



## STROKE – THE LAST BREATH

**B. Venkata Phani Deepthi\* and Dr. J. V. C. Sharma**

Assistant Professor Joginpally B.R. Pharmacy College, Yenkapally (V), Moinabad (Md), Ranga Reddy (Dt),  
Telangana.

**\*Corresponding Author: B. Venkata Phani Deepthi**

Assistant Professor Joginpally B.R. Pharmacy College, Yenkapally (V), Moinabad (Md), Ranga Reddy (Dt), Telangana.

Article Received on 06/11/2018

Article Revised on 27/11/2018

Article Accepted on 17/12/2018

### ABSTRACT

Stroke, a cerebrovascular accident, can be a significant cause of morbidity and mortality. Stroke can be categorized as ischemic, hemorrhagic or subarachnoid. During a stroke, the brain does not receive enough oxygen or nutrients, causing brain cells to die. Stroke needs to be diagnosed and treated as quickly as possible to minimize brain damage. Treatment depends on the type of stroke. The most effective way to prevent stroke is through maintaining a healthy lifestyle and treating underlying conditions that could be a risk factor. Various risk factors involved in getting stroke such as being overweight or obese, physical inactivity, heavy drinking etc. Certain medical and non medical conditions are also responsible for getting stroke. Stroke is brain attack which occurs in the brain just like heart attack which occurs in the heart. Hemiplegia is a condition where paralysis of one side of body occurs. The present review discusses about the risk factors, etiology, causes, classification, diagnosis, treatment strategies for the prevention of stroke.

**KEYWORDS:** stroke, ischemia, thrombus, haemorrhage, embolism.

### INTRODUCTION

Strokes are mainly brain attacks occurs due to the blockage of blood supply to the brain.<sup>[1]</sup> The majority of strokes are due to blockage of an artery in the brain by a blood clot.<sup>[2]</sup> It results in cell death<sup>[3]</sup> which requires immediate medical attention<sup>[1][4]</sup> and it is the frequent cause of adult disability.<sup>[5]</sup> Stroke, is a cerebrovascular accident<sup>[6]</sup>, when the blood supply to the part of brain is interrupted or reduced, depriving brain tissue of oxygen and nutrients.<sup>[4]</sup> Stroke can be categorized as ischemic, hemorrhagic, or subarachnoid.<sup>[6]</sup> Pediatric abusive head trauma (AHT) usually called as shaken baby syndrome (SBS) most often involves brain injury of infants and young children.<sup>[7]</sup> Cognitive syndromes are common after stroke. Patients were divided into following subgroups of vascular cognitive impairment (VCI).

- Dementia of strategic infarct (DSI),
- Cortical dementia (CD),
- Sub cortical dementia (SCD),
- Hemorrhagic dementia (HD) and
- Patients without dementia.

Some of the cognitive functions are significantly impaired in patients with dementia.<sup>[8]</sup> Stroke or a condition referred to as apoplexy or the sudden onset of paralysis.<sup>[9]</sup>

### ETIOLOGY OF THE STROKE

- Cardioembolic
- Large artery disease

- Small Vessel Disease.<sup>[10]</sup>
- Cryptogenic (ESUS)
- Embolic Strokes Undetermined Source (ESUS)
- Other cause.<sup>[11]</sup>
- Arterial-venous malformation (AVM)
- Intracerebral hemorrhage (ICH).<sup>[10]</sup>

The acronym F.A.S.T. is a way to remember the signs of stroke, and can help identify the onset of stroke.<sup>[1]</sup>

- **Face drooping:** If the person tries to smile, only one side of face will droop.
- **Arm weakness:** If the person tries to raise both their arms, only one arm will drift downwards.
- **Speech difficulty:** If the person tries to repeat a simple phrase, their speech will slurr or strange
- **Time to call:** If any of the above signs are observed, immediately contact the emergency services.<sup>[1]</sup>

### RISK FACTORS

#### Lifestyle risk factors

- Being overweight or obese
- Physical inactivity
- Heavy drinking
- Use of illicit drugs such as cocaine and methamphetamines.<sup>[4]</sup>

**Medical risk factors**

- 1. Modifiable/potentially modifiable-** number of physiological and environmental factors include hypertension, elevated total cholesterol, smoking, physical inactivity, alcohol consumption and atrial fibrillation.
- 2. Non modifiable risk factors** – Age, gender, ethnicity.<sup>[5]</sup>

**1. Modifiable/potentially modifiable**

- Blood pressure readings higher than 120/80 millimeters of mercury (mm Hg)
- Cigarette smoking or exposure to second hand smoke
- High cholesterol
- Diabetes
- Obstructive sleep apnea
- Cardiovascular disease, including heart failure, heart defects, heart infection or abnormal heart rhythm.
- Personal or family history of stroke, heart attack or transient ischemic attack.
- Isolated angitis of the central nervous system is also responsible for stroke.<sup>[12]</sup>

Other factors associated with a higher risk of stroke include

- **Age** — People age 55 or older have a higher risk of stroke than do younger people.
- **Race** — African-Americans have a higher risk of stroke than do people of other races.
- **Sex** — Men have a higher risk of stroke than women. Women are usually older when they have strokes, and they're more likely to die of strokes than are men.
- **Hormones** — Use of birth control pills or hormone therapies that include estrogen, as well as increased estrogen levels from pregnancy and childbirth.<sup>[4]</sup>

**CAUSES**

There are mainly two types of causes of stroke

- 1. Infective** – infections of orbit, mastoid, middle ear or face and meningitides are the conditions most commonly associated with cerebral venous thrombosis.
- 2. Non infective** – cancer, myeloproliferative disorders, dehydration, oral contraceptives.<sup>[13]</sup>

**Other causes are****1. Thrombotic stroke**

It occurs when a thrombus (blood clot) forms along the wall of the major arteries supplying the brain and completely blocks blood flow.

**2. Embolic stroke**

It occurs when an embolus (part of a blood clot or piece of atherosclerotic plaque) breaks off and travels through the blood stream until it lodges in a smaller artery supplying the brain thus blocking blood flow. The most common cause of emboli is atrial fibrillation, an abnormal heart rhythm.<sup>[14]</sup>

**3. Cerebral hypoperfusion** – It is nothing but under supplying of blood to the cerebrum.<sup>[13]</sup>

**4. Intracerebral hemorrhage**<sup>[3]</sup>– A common and devastating disease in need of better treatment.<sup>[15]</sup> Intracerebral hemorrhage (ICH) results from the rupture of an intracerebral vessel leading to the development of a hematoma in the substance of the brain.<sup>[16]</sup> ICH caused by bleeding, primarily into parenchymal brain tissue, is responsible for 9% to 27% of all strokes worldwide.<sup>[17]</sup> It occurs mainly due to hypertension, vascular malformations (including cavernous angiomas or arteriovenous malformations), cerebral amyloid angiopathy, or infarcts into which secondary haemorrhage.<sup>[3]</sup>

Causes of ICH which include

- Cerebral aneurysms
- Cerebral arteriovenous malformations
- Cavernous malformations
- Moya-moya disease
- Vasculitis
- Hypertension
- Amyloid angiopathy
- Anticoagulants/ antiplatelet agents
- Recreational drugs
- Post-infarction
- Blood dyscrasias
- Idiopathic
- \*Brain tumors
- \*Unrecognized trauma.<sup>[18]</sup>

**5. Other-** Other causes may include spasm of an artery. This may occur due to cocaine.<sup>[3]</sup> Other causes are trauma, bleeding disorders, amyloid angiopathy, illicit drug use (e.g., amphetamines or cocaine).<sup>[3]</sup>

**6. Silent stroke** – In a silent stroke, no overt neurological deficit is apparent but brain damage affects memory and learning. It dramatically increases the risk of overt stroke.<sup>[19]</sup>

**CLASSIFICATION**

Some people may experience only a temporary disruption of blood flow to the brain (transient ischemic attack, or TIA) that doesn't cause permanent damage.

**1. Ischemic stroke-** Cerebral infarction (blockage)<sup>[20]</sup>

Ischemic stroke occurs when a blood clot blocks an artery leading to the damage of the brain. The blockade is due to the formation of plaques (atherosclerosis). It can occur in the carotid artery of the neck as well as other arteries. The most common ischemic strokes include.

- Thrombotic stroke.
- Embolic stroke.

**2. Hemorrhagic stroke-** (rupture of blood vessel).<sup>[9][20]</sup>

Available studies suggest that subjects with migraine have an increased risk of hemorrhagic stroke.<sup>[21]</sup> Hemorrhagic stroke occurs when a blood vessel in the

brain leaks or ruptures. Brain hemorrhages result from many conditions that affect blood vessels. These include.

- Uncontrolled high blood pressure (hypertension)
- Overtreatment with anticoagulants (blood thinners)
- Weak spots in blood vessel walls (aneurysms)

A less common cause of hemorrhage is the rupture of an abnormal tangle of thin-walled blood vessels (arteriovenous malformation). Types of hemorrhagic stroke include.

- **Intracerebral hemorrhage.** In this a blood vessel in the brain bursts and spills into the surrounding brain tissue, damaging brain cells. These brain cells get damaged due to the lack of blood. High blood pressure, trauma, vascular malformations, use of blood-thinning medications and other conditions may cause an intracerebral hemorrhage.
- **Subarachnoid hemorrhage.** In this an artery on or near the surface of brain bursts and spills into the space between the surface of brain and skull. This bleeding causes a sudden, severe headache. A subarachnoid hemorrhage is commonly caused by the bursting of a small sack-shaped or berry-shaped aneurysm. After the hemorrhage, vasospasm occurs results in widening and narrowing of blood vessels in brain, causing brain cell damage.<sup>[4]</sup>

## SIGNS AND SYMPTOMS

Stroke symptoms typically start suddenly, over seconds to minutes, and in most cases do not progress further.

- Sudden-onset face weakness,
- Arm drift (i.e., if a person, when asked to raise both arms, involuntarily lets one arm drift downward) and
- Abnormal speech are the findings<sup>[1]</sup>

If central nervous system pathways like the spinothalamic tract, corticospinal tract, and the posterior column–medial lemniscus pathway are effected, the symptoms may include:

- Hemiplegia and muscle weakness of the face
- Numbness
- Reduction in sensory or vibratory sensation
- Initial flaccidity (reduced muscle tone), replaced by spasticity (increased muscle tone), excessive reflexes and obligatory synergies.

### Hemiplegia

Stroke is brain attack which occurs in the brain just like heart attack which occurs in the heart. When stroke occurs in the left side of the brain, then the right side of the body is affected and the adverse effects include paralysis, numbness, inability to function properly, complete disability in some physical functions, restrictive movement, insensitivity in some areas, speech, spoken and written language, understanding difficulties etc.

When stroke occurs in the right side of the brain, then the left side of the body is affected and the adverse effects include blurred vision and out of focus, perception and

dimensions become unreal etc. Overall language, communication abilities, memory, paralysis etc. are the outcomes of a stroke incidence. Even personality can be altered by a stroke.<sup>[22]</sup>

If brain stem is effected the symptoms are

- altered smell, taste, hearing, or vision (total or partial)
- drooping of eyelid (ptosis) and weakness of ocular muscles
- decreased reflexes: swallow, pupil reactivity to light
- decreased sensation and muscle weakness of the face
- balance problems and nystagmus
- altered breathing and heart rate
- weakness in sternocleidomastoid muscle with inability to turn head to one side
- weakness in tongue (inability to stick out the tongue or move it from side to side)

If the *cerebral cortex* is involved, the CNS pathways can again be affected, but also can produce the following symptoms.

- aphasia (difficulty with verbal expression, auditory comprehension, reading and writing; Broca's or Wernicke's area typically involved)
- dysarthria (motor speech disorder resulting from neurological injury)
- apraxia (altered voluntary movements)
- visual field defect
- memory deficits (involvement of temporal lobe)
- hemineglect (involvement of parietal lobe)
- disorganized thinking, confusion, hypersexual gestures (with involvement of frontal lobe)
- lack of insight of his or her, usually stroke-related, disability

If the *cerebellum* is involved, ataxia might be present and this includes:

- altered walking gait
- altered movement coordination
- vertigo and or disequilibrium

### Associated symptoms

In hemorrhagic stroke loss of consciousness, headache and vomiting usually occur more often because of the increased intracranial pressure from the leaking blood compressing the brain.

If symptoms are maximal at onset, the cause is more likely to be a subarachnoid hemorrhage or an embolic stroke.<sup>[3]</sup>

## DIAGNOSIS

Stroke is diagnosed through several techniques: a neurological examination, CT scans (most often without contrast enhancements) or MRI scans, Doppler ultrasound and arteriography.

- **Physical examination:** It includes checking of symptoms, medical history, blood pressure. A listen

to the carotid arteries in the neck, and examine the blood vessels at the back of the eyes to check for indications of clotting.

- **Blood tests:** Blood tests reveals the presence of clots, the levels of particular substances in the blood, including clotting factors and whether or not an infection is present.
- **CT scan:** A series of X-rays can show hemorrhages, strokes, tumors and other conditions within the brain.
- **MRI scan:** Radio waves and magnets create an image of the brain to detect damaged brain tissue.
- **Carotid ultrasound:** An ultrasound scan to check the blood flow in the carotid arteries and to see the presence of any plaque formation.

**Cerebral angiogram:** Dyes are injected into the brain's blood vessels to make them visible under X-ray. This gives a detailed view of the brain and the blood vessels in the neck (1). CT angiography (CTA) or contrast enhanced MR angiography(MRA). Like CTA and MRA ultrasound methods can visualize well proximal internal carotid artery (ICA) and intracranial stenosis.<sup>[23]</sup>

- **Echocardiogram:** In this a detailed image of the heart can be obtained to check for any sources of clots that are traveled to the brain to cause a stroke.<sup>[1]</sup>

## TREATMENT

Ischemic stroke – treatments can be divided into emergency treatments to reverse a blockage and preventive treatments to prevent stroke.

### A. Emergency procedures

1. Clot bluster drugs(tPA)- the most common clot bluster is tPA (tissue plasminogen activator). tPA is an enzyme found naturally in the body to dissolve clots. Doctors administered tPA within 3-4 hours of onset will recover immediately. A very small catheter is inserted into the artery in the groin and guided through the blood stream upto the brain where the clot is located. The tpa drug is then released to dissolve the blood clot. The doctor also pushes the catheter back and forth through the clot to help it break up.
2. Clot retrieval devices.<sup>[24]</sup>

### B. Preventive treatments:

1. Blood thinners
2. Angioplasty/stents
3. Carotid endarterectomy.<sup>[24]</sup>
4. Some issues in stroke prevention are specific to women such as oral contraceptives and post menopausal estrogen use.<sup>[25]</sup>

### C. Medical treatment

The role of medications in general supportive care are preferred.<sup>[26]</sup> Most disabling strokes are due to blockage of a large artery in the brain by a blood clot. Prompt removal of the clot with intra-arterial thrombolytic drugs

or mechanical devices, or both, leading to improved recovery. These are called percutaneous vascular interventions.<sup>[27]</sup> Intravenous thrombolysis with alteplase is mainly used for the treatment of acute ischemic stroke (AIS).

### 1. Oxygenation

To prevent hypoxia and potential worsening of the neurologic injury adequate tissue oxygenation is maintained to prevent acute cerebral ischemia. Supplemental oxygen should also be administered if there is evidence of hypoxia by blood gas determination.

**2 Antihypertensives** - Parenteral agents such as labetalol have minimal vasodilator effects on cerebral blood vessels are preferred. In some cases, an intravenous (IV) infusion of nicardipine or labetalol may be necessary for adequate blood pressure control. Oral agents, such as labetalol or lisinopril, are also used for lowering more sustained blood pressure if dysphagia is not a concern.

**3. Insulin-** Subcutaneous insulin is administered to keep glucose less than 180 mg/dL.

**4. Antipyretics-** Antipyretic medications and cooling devices are used for maintaining normothermia (lowering the body temperature)

### 5. Thrombolysis

- Intravenous administration of alteplase
- Alteplase and other plasminogen activators such as streptokinase and urokinase promote thrombolysis by hydrolyzing the arginine-valine peptide bond in plasminogen to form the active proteolytic enzyme plasmin. Thrombolytic agents such as streptokinase and urokinase activate both fibrin-bound and circulating plasminogen indiscriminately. Systemic activation of plasminogen results in the release of large amounts of plasmin into the circulation
- Other thrombolytic agents- Fibrinogen depleting agents reduce fibrinogen in blood plasma, reduce blood viscosity and hence increase blood flow. This will remove the blood clot blocking the artery thereby enhancing blood flow to the affected area of the brain.<sup>[28]</sup> The examples were shown in the tabular column-1.

### 6. Device Therapies

Thrombectomy devices are mainly designed to grab the clot blocking the artery and made it opened. Two different devices are used.

1. Stent retriever or stentreiver is a wire mesh tube attached to a long wire. When the tube is opened in the blocked artery, the clot gets stuck in the mesh. The doctor then pulls out the mesh using the long wire, pulling out the clot with it.
2. An aspiration catheter is attached to a special suction unit and used to suck out the clot.<sup>[24]</sup>

**7. Anticoagulants<sup>[29]</sup>**

**1. UFH Heparin** – It acts by inactivating thrombin and activated factor X. This is achieved by binding to antithrombin. The inactivation of thrombin by UFH prevents fibrin formation and inhibits thrombin-induced activation of platelets and factors V and VIII.

**2. Low Molecular Weight Heparin and Danaparoid.<sup>[30]</sup>** - LMWHs have a decreased ability to bind thrombin. Some of the available LMWHs are enoxaparin, dalteparin, nadroparin, tinzaparin, and certoparin.

**3. Warfarin-** It is a vitamin K antagonist. It inhibits factors II, VII, IX, X and the anticoagulant proteins C and S

**4. Dabigatran-** Dabigatran is an oral anticoagulant that acts as a direct thrombin inhibitor

**5. Rivaroxaban** –It is an oral anticoagulant that is an inhibitor of factor Xa

**6. Apixaban-** Apixaban is another direct thrombin inhibitor.<sup>[26]</sup>

**8. Antiplatelet Agents**

Antiplatelet therapy for acute ischaemic stroke<sup>[31]</sup>

**a. Aspirin-** Aspirin irreversibly inhibits cyclooxygenase, which prevents the conversion of arachidonic acid to thromboxane A<sub>2</sub> (TXA<sub>2</sub>). Thromboxane A<sub>2</sub> is a vasoconstrictor and stimulator of platelet aggregation. Aspirin also inhibits prostacyclin activity and this inhibits platelet aggregation.

**b. Clopidogrel** - Clopidogrel irreversibly blocks ADP receptors on platelets and thus prevents the cascade resulting in activation of GP IIb/IIIa receptor

**c. Combination Antiplatelet Therapy-** clopidogrel in combination with aspirin is used for high risk patients.

**d. Dipyridamole** is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells. Dipyridamole is used for preventing stroke and other vascular events in patients with vascular disease.<sup>[32]</sup>

**e. Tirofiban and eptifibatide** are antiplatelet drugs belonging to the class of glycoprotein IIb/IIIa inhibitors with potential to be adjuncts to thrombolysis acutely.

**f. Newer antiplatelet agents** including ticagrelor, Cangrelor, and prasugrel were not tested in AIS patients but they have been studied in clinical trials. Ticagrelor and Cangrelor block adenosine diphosphate (ADP) receptors of subtype P2Y<sub>12</sub>. Prasugrel is also an irreversible ADP inhibitor.

**9. Drugs related to treatment of acute neurological complications**

**a. Cerebral edema and increased intracranial pressure**  
Mannitol is an osmotic diuretic, typically used at 0.25–0.5 g/kg IV administered over 15 minutes. It lowers intracranial pressure, and can be given every 6 hours.<sup>[26]</sup>

A 10% solution of glycerol is a hyperosmolar agent that is claimed to reduce brain oedema.<sup>[33]</sup>

**b. Seizures**

**c. Hemorrhagic transformation**

**d. Angioedema.**

**Table-1: Specific drug therapy considerations for acute ischemic stroke<sup>[26]</sup>**

S.no	Category	DRUG	DOSE	Route	Mechanism	Monitoring adverse effect
1.	Antihypertensives	Labetalol	10–20 mg or 1–5 mg/min	IVP CIV	β-blocker α-blocker	BP, HR, nausea, wheezing
		Nicardipine	2.5–15 mg/h	CIV	Calcium channel Antagonist	BP, HR, volume overload
		Nitropaste	1–2 in (2.5–5 cm)	Topical	Nitrate	BP
		nitroprusside	0.25 µg/kg/min	CIV	Vasodilator	BP, HR, cyanide toxicity
		Labetalol	100–2400 mg/day	PO	β-blocker	BP, HR
		Lisinopril	5–40 mg/day	PO (multiple other ACEI)	ACEI	BP, HR, cough
2.	Thrombolytics	Hydralazine	20–100 mg/day 5–40 mg/day	PO IV	Vasodilator	BP
		Alteplase (tPA)	0.9 mg/kg	IV 10 % of dose as bolus and 90 % as 60-min infusion	Thrombolytic	Bleeding, BP
3.	Antiplatelets	Aspirin	80–325 mg/day	PO	Inhibits TXA <sub>2</sub> /PGI <sub>2</sub>	GI intolerance, use EC Forms
		Clopidogrel	75 mg/day	PO	Inhibits ADP	Diarrhea, rash
		Aspirin+ER dipyridamole	25+200 mg	1 cap PO twice daily	Inhibits TXA <sub>2</sub> /PGI <sub>2</sub>	Headache
4.	Anticoagulants	Heparin	5000 units 2–3 times per day	SC		For DVT prophylaxis
		Warfarin	2.5–10 mg/day	PO	Vitamin K antagonist	INR, Bleeding

ACEI -angiotensin-converting enzyme inhibitor,  
 ADP - adenosine diphosphate,  
 BP - blood pressure,  
 CIV - continuous IV,  
 DVT - deep venous thrombosis,  
 EC - enteric coated,  
 ER - extended-release,  
 GI - gastrointestinal,  
 HR - heart rate,  
 INR- international normalized ratio,  
 IV- intravenous,  
 IVP - IV push,  
 PGI<sub>2</sub>- prostacyclin,  
 PO -oral,  
 SC - subcutaneous,  
 TXA<sub>2</sub>. thromboxane A

### SURGICAL TREATMENT

Surgery is often recommended to either place a metal clip at the base of an aneurysm or to remove the abnormal vessels that make up an AVM.<sup>[34]</sup> The Intraoperative stereotactic computer tomography-guided endoscopic surgery (ICES) study demonstrated a good functional outcome for endoscopic minimally invasive evacuation.<sup>[35]</sup>

### SIDE EFFECTS

The risk of haemorrhage with fibrinogen depleting agents is less than with thrombolytic agents.<sup>[28]</sup> Anaphylactic shock is the main adverse effect that is associated with the use of intravenous thrombolytics.<sup>[36]</sup> The first evidence of an anaphylactic-type reaction is observed due to the reaction of specific IgE antibodies with alteplase in man.<sup>[37]</sup>

### CONCLUSION

Finally it is concluded that stroke can be prevented through lifestyle changes, including: eating a healthy diet, maintaining a healthy weight, exercising regularly, not smoking tobacco, avoiding alcohol or drinking moderately, eating a nutritious diet means including plenty of fruits, vegetables, and healthy whole grains, nuts, seeds, and legumes. But eating little or no red or processed meat and limit intake of cholesterol and saturated fats, minimize salt intake to support healthy blood pressure and managing diabetes etc.

### REFERENCES

- Adam Felman: James McIntosh; Everything you need to know about stroke (<https://www.medicalnewstoday.com/articles/7624.php>) accessed 23 november 2017.
- Wardlaw JM<sup>1</sup>, Zoppo G, Yamaguchi T, Berge E.: Wardlaw JM<sup>1</sup>, Zoppo G, Yamaguchi T, Berge E.: Thrombolysis for acute ischaemic stroke.: Cochrane Database Syst Rev, 2003; 3: CD000213.
- Stroke; (<https://en.wikipedia.org/wiki/Stroke>).
- Mayo clinic staff; Stroke symptoms and causes; (<https://www.mayoclinic.org/diseases-conditions/stroke/symptoms-causes/syc-20350113>) accessed march 16, 2018.
- Bo Norrving: Oxford textbook of stroke and cerebrovascular disease: *Oxford textbooks in clinical neurology*; published by Oxford University Press, 2014 in illustrated edition.
- Hui C, Patti L: Stroke, Ischemic: Stat Pearls [Internet]. Treasure Island (FL): StatPearls Publishing; accessed May 13, 2018.
- Joyce T<sup>1</sup>, Huecker MR<sup>2</sup>: Pediatric Abusive Head Trauma (Shaken Baby Syndrome).: StatPearls [Internet]. Treasure Island (FL): Stat Pearls Publishing, 2018 May 15.
- Salihović D, Smajlović D, Mijajlović M, Zoletić E, Ibrahimagić OČ.: Cognitive syndromes after the first stroke.: *Neurol Sci*, 2018 May 19. doi: 10.1007/s10072-018-3447-6. [Epub ahead of print]
- Paul A. Lapchak, John H. Zhang; Neuroprotective Therapy for Stroke and Ischemic Disease; *Springer Series in Translational Stroke Research*; published by Springer, 2017.
- Robert E. Replogle; Diagnosis and Treatment of Hemorrhagic Stroke; (<https://pdfs.semanticscholar.org/presentation/9e47/05df7ffa510e969ee03bbe8bd6ad725e7bfb.pdf>) accessed march 28, 2012.
- Rothwell et al; ACUTE STROKE AND EARLY MANAGEMENT; The Lancet Volume 388, Issue 10042, Pages 365-375 (July 2016) (<https://www.heartandstroke.ca/-/media/pdf-files/canada/clinical-update/f1-02-mandzia-acute-stroke-early-management.ashx?la=en&hash=27D3541C238877A594C2AA09B1C0DBE2B9423014>).
- Julien Bogousslavsky, Louis R. Caplan; Uncommon Causes of Stroke; *Stroke Syndromes (Second Edition) and Uncommon Causes of Stroke 2 Volume Hardback Set*; published by Cambridge University Press, 2001; illustrated edition.
- Robert S. Bonser, Domenico Pagano, Axel Haverich; Brain Protection in Cardiac Surgery, Brain Protection in Cardiac Surgery; published by Springer Science & Business Media, 2010; Illustrated edition.
- Lawrence Appel, Rafael H. Llinas; Hypertension and Stroke 2007; *Johns Hopkins White Papers*; published by Johns Hopkins Health, 2007
- Fiorella D<sup>1</sup>, Zuckerman SL<sup>2</sup>, Khan IS<sup>3</sup>, Ganesh Kumar N<sup>4</sup>, Mocco J<sup>5</sup>.: Intracerebral Hemorrhage: A Common and Devastating Disease in Need of Better Treatment.: *World Neurosurg*, 2015 Oct; 84(4): 1136-41. doi: 10.1016/j.wneu.2015.05.063. Epub 2015 Jun 10.
- Aninda Acharya; Evidence Based Management of Intracerebral Hemorrhage; (<http://www.strokecenter.org/wp-content/uploads/2011/08/Evidence-Based-Management-of-Intracerebral-Hemorrhage.pdf>).
- Thorsten Steiner et.al: European Stroke Organisation (ESO) guidelines for the management of

- spontaneous intracerebral hemorrhage: [http://www.spavc.org/Imgs/pages/eso%20wso/ESO\\_Guidelines\\_10\\_1111\\_IJS\\_12309\\_2014\\_03.pdf](http://www.spavc.org/Imgs/pages/eso%20wso/ESO_Guidelines_10_1111_IJS_12309_2014_03.pdf))
18. Hemorrhagic Stroke; (<https://www.peacehealth.org/sites/default/files/Documents/Halliday%20-%20Hemorrhagic%20Stroke%20v2.pdf>)
  19. Martha Craft-Rosenberg, Shelley-Rae Pehler; *Encyclopedia of Family Health*, Martha Craft-Rosenberg; published by SAGE, 2011; illustrated edition.
  20. Judith Mackay, George A. Mensah, Kurt Greenlund; *The Atlas of Heart disease and Stroke:academic Search complete*; published by World Health Organization, 2004; illustrated edition.
  21. Sacco S<sup>1</sup>, Ornello R, Ripa P, Pistoia F, Carolei A.: Migraine and hemorrhagic stroke: a meta-analysis.: *Stroke*. 2013 Nov;44(11):3032-8. doi: 10.1161/STROKEAHA.113.002465. Epub 2013 Oct 1.
  22. Prem K. Bhandari; *Heal & Prevent Stroke & Heart Disease*; published by iUniverse, 2007.
  23. Natan M. Bornstein; *Stroke: Practical Guide for Clinicians*; published by Karger Medical and Scientific Publishers, 2009; illustrated edition.
  24. Andy Ringer and Lincoln Jimenez; Mayfield clinic, Cincinnati Ohio; *Stroke (Brain Attack)* (<https://www.mayfieldclinic.com/PDF/PE-Stroke.pdf>).
  25. John W. Norris, Vladimir Hachinski; *Stroke Prevention*; published by Oxford University Press, 2001.
  26. Sameer Bansal,<sup>1</sup> Kiranpal S. Sangha,<sup>2</sup> and Pooja Khatri et al: Drug Treatment of Acute Ischemic Stroke: *Am J Cardiovasc Drugs*. 2013 Feb; 13(1): 10.1007/s40256-013-0007-6.
  27. O'Rourke K<sup>1</sup>, Berge E, Walsh CD, Kelly PJ.: Percutaneous vascular interventions for acute ischaemic stroke.: *Cochrane Database Syst Rev*. 2010 Oct 6; (10): CD007574. doi: 10.1002/14651858.CD007574.pub2.
  28. Liu M<sup>1</sup>, Counsell C, Zhao XL, Wardlaw J.: Fibrinogen depleting agents for acute ischaemic stroke.: *Cochrane Database Syst Rev*, 2003; (3): CD000091.
  29. ESO-Guidelines for Management of Ischaemic Stroke 2008; Guidelines for Management of Ischaemic Stroke and Transient Ischaemic Attack 2008; ([http://www.congrex-switzerland.com/fileadmin/files/2013/eso-stroke/pdf/ESO08\\_Guidelines\\_Original\\_english.pdf](http://www.congrex-switzerland.com/fileadmin/files/2013/eso-stroke/pdf/ESO08_Guidelines_Original_english.pdf)).
  30. W.Wolfgang Fleischhacker, David J. Brooks; *Stroke-Vascular Diseases; Volume 63 of Journal of Neural Transmission Issue 63 of Journal of neural transmission: Supplementum*, ISSN 0303-6995 *Volume 63 of Supplementum*, Journal of neural transmission; published by Springer Science & Business Media, 2002; illustrated edition.
  31. Sandercock P<sup>1</sup>, Gubitz G, Foley P, Counsell C.: Antiplatelet therapy for acute ischaemic stroke.: *Cochrane Database Syst Rev*, 2003; 2: CD000029.
  32. De Schryver EL<sup>1</sup>, Algra A, van Gijn J: Dipyridamole for preventing stroke and other vascular events in patients with vascular disease.: *Cochrane Database Syst Rev*, 2003; 1: CD001820.
  33. Righetti E<sup>1</sup>, Celani MG, Cantisani T, Sterzi R, Boysen G, Ricci S.: Glycerol for acute stroke.: *Cochrane Database Syst Rev*, 2000; 4: CD000096.
  34. Hemorrhagic Stroke; American heart association; ([https://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@hcm/documents/downloadable/ucm\\_309710.pdf](https://www.strokeassociation.org/idc/groups/stroke-public/@wcm/@hcm/documents/downloadable/ucm_309710.pdf)).
  35. Hersh EH<sup>1</sup>, Gologorsky Y<sup>1</sup>, Chartrain AG<sup>1</sup>, Mocco J<sup>1</sup>, Kellner CP: Minimally Invasive Surgery for Intracerebral Hemorrhage.: *Curr Neurol Neurosci Rep*, 2018 May 9; 18(6): 34. doi: 10.1007/s11910-018-0836-4.
  36. Zarar A<sup>1</sup>, Khan AA<sup>2</sup>, Adil MM<sup>1</sup>, Qureshi AI<sup>1</sup>.: Anaphylactic shock associated with intravenous thrombolytics: *Am J Emerg Med*, 2014 Jan; 32(1): 113.e3-5. doi: 10.1016/j.ajem.2013.08.046. Epub 2013 Sep 30.
  37. Rudolf J<sup>1</sup>, Grond M, Prince WS, Schmölling S, Heiss WD.: Evidence of anaphylaxis after alteplase infusion.: *Stroke*, 1999 May; 30(5): 1142-3.