachnoid hemorrhage [imaging or clinical symptoms]
- CT (ICH, SAH, or core symptoms of stroke Haddzrg) [eg, hypodensity more than 1/3 of the cerebral hemisphere

Conditions that may increase the risk of adverse health effects but are not necessarily a contraindication to treatment include:
- Stroke severity is too intense (NIHSS greater than 22)
- blood sugar less than 50 or more than 400 mg / dL [if the metabolism changes and injuries remain. If the artery is early detection, treatment may be started.]
- thrombosis of the left side of the heart

Calculate the exact dose based on the patient's weight rTPA known or measured.

<table>
<thead>
<tr>
<th>Conversion to Kilograms (Kg)</th>
<th>Total iv t-PA Dose (mg) at 0.9 mg/kg</th>
<th>t-PA Relux (mg) *10% of total</th>
<th>t-PA Relux (ml)</th>
<th>Discard Dose t-PA (mg)</th>
<th>Infusion Dose (mg)</th>
<th>Infusion Rate (ml/hr)</th>
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</thead>
<tbody>
<tr>
<td>100.0</td>
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</tbody>
</table>

Important points:
- injected up to 24 hours of fasting like.
- dressing up to 24 hours not only the patient's clothing is loose and comfortable.
- blood and other invasive procedures do not apply to the first 24 hours the risk of bleeding.
- second day echocardiogram is done to control patients.
Nursing care of cerebral angiography

**Masoumeh. Sobhani**  
Stroke ward of Namazi Hospital Shiraz University of Medical Sciences

Cerebral angiogram: angiogram of the carotid, cerebral angiography, also called cerebral arteriogram.

Cerebral angiogram (arteriogram) diagnostic images of the arteries in the brain or head that the blood flow in them. This action provides diagnostic to physicians in the diagnosis group of conflicts with blood vessels in the head and neck of a ruptured artery or arterial blockage, usually If a vein is blocked by plaque fat, the patient may be at increased risk for stroke. Other conditions (eg cerebral aneurysm) may appear during cerebral angiogram.

Physician to perform an angiogram, dye for (contrast medium) into a long thin tube called a catheter through the arteries of the brain through blood vessels passed catheter injected, usually into the upper parts of the catheter at the desired location the doctor injects dye through the catheter arteries. After the dye into the arteries was the target of an x-ray can be taken Although mainly body numb the catheter insertion site, the patient until the end of the action The patient is usually awake before performing a brief sedate movements of the catheter during vascular Knd.bhr not feel like the incandescence had some feelings or heat as the contrast agent will be played there.

Preparations before the operation may vary and patients to discuss and consult with your doctor about how the brain anjogram also like to encourage this action coronary angiography is usually done outpatient and day surgery patients are generally able to own homes return. In some cases, patients remain in the hospital for care or do more tests. The most common risk associated with allergic reaction to the contrast material is angiographical brain. Patients should their doctors of any known allergies, especially to iodine, shellfish or strawberries aware. The risk of a ruptured artery catheter or moved by a piece of plaque that can block blood flow and cause a stroke there.

Pregnant women or women who are pregnant or women who care tend to have significant period of time needed to discuss and consult with your doctor about the use of this action due to the risk of damage to the fetus in pregnant women usually not done by x-ray.

**Before cerebral angiogram:**

The day before surgery Doctors necessary information about the patient’s medical history and medications appropriately collect Myknnd.afrad to your doctors and nurses pregnancy, try to notify pregnant before s In addition, if you have been diagnosed with one of the following to tell:

- coagulation disorders
- liver or kidney disease
- thyroid disorders (Hyperthyroidism or hypothyroidism)
• allergy to iodine (contrast material previous experiments), shellfish (crab or shrimp) or strawberries

Preparations for cerebral angiogram may vary, depending on the patient's condition or control strip that has been detected. Patients will be provided with the required instructions, which may include the following:
• Refrain from eating for 6 to 12 hours before the test
• Drinking 8 to 10 glasses of water (other than juice and lemonade) in the 24 hours before surgery
• Ensure that the drug changes applied. The doctor may ask patients taking certain medications (aspirin, etc.) for several hours and/or days before the operation stop, or change the dose of medication or the use of simple Bdhnd.bymaran should bring their medication to Although skeptical of drugs bring a temporary hospital to have the operation.urgery.

Blood tests. Special blood tests before surgery may be required, including, BUN, Cr and blood coagulation studies.
• Arrange to move and transfer the patient from the operation to be performed if the man regarded as an outpatient.

Day surgery is usually an outpatient hospital patient is admitted. Physician (usually a specialist radiology) and other health care professionals and patients how to perform the desired action described patients will respond to all questions.

After cerebral angiogram:
Patients in the hospital for several hours to ensure no bleeding and allergic reaction to the contrast material used during angiography under the care of some of the desired results may not be immediately discussed with the patient after surgery be. Full results may take several days or longer after other meetings to discuss. Patients discharged for 12 to 24 hours of compete bed rest.
Should gradually to normal activities and their daily special about diet and activity levels before discharge, pelvic pain patients will have to drink 8 to 10 glasses of water daily, and for several days after an angiogram continue to discharge material. Contrast the remainder of the body systems help patients Think recommended action area (arm, leg, etc.) or keep the ice in place 6 to 12 hours after angiography topical use. Special orders and other wound care and follow-up meetings subsequent angiogram. However, complications are rare, but the physician should immediately alert the patient experience any of the following:

Wound red, swollen or warm to the touch
• bleeding from the wound that can not be stopped except by local press on it
• itching or rash
• fever and sweating
• breathing problems (shortness of breath, etc.)
• weakness, tingling or burning sensation and numbness in member
• visible problems
• confusion or loss of consciousness
• seizure
Nursing care of Motor deficits

Masoumeh. Sobhani
Stroke ward of Namazi Hospital Shiraz University of Medical Sciences

For mobility problems, the most important step is to consult with a physiatrist
• Keep objects close to half of her body healthy.
• the patient's body position should be changed every two hours.
• The patient can be positioned from one side to the other side, but over half injury
time when he sleeps body should be limited.
• act in furtherance of the interpreter and the patient can help (such as a cane, walker, wheelchair).
Help the patient to exercise their powers in a semi-normal, half-normal increase
and also, do some exercise.
• to exercise the affected leg or arm strength, mobility, and users will have to
increase it.
• The exercise at least 5 times a day and should be done every ten minutes.
• The sooner the patient can be helped down from the bed.
patients with lumbar support and can keep his balance. If you have symptoms
(dizziness, sweating and shortness of breath) immediately return the patient to a
sitting position.
If the patient needed a wheelchair, a variety of folding the hand brake is more
effective because it can help patients to control it by hand. When the patient was able to maintain balance while standing, walking slowly to
start. In this way, the patient is standing between two parallel rails and put your
weight on both feet.
Patients should be given individualised positioning and early mobilisation
management plans as soon as possible after a stroke to prevent complications and
to regain function.

Complications of poor positioning
• Pressure damage
• Poor blood oxygen saturation
• Chest infections
• Pulmonary embolism
• Urinary tract infections
• Constipation
• Decreased range of movements
• Muscle atrophy
Joint contractures  
Orthostatic blood pressure problems  
Oedema  
Psychological problems  

Sources: Askim et al (2012); Kilbride and Kneafsey (2010); Indredavik (1999)

Nurses may give mobilising and positioning patients a lower priority than their other nursing activities. When they change a patient’s position, it may be unrelated to positional correction or rehabilitation (Kilbride and Kneafsey, 2010; Long et al, 2002; Dowswell et al, 2000).

The Trondheim model, which is often considered the gold standard for a stroke unit, involves nurses receiving training and working with the unit-based physiotherapist. This enables nurses to become experts in early mobilisation, and to use cooperative working practices with other team members.

Nurses can then work beyond the confines of their professional knowledge. This interdisciplinary working (rather than just multidisciplinary teamworking where all the team may be present but not necessarily working cooperatively) ensures that therapy continues 24 hours a day; it also avoids patients waiting for the physiotherapist to mobilise them.

To develop the expertise to provide this gold-standard care in their stroke service, nurses need specialist knowledge and skills as defined in the stroke-specific education framework, and therefore need appropriate training. They should acquire this in formal training sessions and in practice, by working with physiotherapy and occupational therapy staff to learn safe and correct ways to move and handle individual patients.

**Recommended positions and movements**

- Sitting supported in bed  
- Sitting supported out of bed  
- Transferring with hoist  
- Rolling to sit up  
- Sitting with no support  
- Transferring with feet on the floor  
- Standing

Preventing complications of stroke

‘Early’ mobilisation takes place within the first week after a stroke while ‘very early’ mobilisation takes place within the first 24 hours (Bernhardt, 2008). In the first 24 hours, patients often have problems such as reduced levels of consciousness and awareness, weakness and/or reduced coordination of one or more limbs, and sensory and visual loss. These symptoms may make it difficult, and in some cases unsafe, to get out of bed.
However, it is thought that the benefits of early mobilisation, when patients’ clinical condition allows, are greater than the risks when it is delivered by appropriately trained staff using a management programme on a stroke unit (Skarin, 2011; ICSWP, 2008).

An estimated 85% of patients develop complications following a stroke, and up to 51% of deaths in the first 30 days after stroke are due to immobility (Bernhardt, 2008).

Positioning patients correctly, and assisting them to sit up in bed early in their stroke care helps to prevent complications such as those listed in Box 1. Sitting up also helps with maintaining nutrition and hydration and patients feel it has psychological

Aids to mobilising and positioning
The national stroke strategy (DH, 2007) states that stroke units should provide an appropriate environment for rehabilitation, or recovery can be delayed and patients’ final level of independence may be limited.

Patients should be assessed on their need for equipment that provides postural support and pressure relief; many also need specialist equipment to assist with early mobilisation and 24-hour positioning. This could include specialist seating, splinting, orthoses, and specialist positioning accessories.

Nurses have a critical role in mobilisation, which can begin immediately on admission with use of a profiling bed for severely affected patients.

Nurses can work with the therapy team to use the profiling bed to support upright seating and other positions for patients who are too medically unstable to tolerate sitting out of bed (SIGN, 2010). An upright chair position can be simulated by use of the backrest, knee break and downward tilt of the bed.

Patients should be assessed by an occupational therapist and physiotherapist to establish their need for equipment to support positioning and mobilisation. This equipment will need to be incorporated into the individualised positioning plan. When they can begin to sit out of bed, the occupational therapist and physiotherapist will assess their sitting balance and determine what type of seating is suitable.

Many patients only require a bedside chair of suitable dimensions (such as one with a seat height that allows them to place their feet flat on the floor), is comfortable and facilitates normal movement and good posture.

Stroke units should also have a variety of specialist seating available to support patients of varying abilities.

This should include tilt-in-space seating systems, both chairs and wheelchairs (Fig 1). This type of system allows for changes of position and redistribution of pressure through small adjustments to the position of the chair; it may also
incorporate a back recline. Chairs that allow adjustment in seat depth, width and accessories can be adapted to patients’ size, shape, height and weight. It is essential that nursing staff have the training and competence to use specialist seating and other equipment correctly, and know who to contact if problems develop with it (ICSWP, 2008). They can then ensure safe comfortable positioning and early mobilisation for their patients.

**Conclusion**

Nurses who develop expert skills by working as part of an integrated stroke team play a crucial role in improving patient outcomes. By applying individualised positioning and early mobilisation management plans, and by using appropriate equipment, nurses can improve survival, promote patients’ functional recovery, and reduce the risk of secondary complications.
Nursing care of stroke

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What is a Stroke? Brain tissue is damaged from a sudden loss of blood flow, resulting in a loss of neurological function.

Causes: Blockage (blood clot) occurring inside a blood vessel Blood vessel leaks blood due to rupture. Ischemic Stroke Embolic Stroke Blood clot travels to the brain. Thrombotic Stroke Blood flow is blocked to the brain. Hemorrhagic Stroke

Possible complications of stroke:-permanent loss of movement or sensation of a part of the body. -joint contractures -muscle spasticity -permanent loss of cognitive or other brain functions. -disruption of communication, decreased social interaction. -decreased ability to function or care for self. -decreased life span. -urinary and respiratory tract infection. Malnutrition. Pressure ulcers.

Malnutrition: Malnutrition is common both before and after stroke, with dysphagia adding to nutrition risk. Many patients require specialized nutrition support in the acute phase and beyond when swallowing function does not improve or return to allow for nutrition autonomy. When neurologic deficits improve, assessment of the swallowing function, introduction of dysphagia diets, and specialized swallowing techniques are used to transition away from enteral feeding tubes to oral diets. A-When patients cannot meet their nutritional needs by mouth or are at high risk of aspirating food, tube feedings may be required. B-Poor nutritional status post stroke increases length of hospital stay and risk of complications and undernourishment on admission is an independent marker of poor outcome at six months post stroke. C-selection of GASTROSTOMY FEEDING for patient.

Pressure ulcers: Pressure ulcers may form when a stroke patient is left alone in bed or sitting for a period of time. Due to their diminished sensation they do not feel that they have stayed on that same position for quite some time: it is important to pay attention during the stroke rehabilitation.

- The stages of pressure ulcers are related to the amount of damage done on the soft tissues. These are: -Stage I – nonblanchable erythema. There is a red spot on the skin that would not go away. This is a sign that ulceration may develop. -Stage II – partial thickness loss. An abrasion, a blister or a shallow crater may form during this stage. The pressure ulcer formed involves the epidermis and the dermis. -Stage III – full-thickness skin loss. There is damage or necrosis of subcutaneous tissue which may reach down to but not through the underlying fascia (tissues which surrounds muscle tissues). The pressure ulcer looks like a deep crater but has not reached the stroke patient’s muscle. -Stage IV – full-
thickness skin loss with tissue necrosis or damage to muscle, bone or supporting tissues which are the tendon, ligaments, etc Effective guidelines for the prevention of stroke:

• Choose a diet that is beneficial for a healthy heart:
  • This diet is usually rich in fruits and vegetables, reducing salt intake, consumption of large amounts of vitamin C and omega-3 fish oil.
  • Have your blood pressure down.
  • Do not forget to exercise daily for 30 minutes.
  • Low natural ways to keep your cholesterol.
  • Have your blood fat levels are always kept in mind control.
  • If you suffer from diabetes prevention and control it.
  • Lose weight and keep weight at a healthy level avoided.
  • Relaxation techniques for stress reduction and relaxation take advantage.
  • If you smoke, quit smoking.
Updated Pharmacotherapy Strategy in Management of Stroke with Extending to a Matter for Debate related to Drugs Distribution within Ischemic Brain

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BACKGROUND: Disturbance in blood-brain barrier is connected with cerebral ischemia and clues to vasogenic edema, a key reason of stroke-associated mortality. To date, only a single drug has established FDA agreement for severe ischemic stroke management, recombinant tissue plasminogen activator (rt-PA).

OBJECTIVE: Reviewing molecular models connected with cerebral ischemia and novel methods for transporting drugs to treat ischemic disease was of interest that investigated.

METHODS: Directory of Open Access Journals (DOAJ), Google Scholar, Pubmed (NLM), Library, Information Science and Technology Abstracts (LISTA, EBSCO publishing) and Web of Science with key words relevant to topic of this review were searched.

RESULTS: Recombinant tissue plasminogen activator (rt-PA) re-establishes perfusion to ischemic brain, significant tissue injury happens after cerebral blood flow is regenerated. Thus, there is a serious need for original healing methods that can “save” salvageable brain nerve to defend BBB veracity throughout ischemic stroke. In different grades of stroke such as Grade 1A (within 3 h of symptom onset), Grade 2C (within 4.5 h of symptom onset) pharmacotherapy study showed beneficial outcome. Another category of drugs that may allow neural cell save subsequent cerebral ischemia/reperfusion damage is the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors or statins. Understanding prospective central nervous system drug distribution tracks for statins is serious to their efficacy in ischemic stroke.

CONCLUSIONS: To complete benefit-risk assessment, direct thoughtful and well-adjusted pharmacotheray data, intervention in Iranian patients with stroke should be based on linear regression models of pharmacokinetics parameters.

Key words: Stroke; recombinant tissue plasminogen activator; Pharmacokinetics
Evaluation of Cardiac Sources of Emboli by Transesophageal Echocardiography in the Ischemic Stroke Patients in Shiraz

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Abstract

Background: Embolus is one of the causes of ischemic stroke that can be due to cardiac sources such as valvular heart diseases and atrial fibrillation and atheroma of the aorta. Transesophageal echocardiography (TEE) is superior for identifying potential cardiac source of emboli. Due to insufficient data about TEE findings in ischemic stroke in Iran, the present study was done to evaluate cardiac source of emboli by TEE.

Methods: This is a hospital-based cross-sectional study conducted during May to February of 2012 in Shiraz Nemazee teaching hospital. Patients that referred to this centre and were admitted with stroke diagnosis were included but hemorrhagic stroke cases were excluded. 229 patients with ischemic stroke diagnosis were included and underwent TEE.

Results: Causes of cardiac emboli were detected in 65 cases (40.7%) and categorized to high-risk (29.7%) and potential risk (11%). High risk cardiac sources including atrial fibrillation (8.7%), mitral valve disease (MS or MI) 11 cases (4.75%), aortic valve disease (AS or AI) 8 (3.5%), prosthetic valve 3 (1.35%), dilated cardiomyopathy 45 (19.65%) and congestive heart failure with ejection fraction < 30% in 8 cases (3.5%). Potential cardiac sources of emboli comprising 7 cases (3.05%) septal aneurysm, 4 (1.75%) left ventricular hypokinesia, 13 (5.7%) mitral annular calcification and 9 cases (3.95%) complex atheroma in the ascending aorta or proximal arch.

Conclusion: Our study showed that high risk cardiac source of emboli can be detected by TEE in a considerable percentage of ischemic stroke patients. The most common high risk cardiac sources were dilated cardiomyopathy and valvular heart diseases.

Keywords: transesophageal, echocardiography, stroke, embolic
Comparison of serum lipids levels in patients with ischemic and hemorrhagic strokes (Rafsanjan 2013-14)

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Abstract

Background: Stroke is based on disturbance in the blood flow, either ischemic or hemorrhagic type. Although serum lipids were known as a risk factor for atherosclerosis, but the relation between serum lipid level and type of stroke is not well known. Previous studies have different results on the role of dyslipidemia in various types of strokes and remain controversial. The aim of this study was to compare the serum lipid profile in patients with ischemic and hemorrhagic strokes.

Method: In this study 201 patients with ischemic and hemorrhagic stroke in neurology ward of Ali Ebn-Abitaleb hospital, were evaluated in the first day of admission. A check list of all required data was collected in each patient. Lipids, including TG, TC, LDL, HDL, measured in the fasting period and all data were collected.

Results: In this study, 201 patients with stroke were studied. 48/8% of patients were male and 52/2% of them were female. A significant relation between sex and serum levels of TC, LDL and HDL was found. All three lipid levels were higher in female than male. TG levels were respectively higher in SAH patients and after that ischemic stroke cases in comparison to patients with intracranial hemorrhage (ICH). There was a significant statistical relationship between the type of strokes and serum levels of HDL. HDL levels were higher in intracranial hemorrhage in comparison to ischemic strokes.

Conclusion: There was a statistically significant relationship between serum levels of TG and ischemic stroke. HDL levels were higher in intracranial hemorrhage patients compared with ischemic strokes in our patients.

Keywords: Ischemic stroke, hemorrhagic stroke, serum lipids
Management of Stroke Described by Ibn Sina (Avicenna) in the Canon of Medicine

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Abstract:

Background: Stroke or cerebrovascular accident (CVA) is caused by a disturbance to the blood supply to the brain and accruing loss of brain function. The first recorded observations were in 2455 BC and it has been studied intensely by ancient physicians throughout history. Ibn Sina (Avicenna, 980-1025AD) was one of the most prominent Persian scientists in the history. We aimed to clarify his views on stroke and consider his knowledge based on current investigations.

Methods: We studied Avicenna’s Canon of medicine and excluded the related data to the stroke. Also, we used current investigations by searching in main indexing databases like PubMed and Scopus.

Results: Ibn Sina called stroke sekteh and described it extensively. Some of Ibn Sina’s definitions and his etiology of stroke are based on humoral theories and cannot be compared with medical current concepts, but most of his descriptions concur with current definitions. This study examines the definition and etiology, clinical manifestations, prognosis, differential diagnosis, and interventions for stroke based on the Canon. The pharmacological effects of medicinal herbs suggested by Avicenna for stroke are examined in light of current knowledge. Results show among 23 medicinal plants suggested by Avicenna in stroke, the probable effects of 21 of them (based on their mechanism of actions) are supported by current findings. But only one of them directly was evaluated for stroke.

Conclusion: This study shed light a part of history of stroke and also suggested 21 medicinal plants can be good potential remedies to future evaluations on stroke.
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