Review Article

Evaluation of Acute ischemic stroke management approach in the emergency department: Literature review

Abduljalil Hussain Almarzooq[1]*, Nawa Fahad Alshahrani[2], Nadia Ali Al-Hariri[2], Jarah Moayad Alobaid[3], Zahra Haider Alshurafa[4], Turki Jafar Abdulmajid[5], Ameera Ahmad Alhawsawi[6], Almuhannad Saad Alarbash[7], Eman Kamel Alzayer[8], Ibrahim Mutlaq Alotaibi[9]

[1]Emergency Department, King Fahad Hospital Hufof, Alhasa, Saudi Arabia.[2] Faculty of Medicine, King Khaled University, Abha, KSA. [3] Faculty of Medicine, Imam Muhammad Ibn Saud Islamic University, Riyadh, Saudi Arabia. [4] Faculty of Medicine, Alfaisal University, Riyadh, Saudi Arabia. [5] Faculty of Medicine, King Abdulaziz University, Jeddah, Saudi Arabia. [6] Faculty of Medicine, Umm Al Qura University, Makkah, Saudi Arabia. [7] Faculty of Medicine, King Faisal University, Al Ahsa, Saudi Arabia. [8] Emergency Department, Abqaiq General Hospital, Abqaiq, Saudi Arabia. [9] Faculty of Medicine, Shaqra University, Shaqra, Saudi Arabia.

Abstract

Background: Stroke is a clinical syndrome consisting of rapidly developing clinical signs of focal or global disturbance of cerebral function that lasts more than 24 hours; and/or leads to death with no apparent cause other than a vascular -brain-origin. Stroke globally is the second leading cause of mortality; however, it is the third most common cause of mortality in low-income countries. This disease is causing a huge global burden on the economy and health care systems, with one-third of patients being dependent (partially or completely) on a caregiver. Thus, management and treating such cases is a vital and important aspect in the whole medical field, starting from the emergency department up till admission to the ward and long term follow up. **Objectives:** We aimed to review the literature reviewing the pathophysiology of acute ischemic stroke, clinical features, risk factors, diagnosis, and management of this disease in the emergency setting. **Methodology:** PubMed database was used for articles selection, papers on were obtained and reviewed. **Conclusion:** Acute ischemic stroke is one of the most common and fatal diseases that physicians in the emergency departments face almost on a daily basis. Many options of treatment are available, with a significantly better outcome when given early, public knowledge of alarming signs is of utmost importance. Moreover, many new treatment options are being studied and may prove to be the most needed breakthroughs in dealing with one of the greatest causes of morbidity and mortality worldwide.

Keywords: Acute Ischemic Stroke, Presentation, Risk Factors, Diagnosis, Management

Introduction

Stroke is a clinical syndrome consisting of rapidly developing clinical signs of focal or global disturbance of cerebral function that lasts more than 24 hours; and/or leads to death with no apparent cause other than a vascular-brain-origin.[1] Stroke globally is the second leading cause of mortality; however, it is the third most common cause of mortality in low-income countries. Nevertheless, two-thirds of the deaths related to stroke happen in developing countries. Stroke as a spectrum can be subdivided into ischemic and hemorrhagic origins; and both share almost the same clinical presentation but differs greatly in management. Nevertheless, the relative prevalence of either of the two main types varies across countries. In the US, The incidence of acute ischemic stroke is about 800,000 patients per year. Additionally, experts expecting even more rise in the number of cases in the next 10 years due to the aging of the population as a whole, with a higher rise expected in low-income countries to more than 100%.[2] As a result, this disease is causing a huge global burden on the economy and health care systems, with one-third of patients being dependent (partially or completely) on a caregiver.[3] Thus, management and treating such cases is a vital and important aspect in the whole medical field, starting from the emergency department up until admission to the ward and long-term follow up. In this paper, we will review the proper literature discussing pathophysiology behind stroke with a focus on the ischemic type, risk factors, diagnosis, and management options for such cases.

Address for correspondence: Abduljalil Hussain Almarzooq, Emergency Department, King Fahad Hospital Hufof, Alhasa, Saudi Arabia.
Email: jalimar62 @ gmail.com

How to cite this article: Hussain Almarzooq, A., Fahad Alshahrani, N., Ali Al-Hariri N., Moayad Alobaid, J., Haider Alshurafa, Z., Jafar Abdulmajid, T. and *et al.* Evaluation of Acute ischemic stroke management approach in the emergency department: Literature review. Arch Pharma Pract 2020;11(4):26-31.

Methodology

PubMed database was used for articles selection, and the following keys used in the Mesh ((“Ischemic Stroke"[Mesh]) AND (“Diagnosis"[Mesh] OR "Management"[Mesh])). In regards to the inclusion criteria, the articles were selected based on the inclusion of one of the following topics; ischemic stroke evaluation, management, and diagnosis. Exclusion criteria were all other articles that did not have one of these topics as their primary endpoint.

Review

Ischemic stroke is one of the leading causes of death; and, thus, it has major attention in terms of understanding the whole process behind it, how to discover it, and how to treat it. Unfortunately, and up to the late 1990s, the general approach was to “wait and see” in such patients, which resulted in a very poor prognosis and increased burden in both community and health care.[4] However, nowadays with the major advancements in the medical field, we have a better understanding of the processes behind the disease, multiple drugs were developed and proved to be effective, and the overall prognosis and long-term management became a reality for such patients, rather than just wait with no active intervention.

Pathophysiology

The main mechanism behind ischemic stroke is the reduction of blood flow delivered to the brain, which results in an insult to its tissues. Due to the complex brain blood vessels, usually, ischemic strokes are focal. When the insult happens, the central region has almost no blood flow, and the area rapidly dies within minutes. However, the surrounding tissues still have their blood flow above the “death” threshold, but with below functional levels and such zone is named “penumbra”. This penumbra has a very limited time, and cells usually die after a certain period of time. Thus, such a time window is the main focus for clinicians to try and restore the blood flow in order to save such regions from permanent death.[5]

The concept behind cell death in the center area is that the adenosine triphosphate (ATP) usage does not stop in the neurons even though the synthesis is not enough. The net results of such a process are; the drop of the total ATP levels, an increase of the total ADP, and the development of lactate acidosis occur as well due to the concomitant loss of ionic homeostasis. This starts the rapid and fatal ischemic cascade that involves multistep and multicell series of downstream mechanisms. Neurotransmitters release and inhibition of their reuptake is another major event in the neural tissue affected. With multiple neurotransmitters of note, the main one being glutamate, which is the main excitatory one. When this transmitter binds to ionotropic N-Methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) receptors (iGluRs), a major influx of calcium happens. When overloaded, calcium activates phospholipases lipases, nucleases, and proteases that destroy the essential proteins and membranes within the cell. Moreover, glutamate promotes high sodium and water influx, which results in cell swelling, edema, and, thus, shrinking of the extracellular space as a whole.[6]

The aforementioned processes result in excessive mitochondrial oxygen radical production and other sources of free radicals such as degradation of hypoxanthine and prostaglandin synthesis. These overall reactive oxygen species (ROS) will result in direct damage to nucleic acid, carbohydrates, lipids, and proteins These toxic material are very damaging due to the fact that the opposing mechanisms such as antioxidant enzymes –e.g. superoxide dismutase (SOD), catalase, and glutathione- and scavenging mechanisms – e.g. α-tocopherol, and vitamin C- become unable to oppose ROS production.[7] Along with this process, other neuronal death mechanisms responsible for neuronal death are activated, which include lipoxygenase cascade, poly ADP-ribose polymerase (PARP), mitochondrial transition pore formation, and amplified ionic imbalance. The latter happens due to the secondary recruitment of calcium-permeable Transient Receptor Potential Melastatin (TRPM) ion channels.[8] Moreover, reactive nitrogen species that are abundant in these cells, along with ROS can modify the endogenous functions of proteins, which in a lot of cases they function as neuroprotective proteins. As a result, these cascades will eventually lead to a complex mix of necrosis, apoptosis, and autophagy with ultimately neuronal death.[9]

Another factor of these ischemic insults involves the white matter, which is primarily composed of axonal bundles sheathed with myelin –formed by oligodendrocytes-. One of the major differences in terms of blood flow is that the white matter has significantly less blood flood when compared to the grey matter with little collateral blood supply.[10] As a result, the ischemia in this area is severe with tissue edema and rapid cell swelling. Moreover, it activates many proteases, which further weaken the myelin sheath and the structural integrity of axons. More importantly, white matter repairing in neuronal networks after the stroke is essential for recovery and regain of function. This can be induced with different endogenous responses that fix the white matter damage.[5]

Another major event that happens primarily after the stroke is the initiation of inflammatory processes that will happen all over the ischemic region. The main importance of such an event is that this modulation of the immune system may lead to a decrease in the overall size of the infarct. Some examples of the recruited inflammatory cells that play a major part include microglial cells, macrophages/monocytes, neutrophils, and T-cells. However, this process may lead to some major negative changes as well, especially in the post-ischemic; such as cerebral edema, neuronal cell death, and dysfunction of the blood-brain barrier. The microglial cells appear to be the main key in the inflammatory process and increases in the infarcted area after the stroke and can act as a protective and/or destructive to the tissue. It can be neuroprotective thanks to the production of neurotrophic substances including Brain-Derived Neurotrophic Factor

(BDNF), insulin-like growth factor I (IGF-I), and other growth factors. On the other hand, by releasing several pro-inflammatory cytokines for example interleukin-1β (IL-1β), TNF-α, and IL-6, along with Nitric Oxide (NO), ROS, and prostanoids the microglial cells can be destructive to the neighboring tissue. Moreover, these cells can recruit other inflammatory cells to penumbras and thus causing possibly more harm. Thus, a new therapy module has been suggested to reduce the overall inflammation in the infarcted area. Moreover, multiple mediators and cells have been suggested to assess the outcome of stroke and its severity. The main examples include IL-6 and Toll-like receptor 4 for the severity of stroke. However, other cells such as regulatory T-cells have shown a protective role during the stroke, and metalloproteinase, based on its anti-inflammatory properties is suggested to help in the treatment of stroke.[11]

In regard to the origin of such blood flow disturbance, leading to stroke, it is mainly divided into large vessels, small vessels (Lacunar stroke), and cardioembolic stroke. The large artery stroke is when the major arteries supplying the brain including, the internal carotid artery, middle cerebral artery, anterior cerebral artery, or the vertebrobasilar system are affected. The lacunar strokes often involve the smaller or perforating blood vessels, which supply the deeper structures of the brain. The origin of both infarctions are either thrombotic or embolic, and the cardioembolic type is embolic. The cardioembolic variety usually has other diseases or risk factors associated with it (e.g. atrial fibrillation).[12]

Risk Factors

As in every major disease, stroke has been heavily studied to acknowledge the associated risk factors with it in order to lower the risk in special populations. Generally, these risk factors are divided into modifiable (that can be changed or treated) and unmodifiable risk factors. The main non-modifiable risk factors include; older age, race, sex, ethnicity, history of migraine headaches, fibromuscular dysplasia, and family history of stroke or transient ischemic attacks (TIAs). On the other hand, modifiable risk factors are much more common and are of utmost importance due to the intervention and control element for each of them. The most important and prevalent modifiable risk factor is hypertension and for example, can attribute to up to 50% of the total small vessel strokes. Moreover, patients with resistant hypertension have a higher risk of developing stroke with up to 90%.[13] Other chronic diseases such as diabetes mellitus, dyslipidemia, carotid stenosis, hyperhomocysteinemia, and obesity all contribute to a higher risk for cerebrovascular attacks. Some lifestyle activities have been proven to increase the risk as well, these include; excessive alcohol intake, tobacco use, illicit drug use, and physical inactivity. Some drugs have been shown to have the same effect with oral contraceptives and postmenopausal hormones as the main examples of such drugs. Since one of the major causes of ischemic stroke is emboli, which may arise directly from the heart or the aorta, many cardiac diseases have been associated and identified as risk factors. Mainly most valvular heart diseases increase the risk including; infective endocarditis, rheumatic mitral or aortic valve disease, the usage of bioprosthetic (or mechanical) heart valves, fibrous nonbacterial endocarditis (i.e. Libman-Sacks endocarditis), and antiphospholipid syndrome, as well as specific arrhythmias such as atrial fibrillation, paroxysmal atrial fibrillation, sick sinus syndrome, and atrial flutter. Some studies reported that up to 20% of patients presenting with acute ischemic stroke had atrial fibrillation or flutter upon presentation. Existing structural heart abnormalities like dilated cardiomyopathy or any recent myocardial infarction, along with previous coronary artery bypass graft surgery are important points to be kept in mind with any patient presenting with stroke.[14, 15]

Clinical Features

Clinical presentation of stroke depends greatly on which area of the brain is affected by the occlusion and the resulted ischemia. American Heart Association and American Stroke Association (AHA/ASA) presented an algorithm “FAST” to ease the recognition of stroke signs among the general public in a pre-hospital setting. [16] This acronym includes the rapid onset of facial droop, arm (and/or leg, face, or all) weakness, slurred speech (or not clear), and time of onset with all these signs alerting heading to the emergency department immediately. Other signs that can be noted and shall alert seeking medical help are; vertigo (lightheadedness or spinning feeling), severe headache, and disturbance of balance. Some other acronyms used are the 6S and the BEFAST method, which all can indicate the possibility of stroke when criteria are met. The 6S stands for; sudden (for the onset of symptoms), side weakening, slurred speech, spinning, and severe headache. The BEFAST stands for balance (loss of it), eyes (disturbance of vision), face (drop), arm weakness, and speech slur. In the ER setting the NIH stroke scale shall be used by the ER physician or a trained neurologist within 10 minutes of the patient arrival to the hospital.

Diagnosis

The most important factor in stroke diagnosis and management overall is time, the sooner the stroke recognized, and its type is identified is known, the sooner therapy can be initiated and the better is the overall prognosis. Thus, diagnosing stroke is one of the most initial skills any physician shall have. Lately, the NIH stroke scale has taken a great role in the clinical assessment of stroke probability in patients, especially that it assesses multiple clinical points in the patient. This scale addresses the patient’s level of consciousness, vision of the patient (horizontal eye movements and visual field), facial palsy, motor function (for arm and leg), ataxia, sensations, speech (for dysarthria and aphasia), and attention (for multiple types of stimuli). The scoring goes from 0 (which indicates a normal function) up to 3 or 4 (no or absent function) constituting a total of 42. Moreover, the score is based on ranges going from 0 (no stroke symptoms) to 1-4 (minor stroke probability), 5-15 (moderate stroke probability), 15-20 (moderate to severe

stroke probability), and 21-42 (severe stroke probability).[16] However, every clinician shall have the differential diagnoses in the back of his mind so as not to miss any other possible causes. The most common differential diagnoses are TIA, cerebral venous thrombosis, meningitis, subarachnoid hemorrhage, seizure, systemic infection, brain tumors, and toxic-metabolic disorders (e.g. hyponatremia and hypoglycemia).[17]

The next step in diagnosis is with imaging study, which needs to be as urgent as possible, recently a non-contrast CT scan became the mainstay in stroke suspected patients, and it immediately gives a pure differentiation between hemorrhagic and ischemic strokes. Moreover, Multimodal CT imaging (with CT angiography and perfusion) can identify possible large vessel occlusions and the areas of salvageable tissue that can be targeted and followed up. This study shall be aimed to be done within a 20-minute window after the arrival of the patient to the emergency department in at least half of the patients. Other tests that can be done to rule out other differential diagnoses including a lumbar puncture (to rule out meningitis or subarachnoid hemorrhage if CT negative for stroke). Other important imaging modalities are MRI with angiography (MRA), which can provide much more structural detail, detect early cerebral edema, and detect acute intracranial hemorrhage. Nevertheless, this modality is used less due to multiple reasons including less availability in emergency departments, many contradictions to MRI (like pacemakers, implants), and the more difficult interpretation of its scans.[18]

Carotid duplex is becoming more used recently and much earlier in the management process to define the cause behind the stroke. This early recognition can guide clinicians in choosing the medical or the surgical pathway if severe carotid stenosis was diagnosed. The definitive method for recognizing the different vascular lesions, including stenosis, dissections, lesions, and aneurysms is the digital subtraction angiography. Moreover, transcranial Doppler ultrasonography is used to evaluate proximal vascular anatomy (e.g. middle cerebral artery (MCA), intracranial carotid artery, and vertebrobasilar artery).[19, 20] Other radiographic modalities, like echocardiography, which is done when cardiogenic embolism is suspected, and chest radiography can be obtained as long as it does not delay treatment. Single-photon emission CT (SPECT) scanning in stroke patients is exclusively used in selected institutions and may be indicated to further define areas of altered regional blood flow.[21, 22]

Conventional angiography is the gold standard in evaluating for cerebrovascular disease, as well as for disease involving the aortic arch and great vessels in the neck. Conventional angiography can be performed to clarify equivocal findings or to confirm and treat disease seen on MRA, CTA, transcranial Doppler, or ultrasonography of the neck.[23] Along with imaging studies, blood tests are very crucial in these patients to stabilize them and even diagnose the possible pathologies behind the stroke. A complete blood count shall be done immediately in order to establish a baseline study, and its results may help to expose the cause of the stroke such as thrombocytosis, thrombocytopenia, polycythemia, and leukemia. Moreover, CBC can identify possible concurrent illnesses (like anemia), affect the reperfusion approach (if thrombocytopenia is present). Electrolytes are also important to measure in order to establish a baseline, recognize any abnormalities, stroke-like causes (such as hypoglycemia and hyponatremia), and evidence of ongoing illness (e.g. diabetes). Coagulation studies are very crucial in these patients to show any coagulopathy and when fibrinolytics or anticoagulants are intended to use. When the clinician suspects an underlying cardiac pathology along with the stroke cardiac biomarkers can provide an immeasurable factor in diagnosing such cases (like myocardial infarction). Additionally, the elevation of these markers has been associated with poor prognoses in many studies.[24] If the patient is hypoxic and the clinician wants to detect acid-base disturbances via arterial blood gas studies he shall remember that arterial punctures are to be avoided if fibrinolytic therapy is considered (unless absolutely necessary and under supreme care). ER physicians shall always perform a urine pregnancy test in women of childbearing age with stroke symptoms with no exceptions. This is due to the questionable safety of fibrinolytic agent recombinant tissue-type plasminogen activator (rt-PA) and its classification as a class C drug in pregnancy. Other tests like toxicology screening, antinuclear antibody (ANA), rheumatoid factor, homocysteine levels can be taken if the clinician has a high suspicion for a cause of the stroke or to rule out a differential diagnosis that may be identified via such tests.[25]

Treatment

Regarding treatment, the main concept is to be as fast as possible, since time is the most crucial factor. The patient loses up to 1,9 million brain cells per minute and 14 billion synapses in the setting of ischemic stroke.[26]

In the emergency setting, clinicians shall always focus on getting the patients medically stable first and foremost with the ABC approach. The patient's airway, breathing, and circulation need to be assessed and managed accordingly in order to advance in the management of these cases. Some large strokes and/or posterior circulation strokes may present with bulbar dysfunction, loss of consciousness, and respiratory distress. ER physician shall never let these patients be hypoxic and intubation should be thought of immediately if the airway was not protected or a ventilator support need is arising. As mentioned earlier a lot of tests can be done in the setting of any stroke patients but the most important one to do as per protocols, before initiating thrombolytic treatment, is finger stick glucose and ensuring the origin of the stroke (ischemic or hemorrhagic). However, if the patient has any history of a bleeding disorder, using anticoagulants and/or history of thrombocytopenia extra tests may be indicated including; electrocardiogram, CBC, Troponin, PT, INR, aPTT, ecarin clotting time, thrombin

time, direct factor Xa activity assay (if the patient recently started taking oral anticoagulants).[25]

The general management approach afterward depends on the time of onset of symptoms, which is why it is critical to present as soon as possible to the emergency for clinicians to be able to take advantage of this "golden" window. CT is indicated immediately once the patient is stable; with the difference based on the patient's time of presentation. If the patient presents within the first 6 hours of symptoms onset: a CT scan should be combined with a CT angiogram of the brain and neck to rule out large vessel occlusion. CT angiogram should not be delayed to wait for serum creatinine, and whenever possible the angiogram should be completed with the CT scan to save time for a possible mechanical intervention. Moreover, MRI or MR angiogram or MR perfusion is not indicated within the first 6 hours of symptom onset.[27] The main modalities available for treatment are – intravenous- thrombolysis and mechanical thrombectomy. The choice of treatment depends on the patient's condition; for example, if the patient is not using any antithrombotics or anticoagulants, with a normal coagulation profile, then the administration of recombinant tissue plasminogen activator (rt-PA) is indicated. Nevertheless, and if the lab results are not available or may delay the treatment, the clinician can start giving rt-PA if he/she has no suspicions for any coagulation abnormalities after examining the patient and from history. Thrombolytic agents –including rt-PA- aid generally in clot dissolution and restoration of the blood flow, which will prevent the death of neurons; ultimately leading to clinical improvement.[28] Some other medications that may be indicated in these patients include anticonvulsants (e.g. diazepam, and lorazepam) and antiplatelets (such as aspirin and clopidogrel). The main indication for anticonvulsants is in patients with a seizure history or presenting with seizure, the risk of developing recurrent seizures post-stroke is life-threatening. Early antiplatelet therapy is recommended to be given after 24 hours of rt-PA administration and no later than 48 hours from the onset of symptoms. Moreover, it is not an alternative to IV fibrinolysis and to be avoided if the hemorrhagic stroke was not ruled out. Moreover, the American Heart Association recommends starting all patients with atrial fibrillation presenting with stroke on anticoagulation in the treatment approach, but the timing and the effects on outcome remain questionable.[29-31]

Conclusion

Stroke is one of the most common and fatal diseases that physicians in the emergency departments face almost daily. This pathology does not only directly impact patients' life but also their environment and society as a whole. Therefore, lowering the overall mortality and morbidity by seeking the medical attention as soon as possible is critical in these cases. Thus, raising public knowledge to identify the signs of strokes early shall be the main point of emphasis in the approach to this disease as a community. This is especially true since many options of treatment are available with a significantly better outcome when given early. However, many new treatment options are being studied and may prove to be the most needed breakthroughs in dealing with one of the greatest causes of morbidity and mortality worldwide.

Reference

1. Hatano, S. Experience from a multicentre stroke register: a preliminary report. Bull World Health Organ. 1976;54(5):541-53.
2. Benjamin EJ, Virani SS, Callaway CW, Chamberlain AM, Chang AR, Cheng S, Chiuve SE, Cushman M, Delling FN, Deo R, de Ferranti SD. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. Circulation. 2018 Mar 20.
3. Malhotra K, Gornbein J, Saver JL. Ischemic Strokes Due to Large-Vessel Occlusions Contribute Disproportionately to Stroke-Related Dependence and Death: A Review. Front Neurol. 2017;8:651.
4. The top 10 causes of death. Fact sheets [Internet]. 2018. Available from: https://www.who.int/en/news-room/fact-sheets/detail/the-top-10-causes-of-death.
5. Xing C, Arai K, Lo EH, Hommel M. Pathophysiologic cascades in ischemic stroke. Int J Stroke. 2012;7(5):378-85.
6. Lipton P. Ischemic cell death in brain neurons. Physiol Rev. 1999;79(4):1431-568.
7. Lo EH, Dalkara T, Moskowitz MA. Mechanisms, challenges and opportunities in stroke. Nat Rev Neurosci. 2003;4(5):399-415.
8. Aarts M, Iihara K, Wei WL, Xiong ZG, Arundine M, Cerwinski W, et al. A key role for TRPM7 channels in anoxic neuronal death. Cell. 2003;115(7):863-77.
9. Sen N, Hara MR, Ahmad AS, Cascio MB, Kamiya A, Ehmsen JT, Aggrawal N, Hester L, Doré S, Snyder SH, Sawa A. GOSPEL: a neuroprotective protein that binds to GAPDH upon S-nitrosylation. Neuron. 2009 Jul 16;63(1):81-91.
10. Iadecola C, Park L, Capone C. Threats to the mind: aging, amyloid, and hypertension. Stroke. 2009;40(3 Suppl):S40-4.
11. Famitafreshi H, Karimian M. Overview of the Recent Advances in Pathophysiology and Treatment for Autism. CNS Neurol Disord Drug Targets. 2018;17(8):590-4.
12. Chugh C. Acute Ischemic Stroke: Management Approach. Indian J Crit Care Med. 2019;23(Suppl 2):S140-s6.
13. Maïer B, Kubis N. Hypertension and Its Impact on Stroke Recovery: From a Vascular to a Parenchymal Overview. Neural Plasticity. 2019;2019:6843895.
14. Guzik A, Bushnell C. Stroke Epidemiology and Risk Factor Management. Continuum (Minneap Minn). 2017;23(1, Cerebrovascular Disease):15-39.
15. Lasek-Bal A, Kopyta I, Warsz-Wianecka A, Puz P, Łabuz-Roszak B, Zaręba K. Risk factor profile in patients with stroke at a young age. Neurol Res. 2018;40(7):593-9.
16. Lyden P, Brott T, Tilley B, Welch KM, Mascha EJ, Levine S, Haley EC, Grotta J, Marler J. Improved reliability of the NIH Stroke Scale using video training. NINDS TPA Stroke Study Group. Stroke. 1994 Nov;25(11):2220-6.
17. Runchey S, McGee S. Does this patient have a hemorrhagic stroke?: clinical findings distinguishing hemorrhagic stroke from ischemic stroke. Jama. 2010;303(22):2280-6.
18. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, Biller J, Brown M, Demaerschalk BM, Hoh B, Jauch EC. 2018 guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. stroke. 2018 Mar;49(3):e46-99.
19. Camerlingo M, Casto L, Censori B, Ferraro B, Gazzaniga GC, Mamoli A. Transcranial Doppler in acute ischemic stroke of the middle cerebral artery territories. Acta Neurol Scand. 1993;88(2):108-11.
20. Sorensen AG, Copen WA, Østergaard L, Buonanno FS, Gonzalez RG, Rordorf G, Rosen BR, Schwamm LH, Weisskoff RM, Koroshetz WJ. Hyperacute stroke: simultaneous measurement of relative cerebral blood volume, relative cerebral blood flow, and mean tissue transit time. Radiology. 1999 Feb;210(2):519-27.
21. Sagar G, Riley P, Vohrah A. Is admission chest radiography of any clinical value in acute stroke patients? Clin Radiol. 1996;51(7):499-502.

22. Meerwaldt R, Slart RHJA, van Dam GM, Luijckx G-J, Tio RA, Zeebregts CJ. PET/SPECT imaging: From carotid vulnerability to brain viability. European Journal of Radiology. 2010;74(1):104-9.
23. Vilela P, Rowley HA. Brain ischemia: CT and MRI techniques in acute ischemic stroke. Eur J Radiol. 2017;96:162-72.
24. Gebreyohannes EA, Bhagavathula AS, Abebe TB, Seid MA, Haile KT. In-Hospital Mortality among Ischemic Stroke Patients in Gondar University Hospital: A Retrospective Cohort Study. Stroke Research and Treatment. 2019;2019:7275063.
25. Ekker MS, Boot EM, Singhal AB, Tan KS, Debette S, Tuladhar AM, de Leeuw FE. Epidemiology, aetiology, and management of ischaemic stroke in young adults. The Lancet Neurology. 2018 Sep 1;17(9):790-801.
26. Saver JL. Time is brain—quantified. Stroke. 2006 Jan 1;37(1):263-6.
27. Gonzalez RG, Schaefer PW, Buonanno FS, Schwamm LH, Budzik RF, Rordorf G, Wang B, Sorensen AG, Koroshetz WJ. Diffusion-weighted MR imaging: diagnostic accuracy in patients imaged within 6 hours of stroke symptom onset. Radiology. 1999 Jan;210(1):155-62.
28. National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. New England Journal of Medicine. 1995 Dec 14;333(24):1581-8.
29. Latchaw RE, Alberts MJ, Lev MH, Connors JJ, Harbaugh RE, Higashida RT, Hobson R, Kidwell CS, Koroshetz WJ, Mathews V, Villablanca P. Recommendations for imaging of acute ischemic stroke: a scientific statement from the American Heart Association. Stroke. 2009 Nov 1;40(11):3646-78.
30. Diedler J, Ahmed N, Sykora M, Uyttenboogaart M, Overgaard K, Luijckx GJ, Soinne L, Ford GA, Lees KR, Wahlgren N, Ringleb P. Safety of intravenous thrombolysis for acute ischemic stroke in patients receiving antiplatelet therapy at stroke onset. Stroke. 2010 Feb 1;41(2):288-94.
31. Xian Y, Federspiel JJ, Grau-Sepulveda M, Hernandez AF, Schwamm LH, Bhatt DL, Smith EE, Reeves MJ, Thomas L, Webb L, Bettger JP. Risks and benefits associated with prestroke antiplatelet therapy among patients with acute ischemic stroke treated with intravenous tissue plasminogen activator. Jama Neurology. 2016 Jan 1;73(1):50-9.