Observation of stroke in a tertiary care neurology and neurosurgery hospital in Bangladesh: Risk factors, symptoms and treatment strategies

A project submitted

by

Umme Salma Khanam

Student ID: 13346046

Session: Summer 2013

to

The Department of Pharmacy

in partial fulfillment of the requirements for the degree of

Bachelor of Pharmacy (Hons.)

Dhaka, Bangladesh

February, 2018

This work is dedicated to my father and my project supervisor for their unconditional inspiration and relentless support

Certification Statement

This is to certify that this project titled "Observation of stroke in a tertiary care neurology and neurosurgery hospital in Bangladesh: Risk factors, symptoms and treatment strategies" submitted for the partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.) from the Department of Pharmacy, BRAC University constitutes my own work under the supervision of Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, BRAC University. Throughout the project, I have given appropriate credit where I have used the language, ideas or writings of another.

Signed,

Countersigned by the supervisor

Acknowledgement

Alhamdulillah, all the admiration belong to Allah S.W.T. from whom I get strength and health to complete this project work. My heartiest thankfulness and gratitude towards Almighty Allah for blessing me with immense patience, strength, corporation and assistance to complete the processes of Bachelor in Pharmacy.

I am immensely grateful towards my respected project supervisor, Md. Tanvir Kabir, Senior Lecturer, Department of Pharmacy, BRAC University for his patience, enthusiasm, motivation and immense knowledge and continuous support. Without his thoughtful encouragement and careful supervision, this project would never have taken shape.

My sincere thanks goes to Prof. Dr. Eva Rahman Kabir, Honorable Chairperson, Department of Pharmacy, BRAC University.

I am grateful to Prof. Dr. Quazi Deen Mohammed, Director of National Institute of Neurosciences and Hospital (NINSH) and Prof. Dr. Md. Azharul Hoque, Chairman of Ethics Review Committee of National Institute of Neurosciences (NINS), for their cooperation in conducting my survey for the project.

I am also grateful to my only sister, Umme Tanha Khanam for her help to finish this project work.

I am also thankful to four of my fellow mates, Maliha Tasnim Deeba, Md. Mushfiqul Haque, Safa Hossain and Fariha Hossain for their encouragement. They were always by my side whenever I needed them.

Lastly and most importantly, I would like to express my gratitude towards my parents for their constant love, inspiration and support.

Umme Salma Khanam

February, 2018

Abstract

Stroke is a frequently occurring acute cerebrovascular event which is characterized by blood vessel disruption in the brain. We sought to represent the risk factors, symptoms and treatment strategies of stroke in Dhaka, Bangladesh. A prospective, observational and spontaneous reported survey study was carried out among 200 stroke patients who were receiving treatment during study, from national institute of neurosciences and hospital (NINSH), Dhaka, Bangladesh. A case report form (CRF) comprised of questions was formed and obtained data were analyzed and presented by GraphPad Prism version 7. Majority of the patients were male with a percentage of 57.5% and female were 42.5%. Stroke was seen more prevalent in age group of 61-70 years old and 66.5% patients were from rural areas. Hemorrhagic stroke was found in 74.5% cases, ischemic stroke in 24% cases and both ischemic and hemorrhagic stroke were found in 1.5% cases. Hypertension (63.5%) was the commonest risk factor and vomiting (53%) was the top most symptom associated with both types of stroke. The most common forms of diagnosis were computed tomography (CT) scan (100%), complete blood count (CBC) (79.5%), serum electrolyte test (94%), serum creatinine test (89.5%), echocardiography (ECG) (73.5%) and urine examination (68.5%). In terms of treatment strategies, patients were receiving different types of anti-hypertensive agents (90%), anti-bacterial drugs (89%), corticosteroids (76.5%), anti-platelet drugs (21%), cholesterol lowering agents (27%), anti-epileptic drugs (47.5%), anti-psychotic drugs (25.5%), anti-pyretic drugs (50%) and anti-emetic drugs (26.5%). The burden of stroke can be reduced by targeting these risk factors. Recognition of symptoms and contacting to physician without any delay can also alleviate the rate of disability and mortality.

Table of Contents Page No.

Table of Contents **Page No.**

Table of Contents Page No.

List of Tables Page No.

List of Figures Page No.

List of Figures Page No.

List of Acronyms

Acronyms	Full form
AM	One hour after mid-night
ACVS	Acute cerebrovascular syndrome
AED	Anti-epileptic drug
AHA	American heart association
ASA	American stroke association
ACE	Angiotensin converting enzyme
ACAS	Asymptomatic carotid stenosis
CBC	Complete blood test
CRP	C- reactive protein
CS	Cryptogenic stroke
CT scan	Computed tomography scan
CTA	Computed tomography angiography
CRF	Case report form
DALYs	Disability adjusted life years
DM	Diabetes mellitus
DNA	Deoxyribonucleic acid
ECG	Electrocardiography
ECHO	Echocardiogram
Etc.	Etcetera
FT3	Free triidothyronine
FT4	Free thyroxine
HBB	Hemoglobin sub-unit beta
HICs	High income countries
ICH	Intracerebral hemorrhage
IHD	Ischemic heart disease
LMICs	Low and middle income countries
MI	Myocardial infarction
MRA	Magnetic resonance angiogram
MRI	Magnetic resonance imaging
MRV	Magnetic resonance venography
NCCCC	National collaborating centre for chronic conditions
NINSH	National institute of neurosciences and hospital
NSAID	Non-steroidal anti-inflammatory drug
OCP	Oral contraceptive pill
PM	One hour before mid-night
SA	Stroke association
SAH	Subarachnoid hemorrhage
SCD	Sickle cell disease
TIA	Transient ischemic attack

Acronyms	Full form
TSH	Serum thyroid stimulating hormone
US NIS	United States national wide inpatients sample
US TOAST	United State trial of organon in acute stroke treatment
WHO	World health organization

Chapter 1: Introduction

Chapter 1: Introduction

1.1 Stroke: A devastating disorder

Stroke is the most common and devastating cerebrovascular disorder. Cerebrovascular diseases can be explained as those diseases in which injury or dysfunction of the brain cells occur due to pathologic disorder of blood vessels or disruption of blood supply. The mechanism of these cerebrovascular diseases can be described in four simple steps including formation of occlusion by thrombus or embolism, rupture in blood vessels, diseases in blood vessels and disruption of normal characteristics of blood (Lindsay, Bone & Fuller, 2010). It could be present as a form of sudden neurological interruption including weakness of arms and legs on one side of body, inconvenience in speech, disturbance in balance but this cerebrovascular disorder is capable of being prevented and treated (The National Colalaborating Centre for Chronic Conditions [NCCCC], 1990). Stroke can be defined as an event of obstacle to brain blood vessels or when a blood vessel disrupts in the brain. In most cases, this acute cerebrovascular event is mentioned to as the brain is equivalent to a heart attack (World Health Organization [WHO], 2016). In according with World Health Organization (WHO), the definition of stroke can be unexpectedly occurring clinical characteristics of focal (global) brain disability of vascular origin (non- traumatic, non-epileptic) which exceeding for 24 hours or leading to death (Truelsen, Begg, & Mathers, 2000). Stroke is a condition which can be distinguished by four properties such as sudden onset of symptoms which is recorder by the previous history. Then, focal involvement of central nervous system which can be described more accurately by neurologic examinations and confirmed by imaging studies. The third feature is about lack of rapid resolution which described that the duration of neurologic shortage is recorded by the history. The shortage need to persist for at least 24 hours to differentiate stroke from transient ischemic attack (TIA). Moreover, due to absent of detectable clinical features, sometimes imaging studies cannot clearly exhibit prior stroke (Aminoff, Greenberg, & Simon, 2015).

1.2 Stroke: A public health issue

Neurologic disorders affect a large number of populations rather than any other disease like cancer, pulmonary disease or heart disease. Among the neurological disorder, a significant proportion affected due to cerebrovascular disease. Along with cerebrovascular diseases,

alzheimer diseases combine with epilepsy, tetanus account for quarter of disability adjusted life years (DALYs). Parkinson disease combined with multiple sclerosis contributes a little to death which has been shown in figure 1.1. On the other hand, stroke is the leading cerebrovascular disease that contributes to 85% deaths compared to other neurologic diseases (Garcy & Elkind, 2015). Stroke, a frequently occurring acute cerebrovascular event is the noticeable reason of morbidity and mortality through-out the world. In most countries, this cerebrovascular event is one of the four major reasons of mortality and one of the leading reasons of severe neurologic disability in senior citizens. Stroke is also known as silent killer because this neurological disorder interrupts normal living by leading to disability or premature death. By the number, stroke is third dominant cause for disability and second dominant cause for mortality in worldwide. Burden of stroke related death and disability adjusted life years (DALYs) lost are higher in low and middle income countries (LMICs) compared to ischemic heart disease. It is not because of having a vast population in LMICs, stroke incident rate, mortality rate, DALYs life lost indicate the micro economic level of these countries. The inequality between LMICs and high income countries (HICs) is elevating day by day. Approximately 42% stroke related incidents are reduced in HICs whether stroke incidents are increasing in LMICs near to 100% (Mehndiratta, M., Mehndiratta, P., Gulati, & Wasay, 2014).

1.3 Global scenario of stroke

Stroke is the second dominant reason of death across the world and one of the six dominant reasons of disability. Each year 15 million people are suffering from first even stroke and among them approximately 6.6 million people are died (WHO, 2016). During past two decades, the incidence of stroke rises significantly across the world. Even though the occurrence of strokes is reducing in developed countries day by day, the rate of mortality and disability due to stroke in lower developing and middle developing countries are increasing day by day (Li et al., 2017). Stroke related premature death rate and years of life lost rate are greater in less and moderate developing countries compared to developed countries. More than 81% deaths are occurring in low and middle income countries (WHO, 2016). This cerebrovascular event is responsible for the suffering of someone at every two second across the world. In United Kingdom (UK), each year more than 100,000 peoples are suffering from stroke (State of the nation [SA], 2017) and in United States of America (USA), it is responsible for the death of more than 130,000 peoples per year. Again in accordance with

American heart association's stroke statistics 2017, a new or recurrent stroke is experienced by 795,000 peoples across the world. Among them, presumptively 610,000 peoples experience new stroke and rest of them from recurrent stroke. Worldwide stroke mortality accounts for 11.8% of entire death rate. At the year 2013, 6.5 million peoples die worldwide due to stroke making it second dominant global cause of death and the total number of stroke incident were 25.7 million. Among them, about 10.3 million people had experienced first stroke. From 1990-2010, stroke related death increased 40.2% (Benjamin et al., 2017).

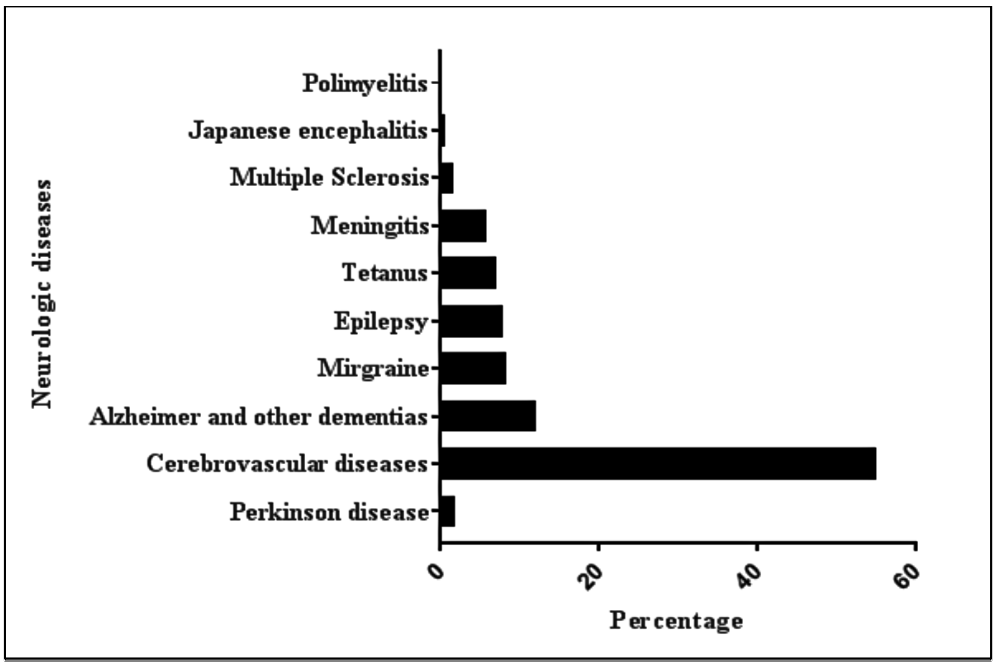

Figure 1.1: Percentage of different neurologic disorders

According stroke statistics 2016, from 2000-2013 stroke related mortality was fell by 33.7% and each year globally new strokes are experience by more than 795,000 peoples and in United State 1 out of every 20 deaths was due to stroke and in every 40 seconds, someone experiencing new or recurrent stroke (Mozaffarian et al., 2016). Currently, 33 million stroke survivors are living in the world and among them, 12 million peoples are living with permanent moderate to intense disability (WHO, 2016).

1.4 Bangladesh perspective

Burden of neurological disorder is high in less and moderate developing countries compared to developed countries and stroke is the most frequent cause of neurologic admission and mortality (Alam, 2015). Among all the low and middle income countries, South Asian

countries are taking into account as a maximum contributor to stroke related death across the world. More than 40% global stroke deaths occur in this region (Wasay, Khatri, & Kaul, 2014). South Asian region has numerous number of stroke patients with limited resources which is responsible for the extreme burden of stroke in this region. After India and Pakistan, Bangladesh is the third biggest South-Asian country with 160 billion population Asian countries contributing 40% of developing countries and 22% of world population. An adequate amount of mortality takes place in Bangladesh due to stroke and become third leading cause of mortality. From 2006 to 2011, stroke related mortality increased from 6% - 9%. Stroke prevalence is 0.3% in case of age 40 or more than 40 years old and its prevalence elevated to 1% for age group 70 or more than 70 years old (Bhowmik et al., 2016). This most populated South Asian country which is accounting for 5.8% (per 1000) stroke related death per year and becoming third leading cause of death and disability. Mortality rate due to stroke in Bangladesh has been ranked as a number 84 in the world by WHO (Islam et al., 2013). One of the potential reasons for these outcomes can be treating acute stroke patients without knowing etiology where computed tomography (CT) scan is not available. In addition, a number of neurodiagnostic tests are unaffordable to many patients.(WHO, 2016) Moreover, adequate number of research and attention in preventing stroke is conducted in developed countries where more than 85% stroke related incidents are occurring in developing countries (Engels et al., 2014).

1.5 Transient ischemic stroke (TIA) or mini stroke

Transient ischemic attack (TIA) is known as medical emergency and it is recently denoted as acute cerebrovascular syndrome (ACVS). Many a time TIA is neglected by patient(s) or family as clinical syndromes resolve without any treatment. Moreover, sometimes TIA is ignored by physicians as it is mini stroke (Uchiyama, 2009). It can be defined as clinical features of focal obstruction of brain function that remain not much than 24 hours (Sacco et al., 2013). The reasons behind this cerebral dysfunction or deficits in blood supply can be as an outcome of low blood flow, thrombus formation or embolus formation related diseases of blood, blood vessels or heart. Within 1-2 hours, most TIA usually resolves but when a TIA lasts for more than 3 hours it is described as “short-lived stroke”. However, more than 50% of these patients have experience cerebral infraction on magnetic resonance imaging (MRI) (Johnston, Gress, Browner, & Sindey, 2000).

An updated “tissue-based” definition of TIA can be an event leading less than 1 hour without any type of cerebral infarction ensured by magnetic resonance brain imaging. But it is required an early imaging of brain which is not reliable in lower developing and higher developing countries (Rothwell, 2007). However, stroke risk of TIA patients is very high as the set of causes of TIA is as same as stroke (Smith, English & Johnston, 2013). According to state of nation stroke statistics 2017, 5% peoples within 48 hours of TIA, 8% peoples at one week of TIA, 12% at one month of TIA, 17% peoples at three months of TIA can experience a stroke. So, this mini stroke or warning stroke should be diagnosed as seriously as stroke (SA, 2017). The concept of ACVS is recently introduced to raise awareness among the patients, physicians and citizens. So, this mini or warning stroke should not be ignored (Okada, 2013) .

1.6 Different pathologic processes of stroke

There are two principle pathologic processes of stroke including ischemic stroke and hemorrhagic stroke which are usually come off from arterial lesion (Aminoff et al., 2015). It is quite impossible to differentiate the two by their history. Neuropathology and neuroimaging have been proven effective for understanding whether it is ischemic stroke or hemorrhagic stroke (Sacco et al., 2013). At the year 2010, the incidents of ischemic stroke were about 11.6 million (63%) and incidents of hemorrhagic stroke were about 5.3 million (37%) (Benjamin et al., 2017). A recent study of 2016 revealed that 87% incidences of ischemic stroke and 13% incidences hemorrhagic stroke (Hering et al., 2016).

1.6.1 Ischemic stroke

Ischemic stroke is one of the heterogeneous disorders with a complex pathophysiology (Woodruff et al., 2011). Ischemic stroke is caused due to sudden blockage of arteries that are supplying oxygen and nutrients to the brain (Truelsen et al., 2000). Tissue of the brain is sensorial to ischemia in such an exquisite manner that small ischemic period towards neurons can introduce an intricate series of an occurrence that lead to maximum cellular death. Due to differential alleviation in blood flow, ischemia do not affects the brain tissue in an equal proportion. Therefore, intense ischemia happens to the core zone, where blood supplies will be alleviated to less than 7 milliliter per 100 gram per minute and due to uncontrolled cell death of tissue through the interruption of blood supply, the neuronal disruption in this region is not reversible. The central region is surrounded by ischemic penumbra, ranging blood flow from 7 to17 milliliter per 100 gram per minute (Mehta & Vemuganti, 2014). Different parts

of brain have different thresholds for ischemic cell injury such as white matter are more elastic than gray matter (Woodruff et al., 2011). Brain edema is another outcome of stroke. The ischemic cell leads to vasogenic edema formation as fluid loses its contents from intravascular compartment into brain. The highest possibility of edema formation could be appropriately 2-3 days after stroke. As a severe effect, brain edema can cause displacement of brain tissue between intracranial compartments and leading to death (Aminoff et al., 2015). Different pathologic procedures of cerebral damage classified ischemic stroke into sub-classes which are cerebral thrombus, cerebral embolism, cryptogenic stroke, lacunar stroke and less documented stroke which has been shown in figure 1.2 (Fitzsimmons & Lazzaro, 2011).

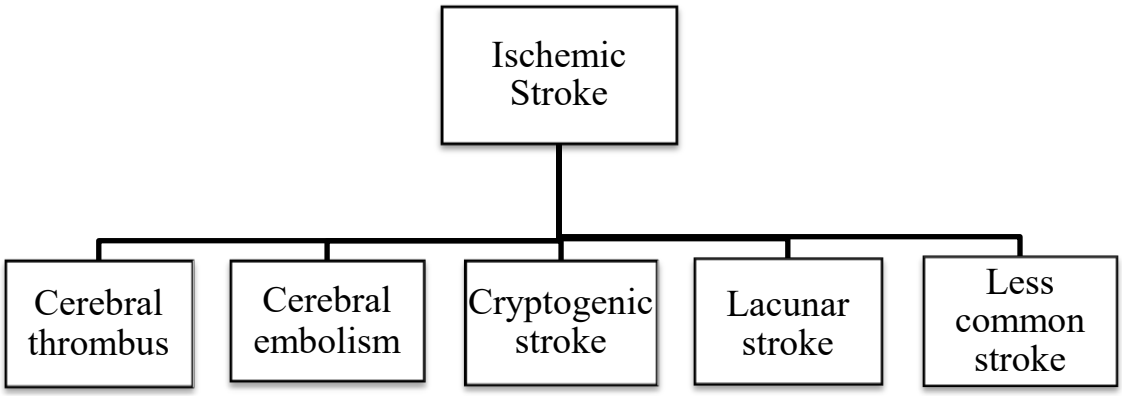

Figure 1.2: Different sub-classes of ischemic stroke

Among them, there are two basic pathogenic mechanisms that can cause ischemic stroke-thrombosis and embolism but many a time, it is not possible to distinguish those on neuroimaging techniques (Aminoff et al., 2015).

1.6.1.1 Thrombotic ischemic stroke or cerebral thrombosis

Cerebral thrombus accounts for approximately 14-25% ischemic stroke and male are more prone to thrombus stroke than female (Fitzsimmons & Lazzaro, 2011). When a blockage or occlusion occurred due to the direct formation of thrombus, it is known as thrombotic ischemic stroke or cerebral thrombosis. In that case, thrombus or clot mainly occurs due to the atherosclerotic occlusion or blockage in large cervical or cerebral arteries (Truelsen et al., 2000). Junction of usual and internal carotid arteries, proximal attachment of middle and anterior cerebral arteries, proximal attachment of vertebral arteries are the most common site of atherosclerosis formation related to stroke. Both intracranial and extra cranial atherosclerosis diseases are equally responsible for the atherosclerotic infraction. Extra

cranial atherosclerosis is more common to whites while intracranial atherosclerosis is more experienced by Hispanics and Asians (Fitzsimmons & Lazzaro, 2011). Symptoms are generally evolved from minutes to hours. Many a times, TIA leads to thrombotic stroke by producing same symptoms as they are affecting same region repeatedly (Aminoff et al., 2015).

1.6.1.2 Embolic ischemic stroke or cerebral embolism

Embolic ischemic stroke is the most commonly identified reason for stroke. Embolic ischemic stroke or cerebral embolism is arising from heart (Fitzsimmons & Lazzaro, 2011) and accounts for 14-30% ischemic stroke (Hering et al., 2016). Thrombus or clot could be formed into any part of the circulation that chases the blood stream unless it succeeds to create obstruction or blockage in the brain and it is known as embolic ischemic stroke or cerebral embolism (Fitzsimmons & Lazzaro, 2011). There are three types of embolism according to their site of emboli formation including cardiogenic embolism which can arise from aortic valves or left cardiac chambers, arteriogenic embolism can arise from proximal cerebral arteries and paradoxical embolism can arise from veins (Hart et al., 2014). Embolism is considered as a non-lacunar stroke associated with open proximal arteries. This type of stroke is usually experienced by the patients who have major risks of cardiac sources like non-rheumatic atrial fibrillation, left ventricular thrombi, prosthetic valves, myocardial infarction (MI), rheumatic heart diseases and ischemic cardiomyopathy. Among them, non-rheumatic atrial fibrillation is the usual cause of embolism and it accounts for more than 5% annual risk of stroke (Smith, English & Johnston, 2013).

1.6.1.3 Lacunar stroke

The word lacunar was first introduced by Deschambre in 1838 to describe small cavities resulting from resorption of small brain infarct (Catalina, 2011). Lacunar infarcts are small infracts, which are usually 2-20 mm in diameter. The location of these infarcts can be basal ganglia or pons and deep cerebral white matter, The etiology of lacunar stroke and similarity and dissimilarity between cortical ischemic stroke and lacunar stroke, remain still under discussion (Wardlaw, 2005).

Another study stated that 20% people account for lacunar stroke (Egeto, Fischer, Ismail, Smith, & Schweizer, 2014) and the risk factors for lacunar stroke are almost same to carotid atherosclerosis (Tegeler, Shi, & Morgan, 1991). Due to their small size, they are more prone to cause restricted neurologic deficits. Syndromes of lacunar infarcts can be generated from

large arteries and occasionally by tumor and multiple sclerosis (Ionita, 2011). Another study stated that shape of lacunar infarcts is related to its development of disease. Irregular shaped lesion may result from a blockage in the largest perforating arteries (Bastos Conforto & Conforto, 2013).

1.6.1.4 Cryptogenic stroke

Cryptogenic stroke (CS) is one of the subtypes of ischemic stroke. It is responsible for approximately 30% of all ischemic strokes (Yaghi, Kamel, & Elikind, 2017). Another study stated that cryptogenic stroke accounts for 10-40% ischemic stroke, specifically embolic in origin. It is also emerging from proximal artery sources or venous sources. So, cryptogenic stroke also can be defined as cerebral ischemia (Saver, 2016). The causes of this stroke remain unclear as the incident is temporary or not reversible. CS is more common among younger than senior citizens. Diagnostic examination of a patient for CS includes transesophageal echocardiography, transcranial Doppler- sonograpgy, CT angiography or MR angiography of the aorta, long term ECG recordings, imaging for venous thrombosis, coagulation tests as well as complete blood count (CBC) test. Repetition rates and recovery rates of CS is still under discussion. There is no distinction between primary and secondary prevention of cryptogenic stroke and stroke of known etiology. Proper identification of etiology of cryptogenic stroke is the indication of appropriate treatment (Finsterer, 2010).

1.6.1.5 Less documented ischemic stroke

There are some less documented etiologies which account less than 5% ischemic stroke. Damage to the inner lining or wall of blood vessels which carry oxygenated blood specifically arteries that supplying oxygenated blood in head and neck, responsible for exactly 2% ischemic stroke. Among them 20% patients are approximately less than 30 years old. Approximately, 50% untreated patients can be victims of inner lining or wall damage which is voluntary or injurious and cause to focal brain necrosis via artery-artery burst, local blood clot formation inside the blood vessels and blood circulation collapse (Fitzsimmons & Lazzaro, 2011).

1.6.2 Hemorrhagic stroke

Hemorrhagic stroke is responsible for 20 % of all stroke but morbidity and mortality rate due to this stroke are disproportionally high (Bernstein, 2011). Hemorrhagic stroke is occurred

due to leakage of blood vessel of the brain and blood spills either directly into or around brain parenchyma (intracerebral hemorrhage) or into or around the subarachnoid space in the brain tissue. It is also sub-divided into three groups including intracerebral hemorrhage, subarachnoid hemorrhage and subdural or epidural hemorrhage and shown in figure 1.3. In one word, these three types of hemorrhagic stroke are called intracranial hemorrhage. Among them, intracerebral and subarachnoid hemorrhage are occurred due to arterial bleeding (Aminoff et al., 2015).

1.6.2.1 Intracerebral hemorrhage

When the bleeding started from one of the brain's artery and bursts the artery and flooding surrounding tissue is known as intracerebral hemorrhage (ICH) (Moulin & Cordonnier, 2015). ICH is responsible for ~10-20% of all stroke (Hering et al., 2016). This type of stroke is more dominant in developing countries than in developed countries (Mehndiratta, M., Khan, Mehndiratta, P., & Wasay, 2014). ICH tends to causes more intense headache, loss of consciousness with neurological disorders (Aminoff et al., 2015).

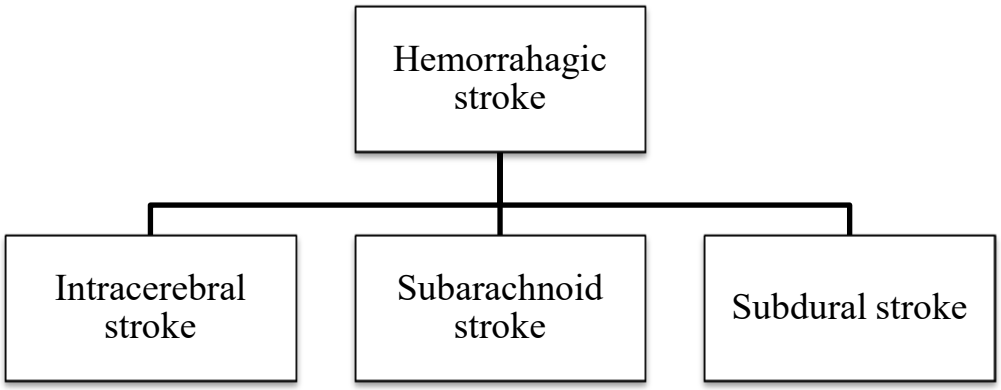

Figure 1.3: Different sub-classes of hemorrhagic stroke

This cerebrovascular accident is primarily occurred due to arteriolar hypertension disease and more often due to clot formation disorders, vascular anomalies within the brain and diet (such as elevated blood pressure, high alcohol consumption, abnormal concentration of lipids etc.). Cortical amyloid angiopathy, an outcome of elevated blood pressure is responsible for cortical hemorrhages which are mainly occurring in elderly people and its frequency increases as the population getting older (Truelsen et al., 2000).

1.6.2.2 Subarachnoid hemorrhage

Subarachnoid hemorrhage (SAH) can be one of the most devastating strokes. If arterial

bleeding is occurred in the space between the two meninges pia mater and arachnoidea then the event will be known as subarachnoid hemorrhage. Sudden onset of very intense headache and usually enfeeble consciousness are the typical symptoms of this cerebrovascular accident (Truelsen et al., 2000). It is leading to cerebral dysfunction by increasing intracranial pressure which cause inadequate perfusion of brain tissue, direct destruction of brain tissue and release toxic substances in subarachnoid blood (Aminoff et al., 2015). As a result, the area of the brain which is previously receiving oxygenated blood from arteries is now deprived of blood which leads to SAH. The causes of SAH could be aneurysm or brain injury. Aneurysm is the balloon like rounded swelling that cause rupture of the arteries and release blood into subarachnoid space in the brain. It is responsible for 1 out of 6 immediate death of the patient at the time of bleeding. Survivor can be dying if the bleeding occurs again or have major complexity (Rabinstein, 2013).

1.6.2.3 Subdural hemorrhage

It is another form of hemorrhagic stroke which is originated from traumatic condition. In this type of stroke, blood is accumulated in subdural space of dura mater and subarachnoid. It is more common among senior citizens because severity of injury is required to generate subdural hemorrhage. Trauma is the principal cause of subdural hemorrhage but after having severe head injury and impairment with nerve at acute stage, spinal cord or brain function are also evident of this stroke. Most usual clinical findings are headache and deflected consciousness but many a times, signs and symptoms are undetected, absent or non-localized (Aminoff et al., 2015).

1.7 How stroke leads to cell death

Activation of glutamate receptors is the first steps that lead to cell death. Glutamate is a major excitatory neurotransmitter in mammalian central nervous system which acts as an ionotropic receptors as well as N-methyl-D-aspartate receptors. This glutamate release and activated its receptors and leads to calcium influxes. This homeostasis leads to activation of a number of calcium dependent pathways such as proteases and nucleases. By forming free radicals that causes disruption of the membranes, proteins and DNA (deoxyribonucleic acid), reperfusion prolongs neuronal cell disruption. Furthermore, mitochondrial permeability transition pore acts as a releaser of a number of proapoptotic molecules including cytochrome C. Release of cytochrome C activates Caspase-9 which further activates Caspase-3 and leads to DNA damage and cell death which has been shown as figure 1.4. Cell death is the ultimate result of

necrotic, apoptotic and necroptotic mechanisms (Lo, Dalkara, & Moskowitz, 2003). F

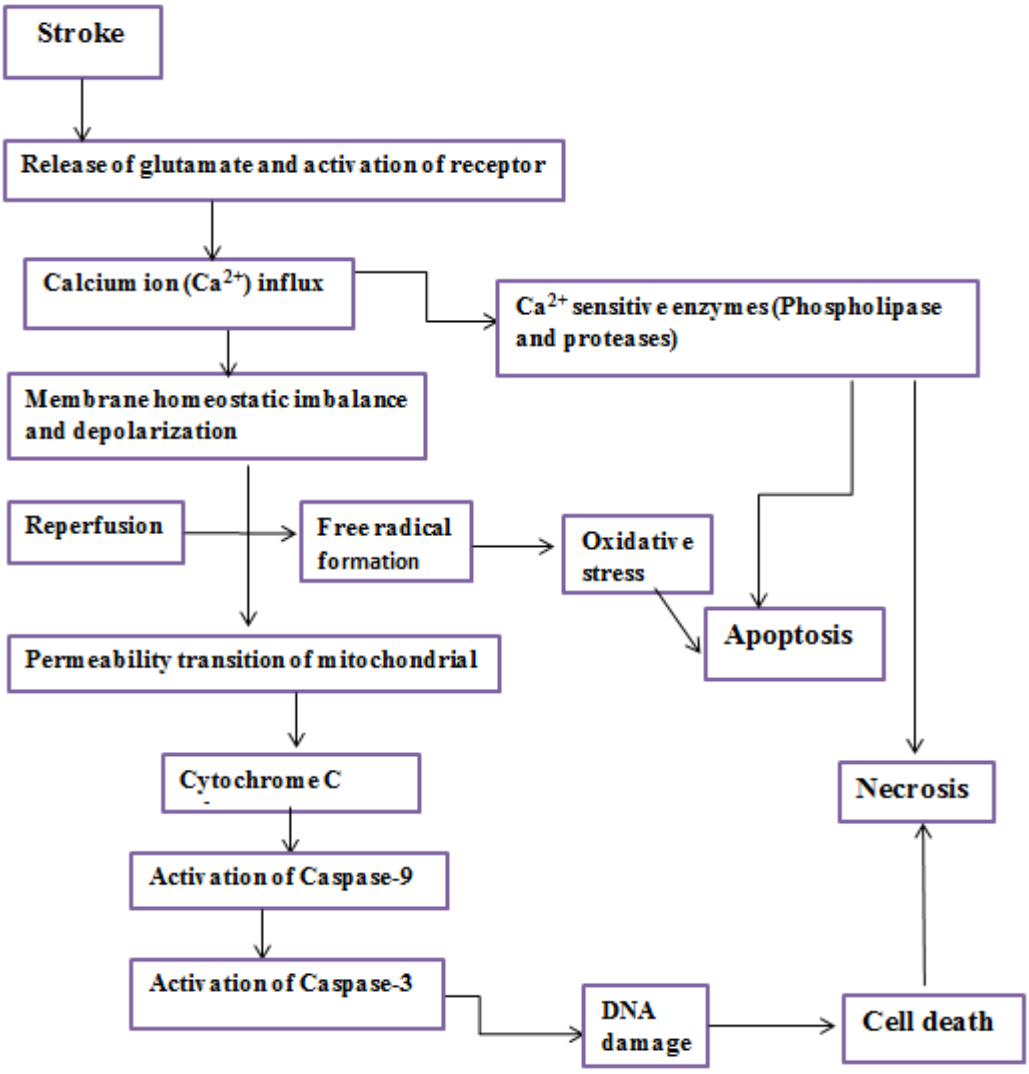

Figure 1.4: A schematic view of stroke mechanism

Adapted from "Mechanisms of stroke induced neuronal death: Multiple therapeutic opportunities" by S. L. Metha, 2014, *Advances in Animal and Veterinary Sciences,* 2 (8), P. 440. Copyright 2014 by Metha.

1.8 Risk factors contributing to stroke

Stroke as a multi-factorial event describes many risk factors or determinants. These determinants or risk factors can be classified into non-modifiable and modifiable which has been shown in table 1.1 (Jahirul, Choudhury, Chowdhury, & Nayeem, 2015).

1.8.1 Non-modifiable risk factors

Non-modifiable or irreversible risk factors are those which cannot be changed or controlled by making change in lifestyle. There are mainly four irreversible determinants for stroke including age, gender, race and family history of stroke and heart disease.

1.8.1.1 Age

Stroke can be experienced at any age but at the year of 2008, half of the stroke occurred in people over 70 years old (Alawneh, Clatworthy, Morris, & Warburton, 2011). According to stroke statistics 2017, 17% of all stroke experienced by the people over the age 85 years old. They have higher rate of mortality, greater disability as well as have longer duration of hospitalization. United States national wide inpatients sample (US NIS) analysis stated that in-patients death rates after stroke had been reduced for each age group or gender except men who are aged more than 84 years old. It is expected that over the next 40 years (2010-2050) stroke incident will be more than twice among the senior citizens (≥75 years old). Besides that, 10% of all strokes are occurring among the people aged from 18-50 years old. Hospital admission due to ischemic stroke increased among young and adolescents at the year between 1995 and 2010. In the same period, hospital admission due to subarachnoid hemorrhage decreased (Benjamin et al., 2017).

1.8.1.2 Gender

Gender is one of the risk factors for stroke that cannot be modified. Men are more victimized by stroke than female. A recent study stated that stroke occurrence rate is 1.6 times higher in man than women (Miah et al., 2012). However, mortality rate among the women due to stroke is greater than of breast cancer in every decade of life. In addition, women who have history of atrial fibrillation are more prone to stroke. According to faculty of health sciences (FHS) data, women having natural menopause before the 42 years old have experienced double ischemic stroke than the women having natural menopause after 42 years old. Though nurses' health study did not find any correlation between stroke and natural menopause at the age 42 (Benjamin et al., 2017).

1.8.1.3 Race

Race is another irreversible determinant of stroke. A study was carried out to explore the negative determinants of stroke among American Indians and found that they had an elevated risk of stroke incident compared to others (Jahirul et al., 2015). Another US based study

elucidated that blacks who are aged between 20-45 years old are more prone to stroke incident and has a higher mortality rate rather than whites (Krishnamurthi et al., 2015) and risk of having stroke in Hispanics is middle between blacks and whites (Bernstein, 2011). At the year 2014, 35.1% non-Hispanic whites (male) died because of stroke incident while stroke death rate among non- Hispanic blacks (male) was 56.5%. In case of female, death rate among Non-Hispanic whites was 35% while death rate of non-Hispanic blacks was 46.3% (Benjamin et al., 2017).

1.8.1.4 Family history of stroke and heart disease

Family members share genes, behaviors, lifestyle and environments that can influence their health as well as risk of disease. Stroke risk can be more prominent in some families than others due to their similar lifestyle, environmental factors or other potential factors. So, family history of stroke (FSH) is another non-modifiable risk factor for stroke. A number of studies found FSH as an independent risk factor for all types of stroke (Caicoya, Corrales, & Rodriguez, 1999) and (Kulshreshtha et al., 2015). Another study indicated that FSH as a strong risk factor for young women (Kim et al., 2004). Another study showed that sibling history of stroke is more strongly interrelated with this cerebrovascular disease rather than parental stroke history (Choi, Lee, Kang, Kang, & Bae, 2009). Family history of cardiovascular disease can also influence the risk of stroke. Gene can pass on the risk of heart disease and they can also be accountable for passing on other conditions like elevated blood pressure or elevated levels of cholesterol which can influence the risk of having stroke (Aminoff et al., 2015).

1.8.2 Modifiable risk factors of stroke

There are some risk factors or determinants which can be introduced as modifiable risk factors because person can modify those risk factors by bringing change in life style and by treating with medicines. Modifiable or reversible risk factors for stroke can be vascular, cardiac, endocrine, and hematologic and change in life style.

1.8.2.1 Cardiac risk factors

There are some risk factors which are associated with heart known as cardiac risk factors. There are some cardiac risk factors which are associated with stroke including chronic heart failure and atrial fibrillation.

Table 1.1: Well-documented risk factors for stroke

Non-modifiable
Age
Gender
Race
Family history of stroke and heart disease
Modifiable
Cardiac
Chronic heart failure (CHF)
Atrial fibrillation (AF)
Vascular
Hypertension
Peripheral artery disease
Smoking
Asymptomatic carotid artery stenosis (ACAS)
Metabolic
Dyslipidemia
Obesity (especially abdominal)
Endocrine
Diabetes mellitus (DM)
Use of oral contraceptive pill (OCP)
Lifestyle
Physical inactivity
Hematologic
Sickle cell disease

Adapted from Clinical Neurology (p. 361) by M. J. Aminoff, D. A. Greenberg, & R. P. Simon (2015), New York, United States: Mc Graw Hill Education. Copyright 2012 by Mc Graw Hill Education.

1.8.2.1.1 Chronic heart failure (CHF)

Chronic heart failure or CHF is one of the dominant reasons of hospitalization, state of being morbid and state of being subjected to death all over the world. It is one of dominant risk factors for ischemic stroke. CHF is directly connected to thrombus formation and thus increased the risk of ischemic stroke two-three times more than normal. In addition, stroke

patients with CHF bring out poor outcome of elevated rate of death. A meta-analysis stated that 18 and 47 out of per 1000 CHF patients have experienced stroke within 1 year and 5 years respectively. According to retrospective studies, 9-10% stroke patients with CHF have the possibility of recurrent stroke (Haeusler, Laufs, & Endres, 2011).

1.8.2.1.2 Atrial fibrillation (AF)

Atrial fibrillation (AF) is a state of heart beat which is not regular and sometimes abnormal heart beat. It occurs when aria or upper chamber of heart contract in a random manner and sometimes the contractions are so fast that heart muscles cannot relax appropriately between contractions. AF do not cause stroke directly. It can modify the other risk factors of stroke such as hypertensive person with cardiac failure, coronary heart disease and atrial fibrillation are directly linked with elevated risk of stroke. It became a risk "marker" among the people over 70 years old. AF associated in elder increases the risk of having stroke 4 to 5 times than normal. Presence of AF in stroke are quite severe than the non-AF stroke patients. Moreover, 70% hospitalized stroke patients associated with AF were resulted death or unacceptable neurologic problems (Wolf, Abbott, & Kannel, 1991).

1.8.2.2 Vascular risk factors

There are some risk factors which are related to vessels of the body specially arteries or veins that carry blood and lymph throughout the body. Among the vascular risk factors hypertension, peripheral artery disease, asymptomatic carotid stenosis and smoking are directly associated with stroke.

1.8.2.2.1 Hypertension

Blood is transported from the heart and pump through blood vessels or arteries to all parts of the body. Each time blood pumps into arteries when the heart beats. When blood is pumped by heart it thrust against blood vessels or arteries with force that leads to blood pressure. Blood pressure is determined in millimeters in mercury (mmHg) and enlisted as two numbers which are written one upon another. Systolic blood pressure (upper number) is the maximum blood pressure in blood vessels and it occurs as a result of heart muscle contraction and the diastolic blood pressure (lower number) is the lowest blood pressure in blood vessels and it occurs as a result of heart muscle relaxation. Normal adult range of blood pressure is 120/80 mmHg; where 120 mmHg is denoted as systolic pressure and 80 mmHg is denoted as diastolic pressure. When blood vessels raised blood pressure in a persistent manner, it is known as hypertension. Hypertension is also known as raised blood pressure or higher blood

pressure. If systolic or maximum blood pressure is at or above than 140 mmHg and diastolic or minimum blood pressure is at or above than 90 mmHg then it is consider as hypertension (WHO, 2013). For both ischemic and hemorrhagic stroke, hypertension is one of the leading negative determinant which accounts for 100 crore people across the world. In case of acute stroke, blood pressure increases in 75% peoples and among them 50% patients have the previous history of hypertension and blood pressure drops in two-third patients within the first 7 days of following stroke. Among them, one-third exhibiting hypertension which elevates the risk of poor outcome (Appleton, Sprigg, & Bath, 2016). A research conducted in 1973 stated hypertension as a dominant negative determinant for hemorrhagic stroke and unspecified stroke (Harmsen, Rosengren, Tsipogianni, & Wilhelmsen, 1973). Another research conducted in 1985 also justified the relationship between hypertension and subarachnoid hemorrhage (Wolf, 1985).

1.8.2.2.2 Peripheral artery disease

Globally vascular disease is one of the main reasons of death. Vascular disease is one arterial locality can detect diseases of other locality with higher strength and diseases of other localities elevate risk of cerebrovascular incident with former stroke or TIA. A recent study indicated that patients who are suffering from peripheral artery disease (PAD) are more prone to stroke compared to patients who have coronary artery disease (CAD) (Raman et al., 2012).

1.8.2.2.3 Asymptomatic carotid artery stenosis (ACAS)

When carotid arteries which pump oxygenated blood from heart to brain become thinner due to plaque formation, then the process is called atherosclerosis. When the carotid arteries are narrowing more than 50% in the absence of interruption in the blood flow in the preceding six months, then is known as asymptomatic carotid artery stenosis (ACAS) (Kappelle, Visseren, & Graaf, 2013). For ischemic stroke, it is marked as a significant risk factor. In The United States, it is responsible for more than 90% of all stoke in both male and female. People who are suffering from elevated blood pressure, diabetes mellitus and elevated level of cholesterol as well as people who are habituate in smoking having higher possibility of having asymptomatic carotid stenosis. As carotid artery atherosclerosis can be occurred suddenly and silently, the initial disclosure can be fatal stroke (Raman et al., 2012).

1.8.2.2.4 Smoking

Various forms of smoking such as tobacco smoking, cigarette smoking or second hand smoking etc. are contributing to stroke in various pathways. Nicotine, oxygen gases and

carbon monoxide are the main ingredients of tobacco and cigarette which lead to stroke. Blood vessels can be damaged by the toxics components present in tobacco and cigarette which induce endothelial cell impairment in function and inflammation, vasoconstriction and buildup of clot. In addition, it can increase the risk of thrombus formation of the non-smokers. Although non-smoke tobacco is less documented as a risk factor of cerebrovascular disease but as it contains more than 200 chemical components, it can lead to stroke by increasing blood pressure in a persistent manner. Researcher found a strong and well-established relationship among stroke and tobacco smoking. Risk of having stroke to a tobacco smoker is two to four times higher than non-smoker and it is eligible for both men and women. An adequate number of The United States of America's Surgeon General's reports indicated tobacco smoking as an elevated risk factor for both ischemic stroke and subarachnoid hemorrhage. Research also pointed out that the risk of stroke can be increased nearly two times with a clear dose response by smoking cigarettes. Cigarette smokers are more prone to stroke than a non-smoker even after reconciliation of all the risk factors. At the year 2011, a review study exposed the dose-response relationship of stroke and cigarette smoking. The study stated that comparative risk for stroke could be raised from 1.16 for smoking five cigarettes per day to 1.56 for smoking 40 cigarettes per day. So, there is no minimum limit of smoking which can be indicated as safe lower limit (WHO, 2016).

1.8.2.3 Metabolic risk factors

The word "metabolic" reflect the biochemical procedures which are involved in body's normal functioning. Risk factors are trail, habit or condition that elevates the risk of having disease like heart disease, stroke. Dyslipidemia and obesity are the metabolic risk factors or determinants that are associated with stroke.

1.8.2.3.1 Dyslipidemia

Dyslipidemia is a state of unnatural concentration of lipoprotein or lipid in the blood. Most of the dyslipidemia could be hyperlipidemia. Hyperlipidemia is an elevated level of lipid like cholesterol and fat. Previously dyslipidemia was considered as a fatal risk factor of cardiovascular diseases but recently this risk factor established a strong relation with cerebrovascular diseases like stroke. One of the dominant facts for hemorrhagic stroke is low density lipoprotein cholesterol level rather than lacunar and cardio-embolic stroke. A recent study of 100 hospitalized stroke patients after analyzing their lipid profile stated that 56% patients had abnormal lipid concentration or dyslipidemia in the blood. Among them, 40%

had higher cholesterol level, 7% patients had elevated triglycerides and 3% patients had low density lipoprotein level (A, Ks, & R, 2014).

1.7.2.3.2 Obesity

Obesity is another risk factor of stroke. Overall, 35.5% first even stroke patients are found to be obese. Stroke is a leading risk factor for the people over 60 years old and with aging population, rate of obesity has become double since 1980-2014 and 600 million senior citizens are classified as obese. Body mass index or BMI is the determinant of obesity which is calculated as dividing the body weight in kilogram by square of height in meter. In accordance with WHO classification, if BMI is more than 25 kg/m^2 then it is overweight and if BMI is more than 30 kg/m^2 then it is marked as obese. Obesity can be further classified as class I, class II and class III. An adequate number of studies identified obesity as a risk factor for ischemic and hemorrhagic stroke in both gender and in nationwide population. Obesity can be considered as a strong risk factor for developing other risk factors like elevated blood pressure, abnormal lipid concentration as well as diabetes mellitus (Haley & Lawrence, 2016).

1.8.2.4 Endocrine risk factors

There are some risk factors which are related to glands that are secreting hormones into bloodstream. Diabetes mellitus (DM) and oral contraceptive pills (OCPs) are endocrine risk factors which are associated to stroke.

1.8.2.4.1 Diabetes Mellitus (DM)

Diabetes mellitus is a chronic disorder which evolved genetically or acquired due to shortage of insulin production by the pancreas. Such shortage increases glucose production in the blood which lead to dysfunction of many body systems specifically nerves and blood vessels (WHO, 2010). This chronic disease is an autonomous risk factor of stroke. It is one of the dominant causes of stroke after TIA or recurrent stroke. The elevated risk of having stroke because of diabetes is 2.1 to 5.6 greater than the patients who are not suffering from diabetes mellitus. About 8-20% acute stroke patients have the history of recognized diabetes mellitus before having stroke and 6 to 42% patients could not recognize diabetes mellitus before having stroke. Transient hyperglycemia was found in 36.3% patients while only 24.8% diabetes mellitus patients were diagnosed (Zahra, Kidwai, Siddiqi, & Khan, 2012).

1.8.2.4.2 Use of oral contraceptive pills (OCPs)

Use of oral contraceptive pills is another reason of stroke. Taking oral contraceptive pills enhance clot formation of the blood which could lead to stroke. Studies stated that high estrogen content increased the risk of all types of stroke whether low estrogen content and low estrogen content had a very minor or no risk of stroke. Every year, 1 out of 20000 woman become victim of stroke due to use of OCPs (Bousser & Kittner, 2000). Overall risk of stroke among women using oral contraceptive pills depend on age. The age range of 15-19 have risk of 3.4 per 100,000 and it elevated quite rapidly to 64.4 per 100,000 in women of middle aged who undergo hormonal replacement therapy. Due to difference in cultural features, frequency of using oral contraceptive pills is higher in Western countries compared to Asian countries. A recent study which was conducted among 958 Asian women who experienced ischemic stroke and the found that only 8% women used oral contraceptive pills and 10% OCP users found among young women who were suffering from cerebral venous sinus thrombosis. This indicates that rate using OCP in Asian countries are quite low compared to developed countries which are varying from 35-60% (Mehndiratta, P., Wasay, & Mehndiratta, M., 2015).

1.8.2.5 Lifestyle

A balanced life-style is essential to prevent a number of diseases. Physical activity is a part of lifestyle which could reduce the risk of stroke.

1.8.2.5.1 Physical inactivity

Physical inactivity could be another risk factor of stroke. This risk factor could be the developer of most of the other risk factors of stroke like elevated blood pressure, dyslipidemia, type-II diabetes mellitus and obesity. Physical activity could improve vascular function as well as help to reduce and control the risk of having stroke. Many of these risk factors are directly associated with physical inactivity which is leading to stroke. So, there is a proportional relationship between physical activity and incident stroke. A meta-analysis study showed that participants who were involved in higher physical activity had 25% less risk of stroke and participants who were involved in moderate physical activity had 17% less risk of stroke compared to inactive participants (Howard & McDonnell, 2015).

1.8.2.6 Hematologic disorder

Hematologic disorder is the disorder of blood. It includes problem with red blood cells, white blood cells, bone marrow, platelets, lymph nodes, spleen, and so on. By leading thrombosis in the cerebral vasculature, hematology disorder increases the risk of stroke. Sickle cell disease (SCD) is one types of disease of red blood cells which elevate the risk of stroke.

1.8.2.6.1 Sickle cell disease

When red blood cells become sickle or oval in shape due to less oxygen supply in the blood, it is known as sickle cell disease. It is a blood related disease and one of the leading genetic disorders. Sickle cell disease can be two types including sufferer and carrier. Mutation of hemoglobin sub-unit beta (HBB) gene is the main cause of this disorder (Bolwar, 2015). For each types of stroke, stroke risk factors in SDC are quite different. In case of ischemic stroke, patients with SCD are linked with previous TIA, elevated systolic blood pressure, previous silent infarct, arterial hypoxemia specifically during rapid eye movement (REM) sleep and severe coronary syndrome. On the other hand, hemorrhagic stroke in SCD is linked with low steady state white blood cells, older age, low steady state of hemoglobin, blood transfusion within 14 days, treatment with corticosteroids within 14 days and non-steroidal anti-inflammatory drugs or NSAIDs (Talahma, Strbian, & Sundararajan, 2014).

1.9 Symptoms of stroke

There are several symptoms of stroke. One patient may have one or two clinical symptoms at a time but it is not possible to have all the features at a time. Clinical symptoms could be hemiplegia or sometimes called hemiparesis is a state that affects one part of the body. So hemiplegia could be right or left depending on the side of affected. Another symptom of stroke is dysphasia in which disruption occurs in productive side such as reading and writing and dysarthria interacts with the muscles that produce speech. In case of dysarthria, patients can produce language but their speech became slowly and jabbers which is hard to understand. In addition, other symptoms of stroke could be difficulty in swallowing which is known as dysphagia, cranial nerve palsy, headache, vomiting, convulsion, diplopia, inflexibility in reading and writing, neck stiffness, sensory loss, ataxia and hiccough (QD, 2003). Among them headache is the most common feature in hemorrhagic stroke including both subarachnoid and intracerebral and in case of ischemic stroke, 25% patients reported to have headache. Nausea and vomiting are reported in case of stroke concerning with

cerebellum and brainstem (Bernstein, 2011). Another study identified hemiplegia, sensory loss and headache as the frequent symptoms of stroke (Masood, Hussain, Rehman & Abbasi, 2016).

1.10 Medical treatment

1.10.1 Anti-hypertensive agents

Control of hypertension is a well-establish target of stroke treatment. Hypertension is found commonly in the stroke patients. It found in both patients who are taking antihypertensive therapy and who don't have previous history of hypertension. The blood pressure could increases due to one or more than one of the following mechanism such as increased sympathetic drive, reflex response to cerebral, autonomic dysregulation, impaired neurogenic cardiovascular control and mental stress (Spence, 1986). American stroke association and European stroke initiative recommended that either labetalol or sodium nitroprusside are administrated intravenously to the patients who have blood pressure values repeatedly above 220/120 mmHg unless there are other signs of myocardial infarction, congestive heart failure etc. The blood pressure target for pre-hypertensive patients is 180/105 mmHg and 160-180/90-100 mmHg for formal normotensive patients. Patients who don't have the history of taking anti-hypertensive agents before occurrence of stroke and have a baseline pressure of 180-220/<120 mmHg, antihypertensive therapy should be postpone for the initial 48 hours after stroke onset. On the other hand, patients who take antihypertensive therapy before stroke and have a baseline blood pressure, in that case antihypertensive agents should be given to get off from counter stroke (Semplicini, Calo, Calò, A., & L., 2005).

1.10.2 Anti-platelet drugs

Aspirin, a non-steroidal anti-inflammatory drug (NSAID) has been proven one of the most effective treatments to alleviate death rate after acute ischemic stroke if introduced within 48 hours of stroke onset. This NSAID also moderately alleviate the chance of early recurrent stroke as well as long term disablement but it might elevate the chances of having intracranial hemorrhage (Sandercock, Gubitz, Foley, & Counsell, 2003). After acute ischemic stroke, all patients should be treated with aspirin as a beginning treatment unless they are being treated with intravenous thrombolysis. In those cases, aspirin must be taken off for minimum 24 hours and can be started after 24 hours if there are no major bleeding complicacies. Newly developed anti-platelet such as clopidogrel and dipyridamole could be introduced as long

time therapies for alleviating the chance of recurrent stroke (Fitzsimmons & Lazzaro, 2011). Initial dose of 325 mg is recommended by American heart association (AHA) stroke guideline (Adams et al., 2013). Another two leading anti-platelet drugs are clopidogrel and combination of extended-release dipyridamole and aspirin. Combination of aspirin and extended-release dipyridamole are proven to be more effective than single aspirin therapy for recurrent stroke prevention (De Schryver, Algra, & van Gijn, 2003). In accordance with European stroke prevention study 2 (ESPS) and European stroke prevention in reversible ischemic trial (ESPRIT) the associate chances of having recurrent stroke is alleviated to 23% but this combination therapy requires two times daily dosing and a serious form of headache could be occurred in closely one-third patients. On the other hand, clopidogrel is better option because it is as effective as combination of aspirin and dipyridamole and has a better tolerance with less possibility of headache and requires just one time daily dosing (Fitzsimmons & Lazzaro, 2011). Clopidogrel has proven more safe and capable of producing desire effect in case of secondary stroke over aspirin and its relative risk reduction is about 8.7% and possibility of major bleeding is also less. Though aspirin is the best anti-platelet drug for stroke prevention, it reduces approximately 15% chance of having secondary stroke. Many physicians prefer to use combination of aspirin and clopidogrel as the combination is more effective than single one (Albers & Amarenco, 2001).

1.10.3 Anti-coagulant drugs

In the emergent treatment of patients with acute ischemic stroke, anti-coagulants are used for many years. Anti-coagulants are given to stroke patients as an attempt to prevent primary or recurrent stroke specially patients with cardio embolism due to atrial fibrillation and large artery atherosclerotic disease. Though anti-coagulants are used worldwide for stroke treatment but its safety and ability to produce desire result are controversial (Shahpouri, Mousavi, Khorvash, Mousavi, & Hoseini, 2012). The panel of stroke council of American heart association reviewed that there is no effectiveness in using anti-coagulants for ischemic stroke treatment (Adams et al., 2013). An adequate number of clinical trials become unsuccessful to bring out any helpfulness in the primary treatment of ischemia. Several investigations have been done to see the effectiveness of anti-coagulants over anti-platelet medications by giving them within 12-24 hours of the initial event. The trail of organon 10172 in acute stroke treatment (U.S. TOAST) investigated the efficacy of low-molecular weight heparin (LMWH) over aspirin and found that there is no benefit of LMWH over

aspirin. Moreover, in some cases it elevated bleeding rates and increases chance of having brain hemorrhage (Smith, English & Johnston, 2013).

1.10.4 Intravenous administration

If recombinant tissue plasminogen activator or rtPA or alteplase is administrated intravenously within 48 hours of the stroke symptoms onset then it will alleviates the disability and death from acute ischemic stroke. The dose of this drug administration is 0.9 mg/kg up to a maximum total dose of 90 mg. Besides that, 10% of the dose is given as an intravenous bolus and rest of the dose is given as a continuous intravenous infusion within 60 minutes. Within the 60 minutes of patient's arrival at the hospital, the treatment should be started which allocate sufficient time for diagnosis and evaluation of possible contraindication (Aminoff et al., 2015). Ischemic stroke either it is thrombotic or embolic stroke, obstruction of the artery by thrombus caused occlusion. When the blood flow reduction is sufficiently severe, a series of events take place at the level of cellular that leads to infarction. Tissue plasminogen activator is a proteolytic enzyme with a serine residue in its active site that acts by promoting the conversion of active plasmin from inactive plasminogen. Plasmin functions on fibrin clots resulting dissolution and breaking down of the clots. The functions of tissue plasminogen activator are greatly promoted in presence of fibrin, enhancing fibrinolysis. Thrombolytic medications become an essential part of stroke treatment after the national institute of neurological disorders and stroke t-PA stroke group trail's (NINDS) publications (Ahasan, Hossain, Das, Minnat, & Chowdhury, 2013).

1.10.5 Anti-bacterial drugs

A quite complicated interaction is occurred between the brain and the immune system after acute stroke. Brain ischemia and tissue injury could activate toll-like receptors or effectors of sensors of non-specific immune system and cells of non-specific immune system which leading to manifestation of the inflammatory cascade. Inflammatory cascade is responsible for toxin release. An elevated number of infection related incidents is perceived after acute stroke and which might be the consequence of activation of long-distance feedback loops (Chamorro et al., 2012). Infection is the most frequent outcome after stroke and 21%-65% stroke patients are diagnosed with the most familiar infections like pneumonia and urinary tract infections. Anti-bacterial drugs reduce the risk of infections but do not reduce death rates. They may either kill or stop the growth of bacteria which cause pneumonia, urinary tract infections (Van de Beek, 2009). Preventive or prophylactic antibiotic are proven to be

effective in a number of meta-analysis and observational studies. Anti-bacterial drugs or antibiotics are used to treat infections where prophylactic antibiotics are used to prevent infections (Westendorp et al., 2012); (Liu, Xiong, Zhang, Fan, & Yang, 2016).

1.11 Review of literature

Review of literature is a significant feature of any research project from starting to end. It provides direction insight of problem and also co-operate in choosing methodology, tools for analyzing data. From these points of view, a profound literature review has been done. The review of literature is presented in the following section:

Mehndiratta et al. conducted a review study among 12 Asian countries to know current epidemiological data, mortality rates due to stroke, stroke prevalence and incident as well as mortality rate due to stroke. The sources of information were PubMed and research gate. The study showed that essential steps are needed to determine risk factors of stroke which being a burden issue for these Asian countries. They also marked the need of standard format or guidelines to conduct research on epidemiological situation in developing Asian countries (Mehndiratta et al., 2014).

Mehndiratta, Wasay, & Mehndiratta conducted review study to expose the lacking in the knowledge of stroke risk factors and variations provided to Asian women in stroke care. They found that Asian women had higher incident of stroke compared to European women and men. Mortality rate due to stroke were significantly higher among Asian women compared to European women except Japan but lower than Asian Men. In terms of risk factors they included hypertension, dyslipidemia, atrial fibrillation and diabetes mellitus and marked elevated blood pressure as a highest reason of morbidity among women. Researchers also elucidated about use oral contraceptive, obesity, metabolic syndrome and addiction of alcohol and tobacco. In addition they described about gender and age-specific risk factors of stroke and stroke during pregnancy. They concluded by expressing their study limitation and future plans (Mehndiratta, P., Wasay, & Mehndiratta, M., 2015).

Miah et al. conducted a comparative study among young group (greater than 15 years old) and adult groups to know the risk factors associated with stroke. Total 102 participants were participating in the study. The study concluded that smoking, oral contraceptive pill, elevated blood pressure, valvular heart disease and TIA were the leading risk factors for arising stoke in tender age group and in case of older, elevated cholesterol level, diabetes mellitus, ischemic heart disease, smoking and TIA were the leading risk factors for arising stoke in old

age group. In addition they added that incident of stroke can be decreased by the modification of risk factors (Miah et al., 2012).

Siddique, Nur, Mahbub, Alam, & Miah conducted a study among 100 stroke in-patients who were admitted into different medical units of Chittagong medical college hospital. Purpose of this study was to show the epidemiology and clinical features of stroke. They found that people aged 51-60 accounts more stroke (51.75% ischemic stroke and 45% hemorrhagic stroke). The ratio between male and female were 1.35:1 in case of blood clot forming stroke (ischemic stroke) and 3:1 in case of blood burst related stroke (hemorrhagic stroke). Hemiplegia was the most familiar symptom for both ischemic and hemorrhagic stroke and vomiting and headache were dominant symptoms of hemorrhagic stroke. The most dominant risk factor for both type of stroke was elevated blood pressure. Smoking and diabetes mellitus were also marked as significant risk factors of stroke. They concluded that by targeting risk factors of stroke, the burden of this cerebrovascular disease can be reduced and more research need to conduct on stroke as it became a global burden (Siddique, Nur, Mahbub, Alam, & Miah ,2009).

Another review study performed by Jahirul et al. to review the various types of irreversible and reversible risk factors of stroke. They described that risk of having stroke increased with age and the risk could be double between ages 45 to 85. Gender as a risk factor, male has more possibility of having stroke than female (except too young age or too old age). In addition afro-Caribbean has higher incident of stroke than Asians and European and heredity is also another irreversible risk factor of stroke. To elucidate modifiable risk factors, they studied on hypertension, diabetes mellitus, heart diseases, obesity, polycythemia, oral contraceptive pills, smoking, and alcohol addiction. They concluded that a number of risk factors of stroke are preventable (Jahirul et al., 2015).

Saha et al. conducted a prospective observational study at Faridpur medical college and hospital among 100 randomly selected clinically and computed tomography (CT) scan proved patients admitted in medicine and neurology ward. The objective of this study was to analyze determinants and clinical features of stroke. They marked elevated blood pressure as the leading risk factor, diabetes mellitus, dyslipidemia, and smoking and previous history heart disease had also found as a significant risk factors. Among clinical features, hemiplegia was the most common in both ischemic and hemorrhagic and headache and vomiting were also found significantly in hemorrhagic stroke patients, sensory loss was also found in one-fourth patients. They concluded that stroke as a significant cause of mortality, morbidity and socio-economic challenge for Bangladesh (Saha et al., 2016).

Another review study was conducted by QD to elucidate management of stroke including stroke risk factors, its clinical features as well as treatment strategies. The study described risk factors of stroke as modifiable and non-modifiable. Among all the risk factors age, elevated blood pressure, cardiac diseases, smoking, abnormal lipid concentration and smoking were significant risk factors of stroke. The researcher also studied about common features and treatment strategies of stroke including general treatment, symptomatic treatment, treatment of complication and specific treatment (QD, 2003).

Islam et al. (2013) conducted another review study to know the burden of stroke in our country. They reviewed different observational study conducted in different hospital and reported that elevated blood pressure or hypertension is the leading reason of stroke. About 485 out of 10,000 lost their life due to stroke which indicates that stroke would become a burden on socio-economic life of Bangladesh. Two non-government organizations (NGOs) working for the primary stroke prevention strategies. Researchers concluded that Bangladesh government needs to take essential steps to cope up with increased population healthcare and to decrease stroke burden (Islam et al.,2013).

Masood, Hussain, Rehman & Abbasi conducted a cross-sectional study among 200 hundred stroke patients in the DHQ teaching hospital's medical units. A questionnaire was prepared to know the frequency of determinants, various symptoms as well as response to treatment strategies. They found that 68% patients had hypertension, 26.50% patients were suffering from endocrine disease like diabetes and 12.50% patients were suffering from cardiac disease such as ischemic heart disease and 27.50% were smoker. Headache, loss of sensory, hemiplegia was the frequent clinical features and ischemic stroke were more dominant than hemorrhagic stroke (Masood et al., 2016).

Bhowmik et al. conducted an observational study among 679 patients admitted in neurology department of Bangladesh institute of research and rehabilitation in diabetes, endocrine and metabolic disorders (BIRDEM) hospital. Patients with hemorrhage and post trauma features were excluded in their study. They summarized that mortality rate due to stroke was not that much high but most of the patients discharged from hospital with tolerable to intense disability. According to their study age, systolic blood pressure, pneumonia, mRS, systolic blood pressure and stroke severity influenced the Barthel score. Barthel score is formed from barthel index which is a record of what a patient could do and what a patient could not (Bhowmik et al., 2016).

Li et al. performed a prospective cross-sectional study among 207323 participants in 31 different regions of china. Data obtained from through a door to door survey to explore the

manifestation of stroke by age, gender, epidemiology variations and education level. Their study documented that 2.08% of 40 years old or more than 40 years older adults are affected by stroke. They also found that men are more affected by stroke compared to female in case of age standard structure. In addition, they marked hypertension as a leading risk factor of stroke which had affected 35.24% (19.8 million) Chinese adults of 40 years old or more than 40 years old and other risk factors like elevated glucose level, elevated cholesterol level were also dominating in the general population. At the same time, elevated prevalence of stroke was noticed in rustic areas compared to urban areas. Less physical activity, unhygienic diet and too much pressure of life could also increase the occurrence of stroke (Li et al., 2017).

Chapter 2: Objectives and Methodology

Chapter 2: Objectives and Methodology

2.1 Objectives

Stroke toll in Bangladesh is high without any doubt. In Bangladesh, adequate number of survey on stroke is not committed by different health care organizations to show the real scenario of stroke. Some cases go undetected and some stroke cases are not registered in a proper data base. Still there is a need to conduct a lot of surveys to illustrate and compare stroke statistics of Bangladesh with other countries. The objective of this study was to represent the current scenario of stroke in a tertiary care hospital of Dhaka, Bangladesh which will emphasize on the distribution of stroke based on different parameters like age, gender, location, education level, lifestyle, and family history of stroke, symptoms, mode of diagnosis, treatment received and medications prescribed to the patients. Another significant objective of this study was to evaluate current treatment strategy of stroke and find out the success rate of treatment strategies as well as to compare it with standard guidelines of treatment strategies. In addition, effort had been taken to find out correlation of stroke with other risk factors and diseases like cardiovascular diseases, blood related diseases. Evaluation of time-critical nature of stroke was another objective of this study. Stroke onsets, first hour to meet a physician, arrival of hospital are the variable to evaluate time critical nature of stroke.

2.2 Methodology

2.2.1 Study site

The study site was national institute of neurosciences and hospital (NINSH), situated at Sher-E-Bangla Nagar, Dhaka, Bangladesh. It is a tertiary care neurology and neurosurgery hospital in Bangladesh. Patients from different regions of Bangladesh come to this institution for treatment purpose and patients' information are well-documented in this institution which represents an overall scenario of stroke in our country. That is why this institution was more appropriate for this survey purpose.

2.2.2 Study design

This was a prospective observational study which was carried out among 200 hospitalized patients of stroke admitted into non-paying neurology units of national institute of

neurosciences and hospital. The period of the study was 28th September, 2017 to 5th December, 2017. Inclusion criteria was the patients having WHO definition criteria for stroke "Unexpectedly occurring clinical signs of focal (or global) brain disability of vascular origin (non-traumatic, non-epileptic) which continue more than 24 hours or leading to death" (WHO, 2016) and age between 18-100 years. Exclusion criterions were patients dying before recording the information, patients' unwillingness to take part in the study. The study protocol was approved by the ethical review committee of national institute of neurosciences (NINS).

2.2.3 Data collection

Each interested patient or patient's family member(s) shared patient's previous disease history, patient's lifestyle, stroke symptoms and prescriptions. All the information was collected in a standardized, structured case report form (CRF) which was also approved by the ethical review committee of national institute of neurosciences (NINS). A brief description of collected information is enlisted in table 2.1.

Table 2.1: Summary of collected information

Patient-related information:
Age
Gender
Residential status
Education
Occupation
Working hazards and working hours
Smoking, tobacco, betel eating habit
Food habits
Disease-related Information:
Patient's previous disease history
Previous TIA and stroke history
Family history of stroke and heart diseases
Symptoms:
a. Symptoms appeared
b. Symptoms onset
c. Recognition of symptoms

Diagnosis-related information:
Blood pressure at arrival
Temperature at arrival
HFMD (Hours to contact the first physician)
Stroke onset
Tests done for brain imaging, vascular imaging and other purpose(s)
Stroke type(s) and location(s)
Complication(s)
Medication-related information:
Anti-hypertensive agents
Anti-platelet drugs
Anti-coagulant drugs
Cholesterol lowering agents
Anti-bacterial drugs
Corticosteroids
Anti-epileptic drugs
Anti-psychotic drugs
Anti-emetic drugs

2.2.4 Ethical consideration

The study protocol was approved by the ethical review committee of national institute of neurosciences and hospital. The study was designed in such a way which would adhere with Bangladesh medical research council's (BMRC) guidelines such as full written consent was obtained from research participants. In addition, protection of privacy and anonymity of the participants in the study were ensured. For the proposed study, data were collected individually and carefully. All types of communication in need of the study were done with honesty and transparency. Use of humiliating, discriminatory or other unacceptable language had been avoided in questionnaire preparation and these instructions were also followed during interview session with research participants. Information provided by the research participants were kept strictly confidential.

2.2.5 Scope for error

The study was not laboratory based study. All the information gathered from answers provided by the research participants and by analyzing their medical reports. The chances of error were also less if the participants did not provide any inaccurate information.

2.2.6 Data analysis

Collected data were analyzed and presented by GraphPad Prism version 7.0. This software is used for commercial scientific 2D graphing and statistics, published by GraphPad Software, USA.

Chapter 3: Results and Discussions

Chapter 3: Results and Discussions

3.1 Results

Out of 200 patients, 57.5% patients were male and rests of 42.5% patients were female. Majority of the patients were belonging to age group 61-70 which was 28%. Most of the patients were attending non-paying neurology wards and some were attending paying neurology wards. Among them, 66.5% patients were coming from rural areas and 31% patients were coming from urban areas and rests of 2.5% patients were coming from semi-urban areas. No patient was found from slum area.

Table 3.1: Socio-demographic profile of the patients obtained in the study

Variable	Percentage (%)
Gender	
Male	57.5
Female	42.5
Age groups (years)	
18-30	1
31-40	13
41-50	18.5
51-60	23.5
61-70	28
71-80	11
81-90	4
91-100	1
Residential status	
Rural	66.5
Urban	31
Semi-urban	2.5

Educational levels	
Illiterate	31
Primary level	21
Secondary or higher secondary level	37
Graduate or post-graduate	11
Working Status	
Working persons	33
Retired persons	27
Housewives	40
Working hours	
1- 5 hours	30.3
6-10 hours	27.3
More than 10 hours	42.4
Working hazards	65.15
Smoking and other addictions	
Smokers	18
Ex-smokers	10
Non-smokers	72
Betel users	53.5
Alcoholic	1.5
Tobacco users	1
Food habits	
Patients liked to have sweet dishes	18.5
Patients liked to have salty dishes	20.5
Patients liked to have spicy and oily foods	22.5

In case of education level, 31% patients were illiterate, 21% patients could not pass primary level, 37% patients were completed secondary or higher secondary level and 11% patients were graduated or post-graduated and the levels of education have been shown in table 3.1. Among these 200 patients, 33% patients were worked in different sectors and 27% patients were retired from their work and rests of the 40% patients were housewives. No unemployed patient was found. In case of working hours, out of 66 patients (33%) who were engaged with

various works, 30.3% patients were worked for less than 5 hours and 27.30% patients were worked for 6-10 hours and rests of the 42.4% patients were worked for more than 10 hours. Working hazards were found in 65.15% patients (among 33% employed patients). Detailed patients' socio-demographic related information has been shown in table 3.1. Among 200 patients, 18% patients were smokers and 10% patients were ex-smokers and rests of the 72% patients were non-smokers, 53.5% patients were habituate to betel, 1.5% patients were found as alcoholic and only 1% patients were habituate to tobacco. In terms of patients' food habit, 18.5% patients liked to have salty foods, 20.5% patients liked to have salty foods and 22.5% patients liked to have oily and spicy foods.

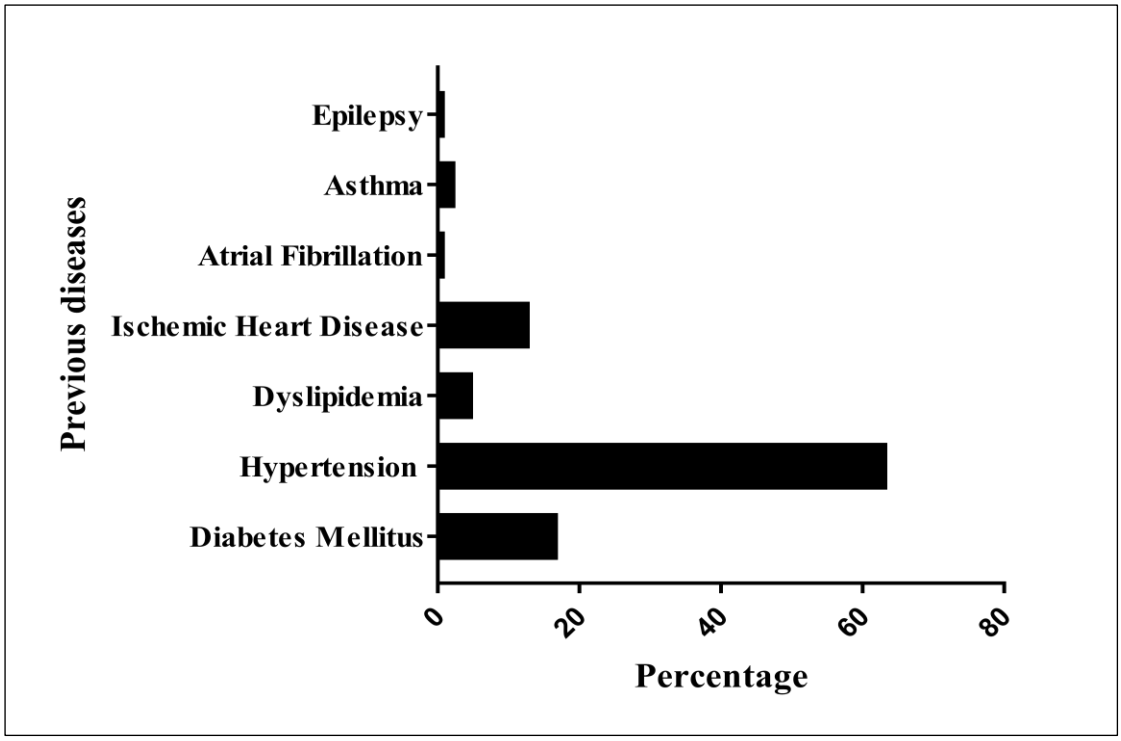

Figure 3.1: Percentage of stroke patients according to previous disease history

In terms of patients' previous disease history, 63.5% patients had previous history of hypertension, 17% patients had diabetes mellitus, 13% patients had ischemic heart disease, 5% patients had dyslipidemia, 2.5% patients were suffering from asthma, 1% patients had history of atrial fibrillation and epilepsy were found in 1% patients and these percentages have been shown in figure 3.1. Out of 200 patients, 67 patients (33.5%) had previous history of TIA and 19.5% patients had previous history of prior stroke. In terms of patients' family history, 24% patients had family history of stroke and 22.5% patients had family history of heart disease like ischemic heart disease and atrial fibrillation. The details information about

previous history of stroke and TIA has been shown in figure 3.2 and family history of stroke and heart diseases has been shown in figure 3.3 as a graphical presentation.

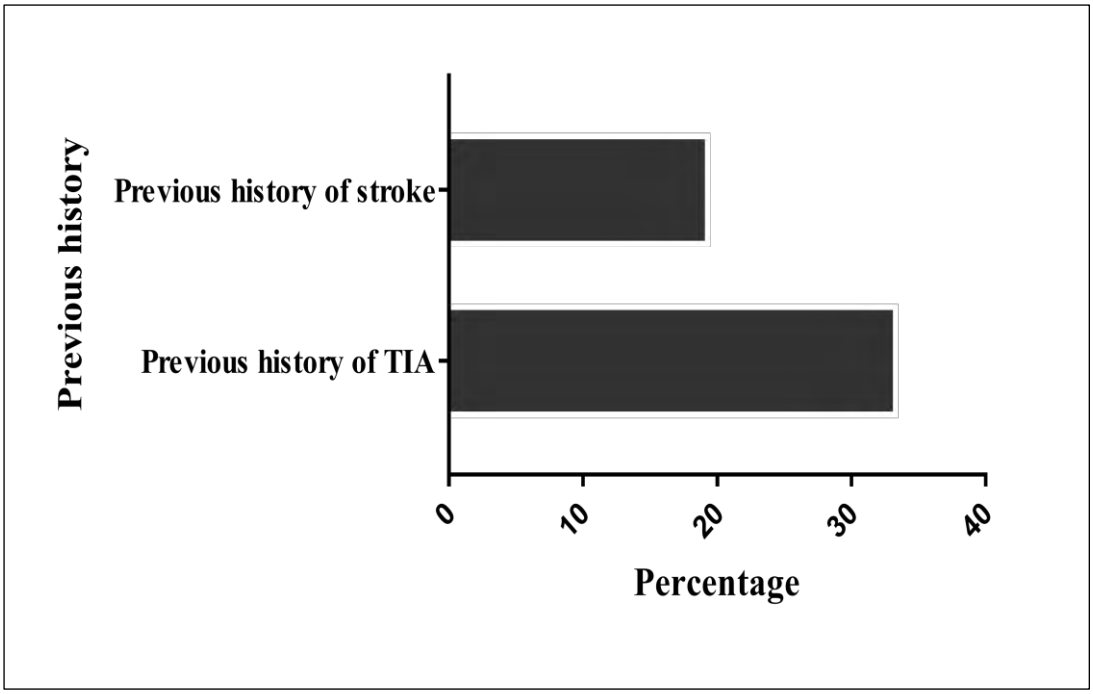

Figure 3.2: Percentage of stroke patients according to previous stroke history

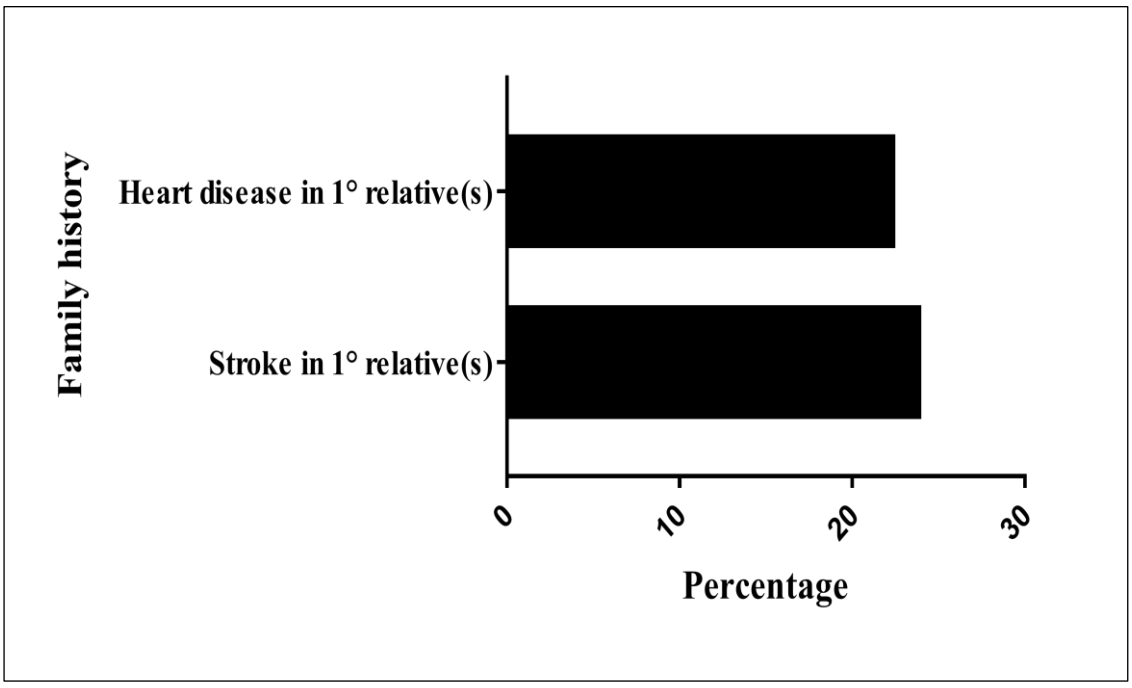

Figure 3.3: Percentage of stroke patients' family history of heart disease and stroke

Among the symptoms, vomiting was most commonly appeared symptom (53%) and sensory loss was found to be second-common symptom (38%). Dysphasia was appeared in 32.5% patients, pain and headache were found in 28% patients, and altered consciousness was found in 27% patients. Hemiplegia was appeared in 26.5% patients, convulsion was found in 17% patients, weakness of the particular side was appeared in 16% patients, losing bowel and bladder control were found in 10% patients, sweating, swallowing problem, restlessness were appeared in 5.5%, 5.5%, 5.5% patients respectively as shown in figure 3.4.

In 98.5% cases, stroke was occurred suddenly. Only one patient (0.5%) experienced stroke during computed axial tomography scan procedure and another two patients (1%) were experienced stroke during kidney transplantation. In terms of stroke onset, most of the patients (31.5%) had been experienced stroke at morning time (6 am to 11.59 am) and secondly 30.5% patients had been experienced stroke at 12 am to 5.59 am, 15.5% patients at

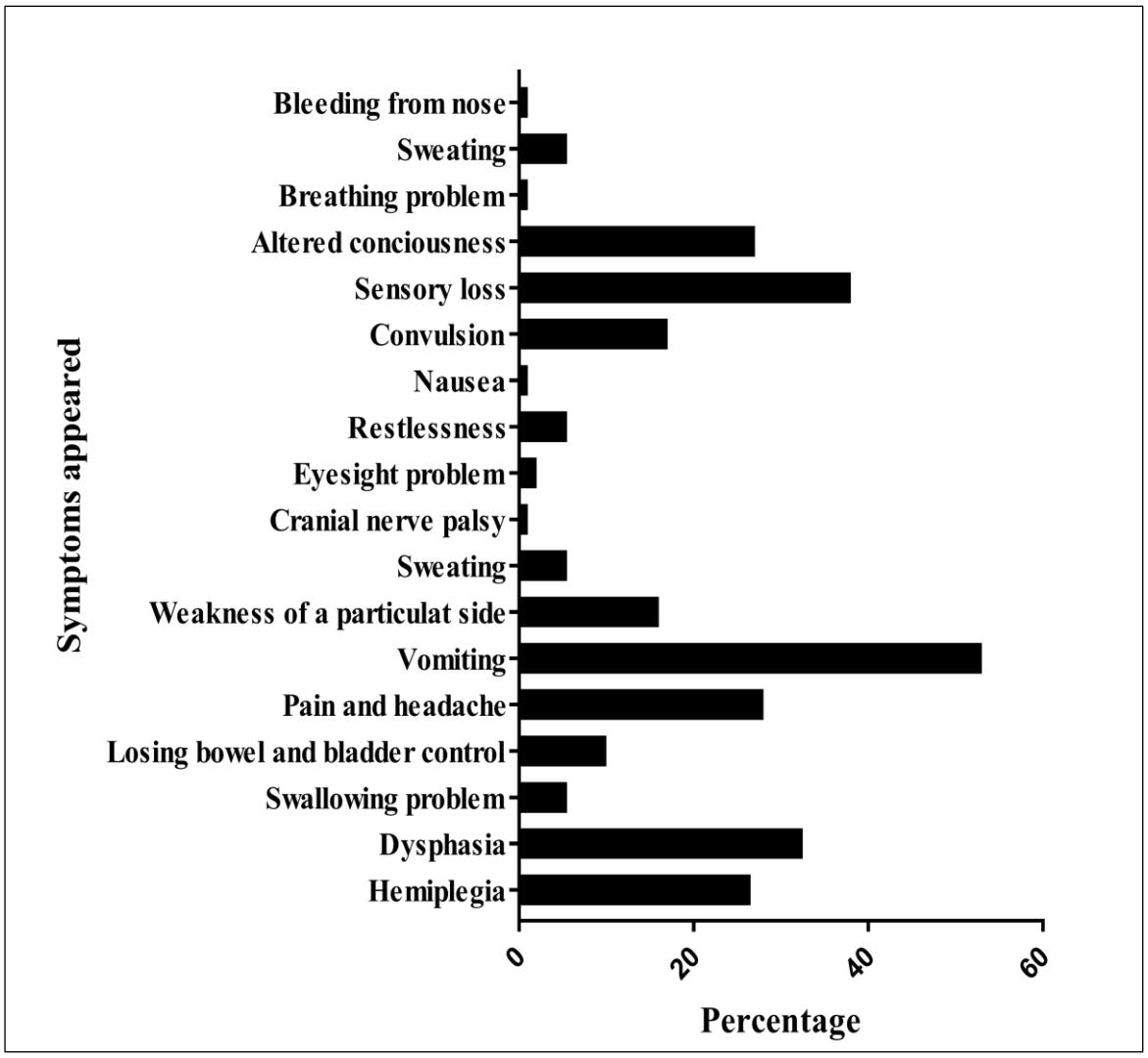

Figure 3.4: Percentage of symptoms reported by stroke patients

6 pm to 11.59 pm and rest of the 14.5% at 12 pm to 5.59 pm. Rests of the 8% patients were experienced stroke in sleep shown in figure 3.5.

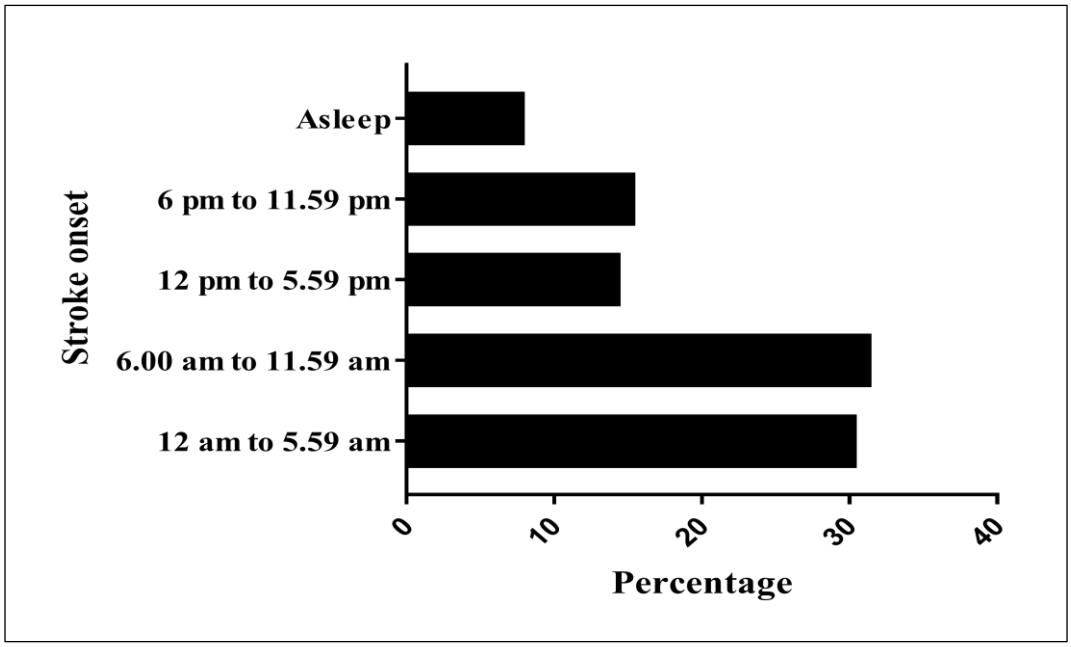

Figure 3.5: Percentage of stroke patients according to stroke onset

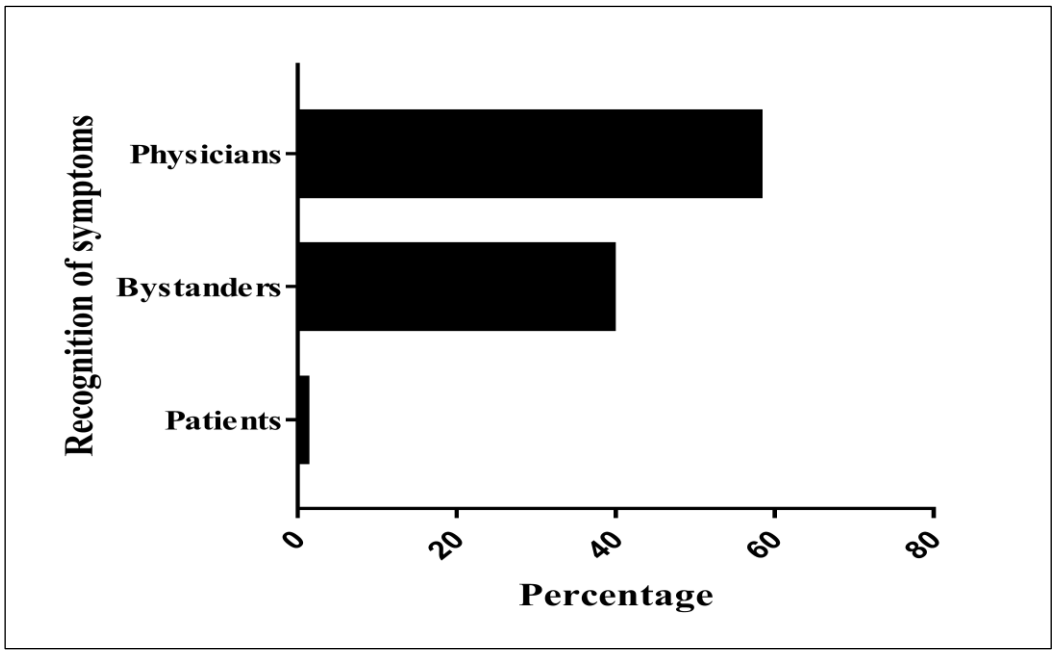

Figure 3.6: Percentage of symptoms' recognizers

In case of symptoms recognition, most of the times stroke was recognized by physicians (58.5%), secondly by patients' family member(s) (40%) who were present during stroke onset and only 1.5% cases, patients itself were able to recognize the symptoms which has been shown in figure 3.6.

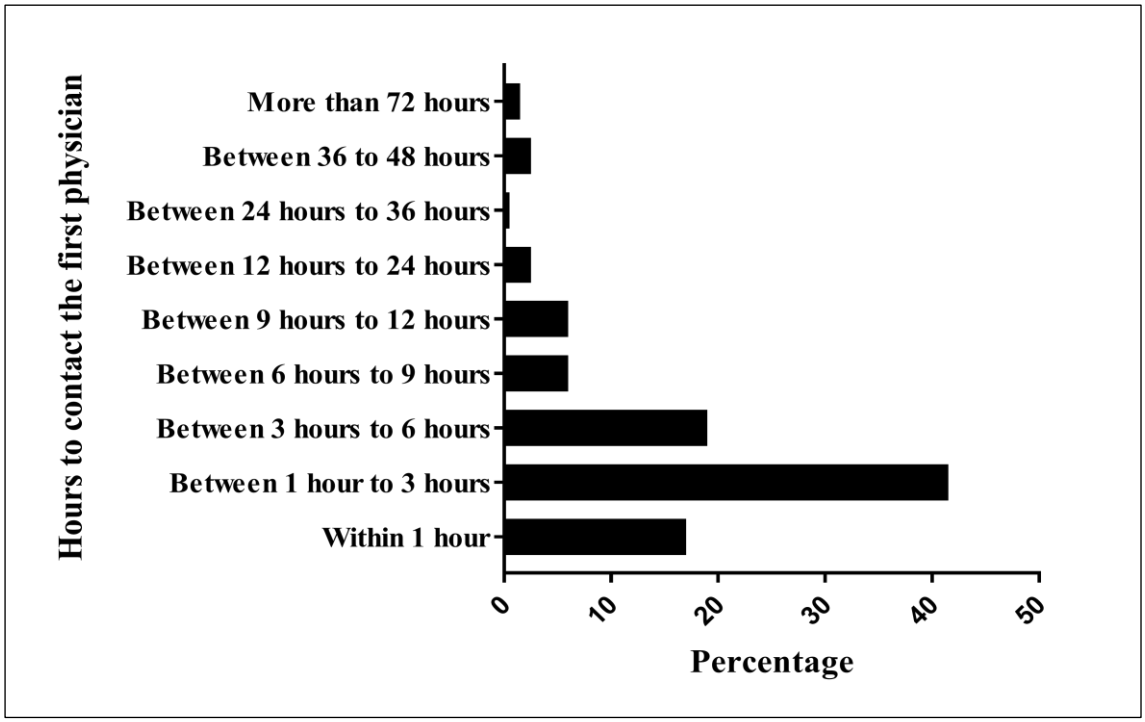

Figure 3.7: Percentage of stroke patients according to HFMD value

HFMD is defined as the number of hours between stroke onset and first contact between patient and physician. HFMD value was found for 96.5% patients though stroke onset was found for 100% patients. Only 17% patients were presented to physician within 1 hour. HFMD value for 41.5% patients was more than 1 hour and less than or equal to 3 hours. For 19% patients, HFMD value was between 3 hours to 6 hours and for 6% patients, it was between 6 hours to 9 hours. More than 9 hours and less or equal to12 hours delay was made in 6% patients, more than 12 hours and less than or equal to 24 hours delay was made in 2.5%, between 24 to 36 hours delay was made in 2.5% cases which shown in figure 3.7.

More specifically, in 41.5% cases where symptoms of stroke were recognized by bystanders (40%) or patients (1.5%) itself but still the HFDM value for less than 1 hour was found in only 9.5% cases. More than 1 hour delay was made in 19.5% cases, 6% patients were presented to physician between hours 3 to 6 hours of stroke onset.

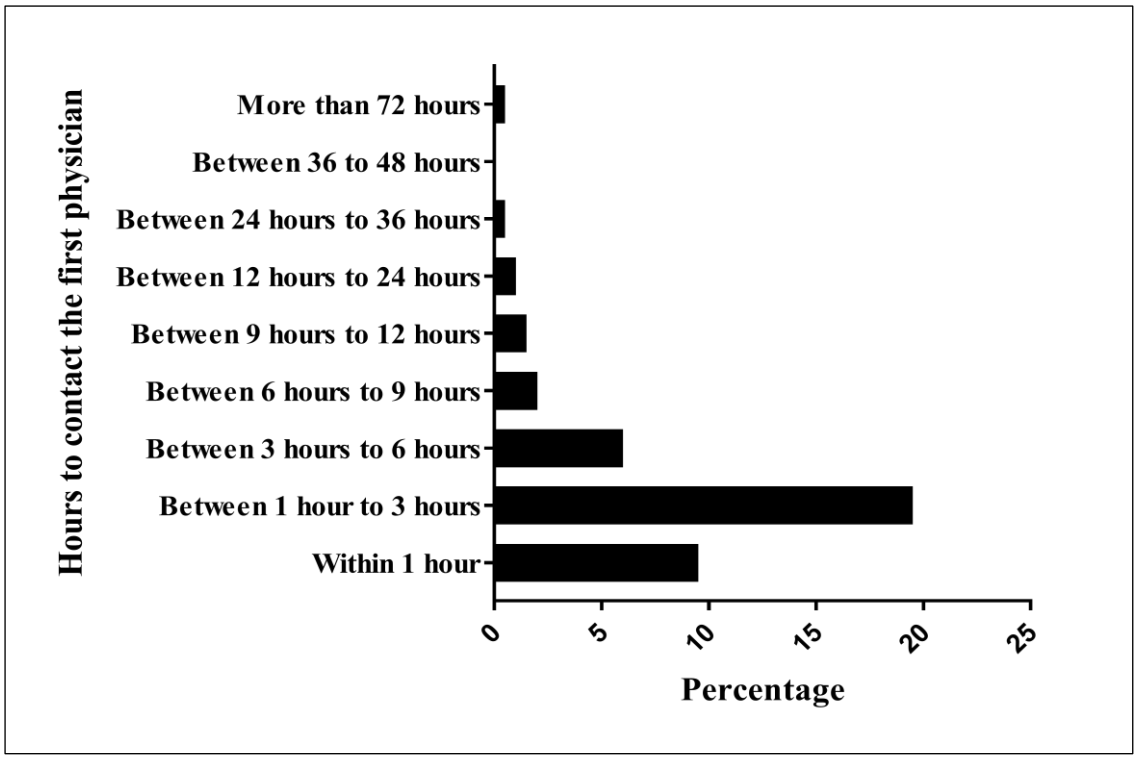

Figure 3.8A: Percentage of stroke patients' HFMD value when symptoms were recognized by bystanders and patients

More than 6 hours and less than or equal to 9 hours delay was made for 2% patients and more than 9 hours and less than or equal to 12 hours delay was made for 1.5% patients and details information has been shown through graphical presentation in figure 3.8A.

Rest of the 58.5% cases, where symptoms were recognized by the physician, HFMD value was found less than 1 hour for 7.5% patients, between 1 hour to 3 hours for 22% patients, between 3 hours to 6 hours for 13% patients, between 6 to 9 hours delay for 4% patients, between 9 to 12 hours delay for 4.5% patients, between 12 hours to 24 hours delay for 1.5% patients, 36 hours to 48 hours delay for 2.5% patients and in 1% cases, more than 72 hours delay was made which has been shown in figure 3.8B.

In our study, we found that most of the patients had hypertension (76%) during hospital arrival. Among them, 26% patients were categorized in hypertension stage I and 27% patients were categorized in hypertension stage II, 11% patients were in hypertension crisis, 20% patients had normal blood pressure and 12% patients had pre-hypertension. Stroke patients with low blood pressure range were not found significantly. Only 4% patients had low blood pressure which has been shown in figure 3.9.

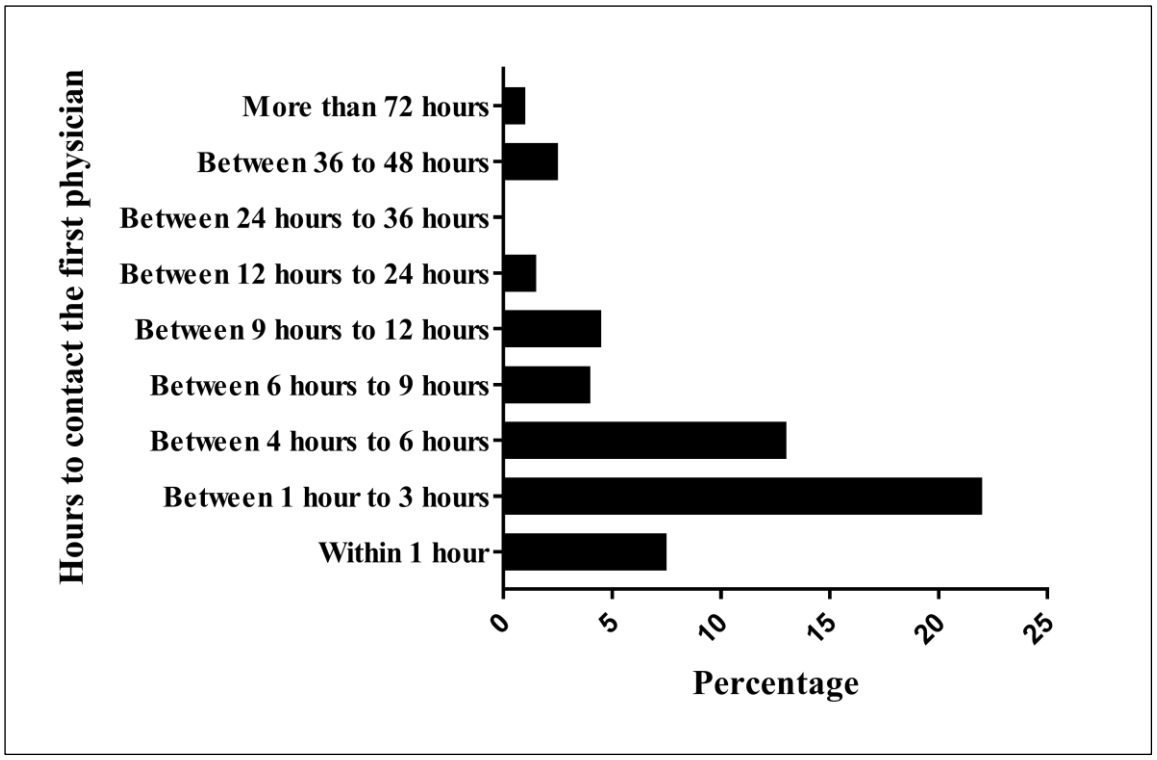

Figure 3.8B: Percentage of stroke patients' HFMD value when symptoms were recognized by physicians

The stages of blood pressure were categorized according to American heart association (AHA) and blood pressure United Kingdom (UK) guideline where below 90/60 marked as low blood pressure, between 90-120/60-80 as normal blood pressure, 121-139/81-89 as prehypertension, 140-159/90-99 as hypertension (stage I), 160/110 or higher than 160/110 as hypertension (stage II) and more than 180/110 as hypertension crisis. In case of body temperature, only 3% patients had hypothermia that means body temperature was below 37.6^0 C. In our study we found that only 9.5% patients had hyperthermia which indicated that body temperature was above 37.6^0 C shown in figure 3.10. The ranges of hypothermia, hyperthermia and normal body temperature were categorized in accordance with American stroke association (ASA) guideline.

For confirming stroke, computed tomography (CT) scan was done for all patients; magnetic resonance imaging (MRI) was done for 6% patients, and computed tomography angiography (CTA) was performed for 13%. Magnetic resonance angiogram (MRA) was performed for only 3% and magnetic resonance venography (MRV) was done for 1.5% patients shown in figure 3.11.

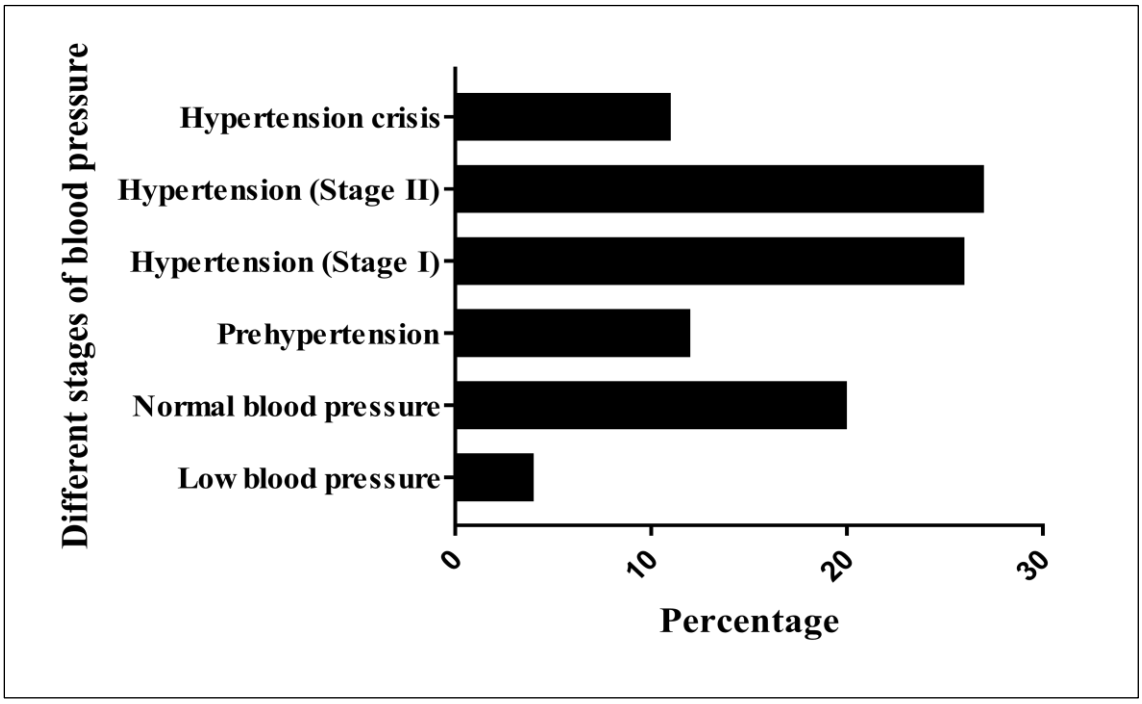

Figure 3.9: Percentage of stroke patients according to their blood pressure at hospital arrival

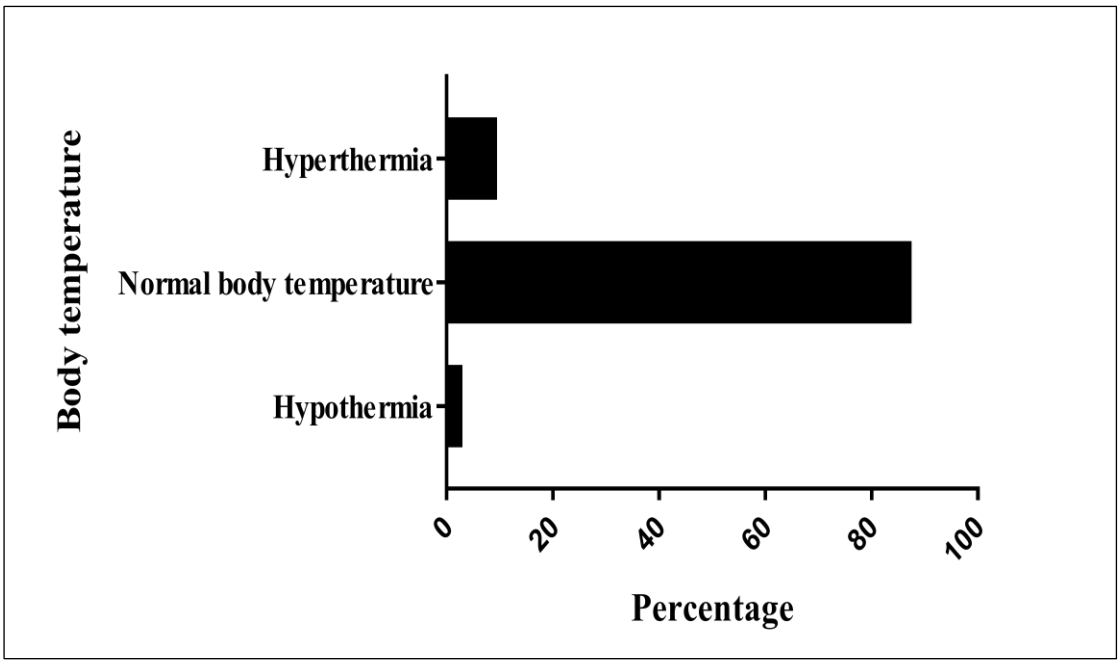

Figure 3.10: Percentage of stroke patients according to body temperature at hospital arrival

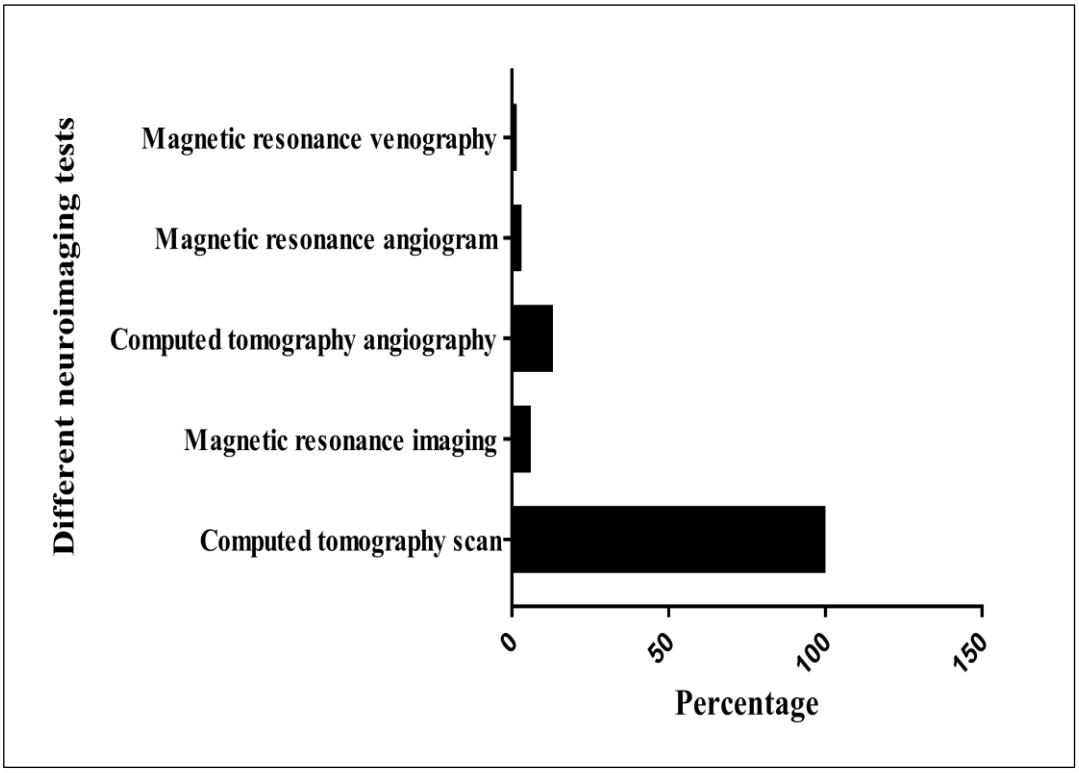

Figure 3.11: Percentage of stroke patients receiving different neuroimaging tests

In terms of other test, complete blood count test (CBC) was performed for 79.5% patients, serum electrolyte test was done for 94% patients, and serum creatinine test was done for 89.5% patients, electrocardiography (ECG) was done for 73.5% patients and urine examination was done for 68.5% patients, serum glucose test was done for 51.5% patients for the second time, chest radiography was done for 36.5%, glycated hemoglobin (HBA_1C) test was done for 30.5%, serum cardiac troponin I test was for 22% patients, echocardiogram (ECHO) was done for 16% patients, serum alanine aminotransferase test (ALT) was done for 14%, peripheral blood smear (PBF) test was done for 11.5% patients. Serum lipid profile was done for 17%, bleeding and clotting time test was done for 6% patients, activated partial thromboplastin (APTT) and prothrombin time (PT) test were done for 7%, duplex study of neck vessel was done for 4.5% patients. Serum urea test was done for 4%, ultrasound sonography (USG) test was done for 4% patients and C-reactive protein (CRP) test was done for 2.5% patients. Serum thyroid stimulating hormone (TSH) test was done for 2.5%, serum free triidothyronine (FT3) and serum free thyroxine (FT4) test was also done for 2.5% patients and percentages of all these tests were shown in figure 3.12.

In our study, hemorrhagic stroke was found in two-third (74.5%) cases. Among these 149 (74.5%) cases, 2.5% stroke cases were recurrent hemorrhagic stroke. Among the rest of 72%

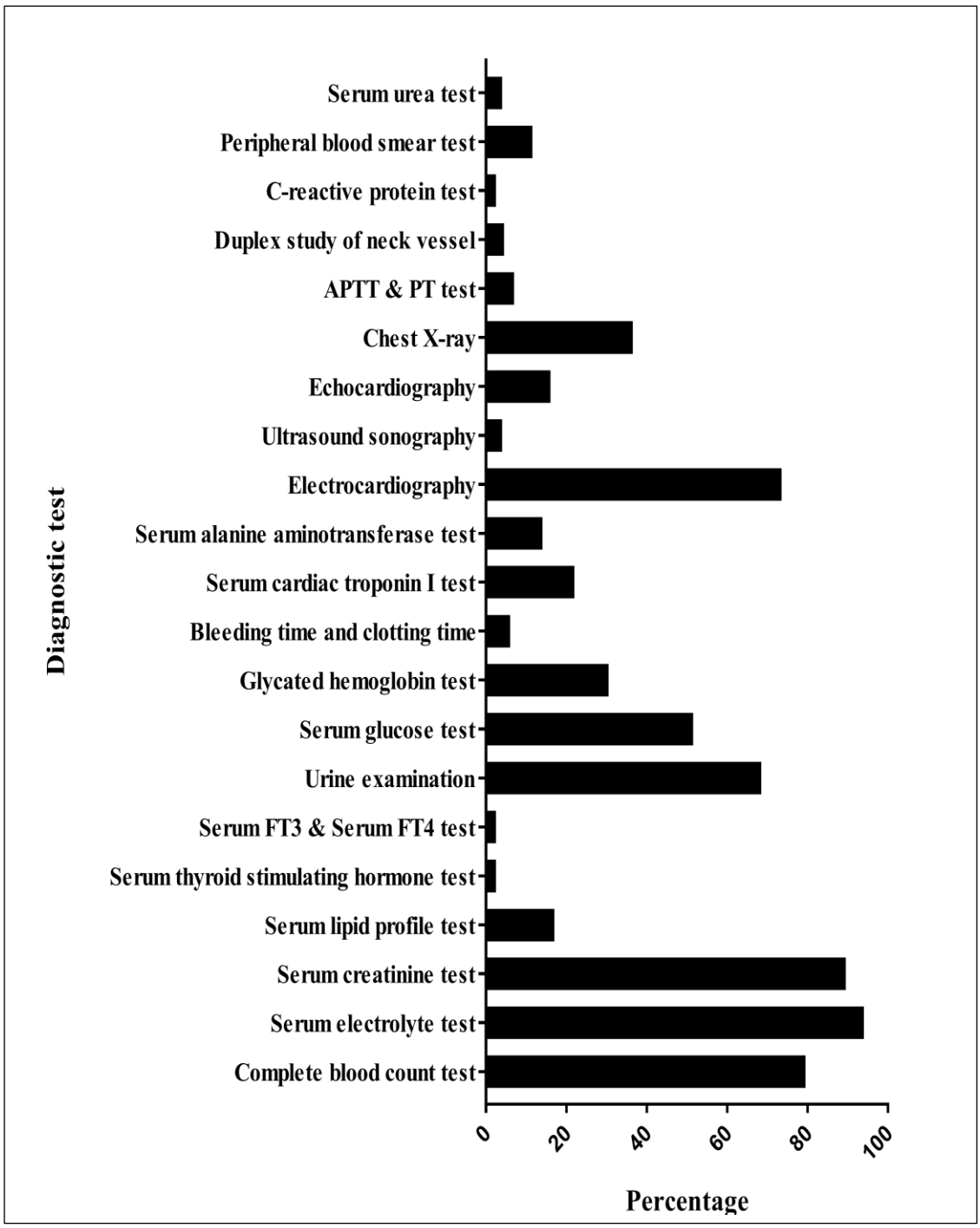

Figure 3.12: Percentage of stroke patients receiving different diagnostic tests

cases, 47.92% patients had intracerebral hemorrhagic stroke and 27.08% patients had subarachnoid hemorrhagic stroke, 6.25% patients had intraventricular stroke, 1.38% patients had both intracerebral and subarachnoid hemorrhage and only patient was found who had both subarachnoid and subdural hemorrhage and rest of the 15.28% patients' stroke type was remain undetermined whether it was intracerebral or subarachnoid or intraventricular. Among

200 patients, 24% patients' stroke types were ischemic stroke. Among these 48 ischemic stroke patients, 5% patients were admitted due to recurrent stroke and 1.5% patients were admitted due to both ischemic and hemorrhagic stroke as shown in figure 3.13.

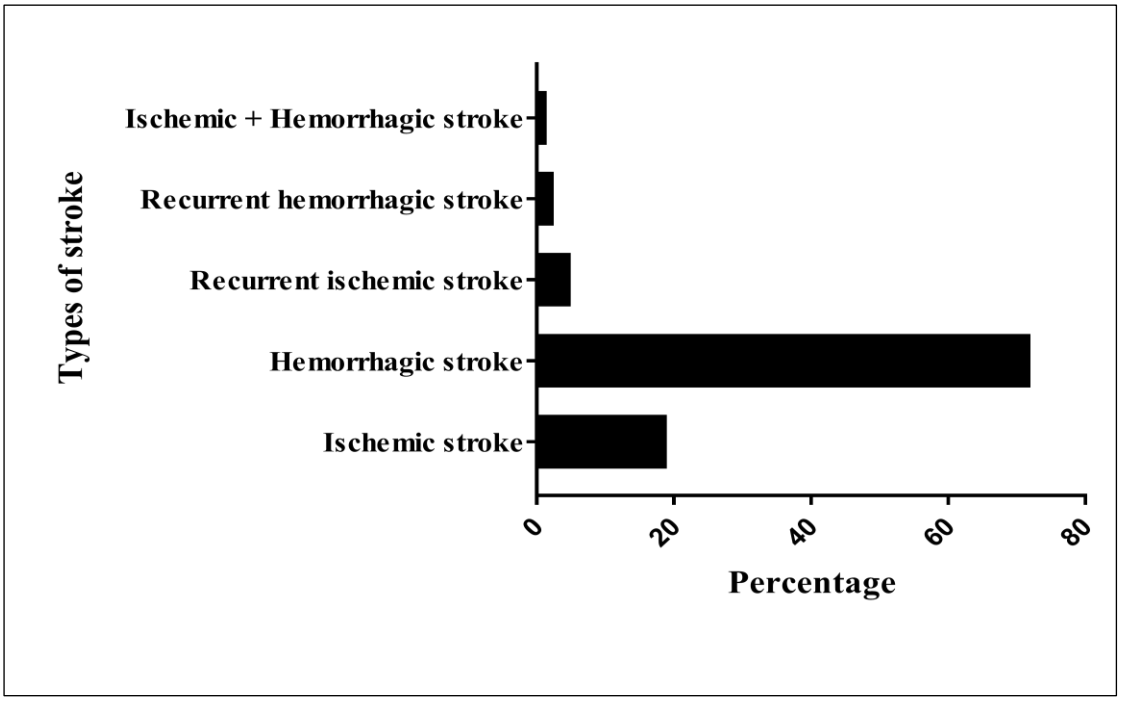

Figure 3.13: Percentage of stroke patients according to stroke types

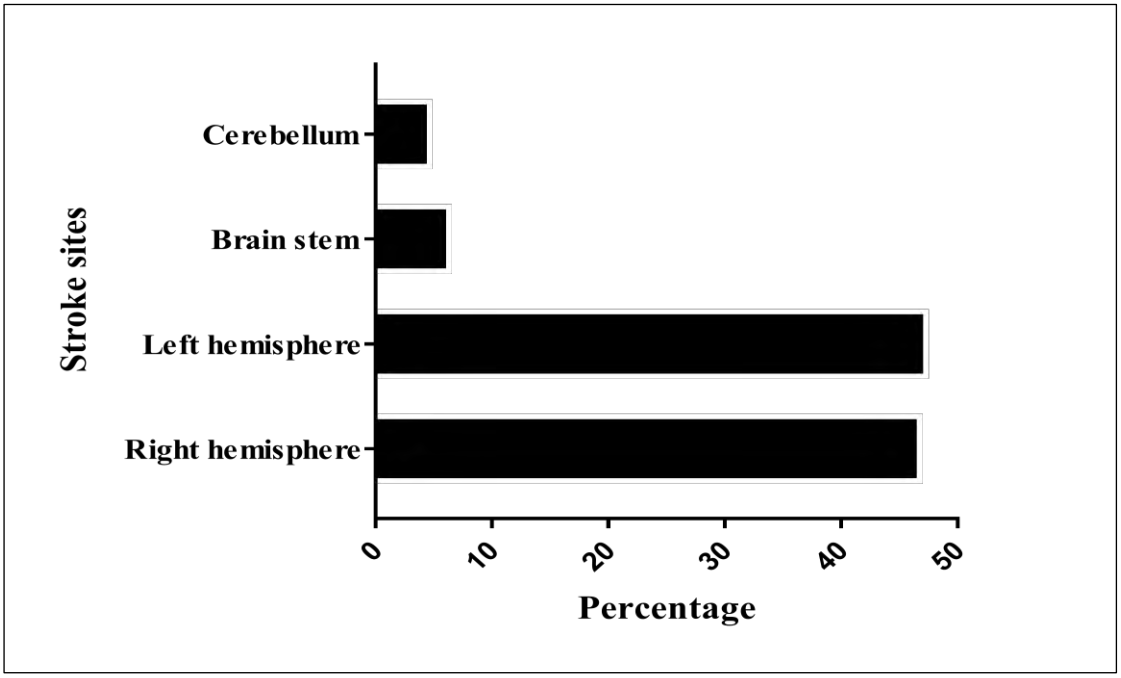

Figure 3.14: Percentage of stroke patients according to stroke sites

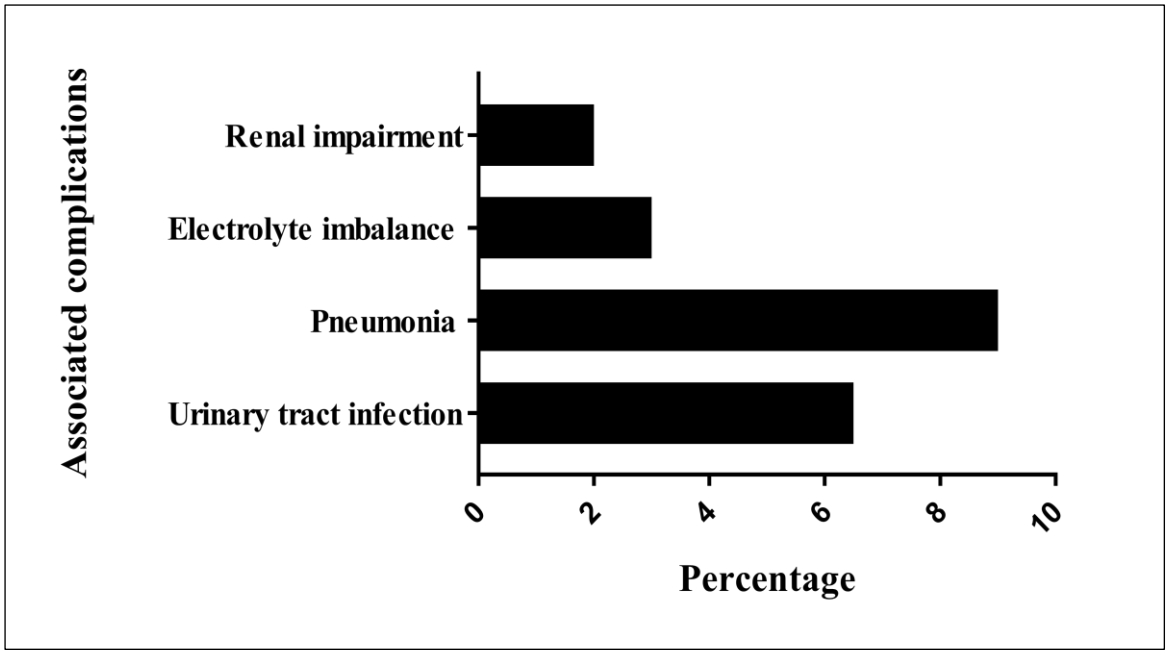

Figure 3.15: Percentage of stroke patients according to stroke prior to complications

In terms of stroke location, 78 patients' stroke location was not found. Rest of the 122 patients, 47% patients' stroke location was right hemisphere, 47.54% patients stroke location was left hemisphere. Brain stem stroke was occurred in 6.56% patients and 4.92% stroke's location was cerebellum shown in figure 3.14.

Most common complication among stroke patients were urinary tract infection (6.5%), pneumonia was found in 9% patients, electrolyte imbalance was found in 3% patients and renal impairment was found in 2.5% patients shown in figure 3.15.

In terms of first CT scan timing, 85% patients' first CT scan timing was between 24 hours of stroke onset and rest of the 14.5% patients' first CT scan timing was more than 24 hours to 7 days and 0.5% patient CT scan timing was more than 7 days of stroke onset.

Out of 200 patients, 144 (72%) patients were given food through nasogastric intubation and rest of the 56 (28%) patients had normal diet including liquid or semi-liquid foods. Approximately, 81% patients were infused normal saline and 8% patients were infused dextrose saline.

Among the different classes of anti-hypertensive agents, calcium channel blockers were used in an adequate amount (63%). Among different types of calcium channel blockers, nimodipine (67.46%) was prescribed mostly. Amlodipine was received by 30.16% and clinidipine was prescribed to 2.38% and combination of amlodipine and olmensartan was

prescribed to 19.5% patients. Angiotensin II receptor inhibitors (losartan potassium) was prescribed to 19.5% patients. Angiotensin-converting-enzyme (ACE) inhibitors were prescribed to 3.5% and diuretics (hydrochlorothiazide) were prescribed to only one patient and β blockers were prescribed to 7% patients as shown in figure 3.16.

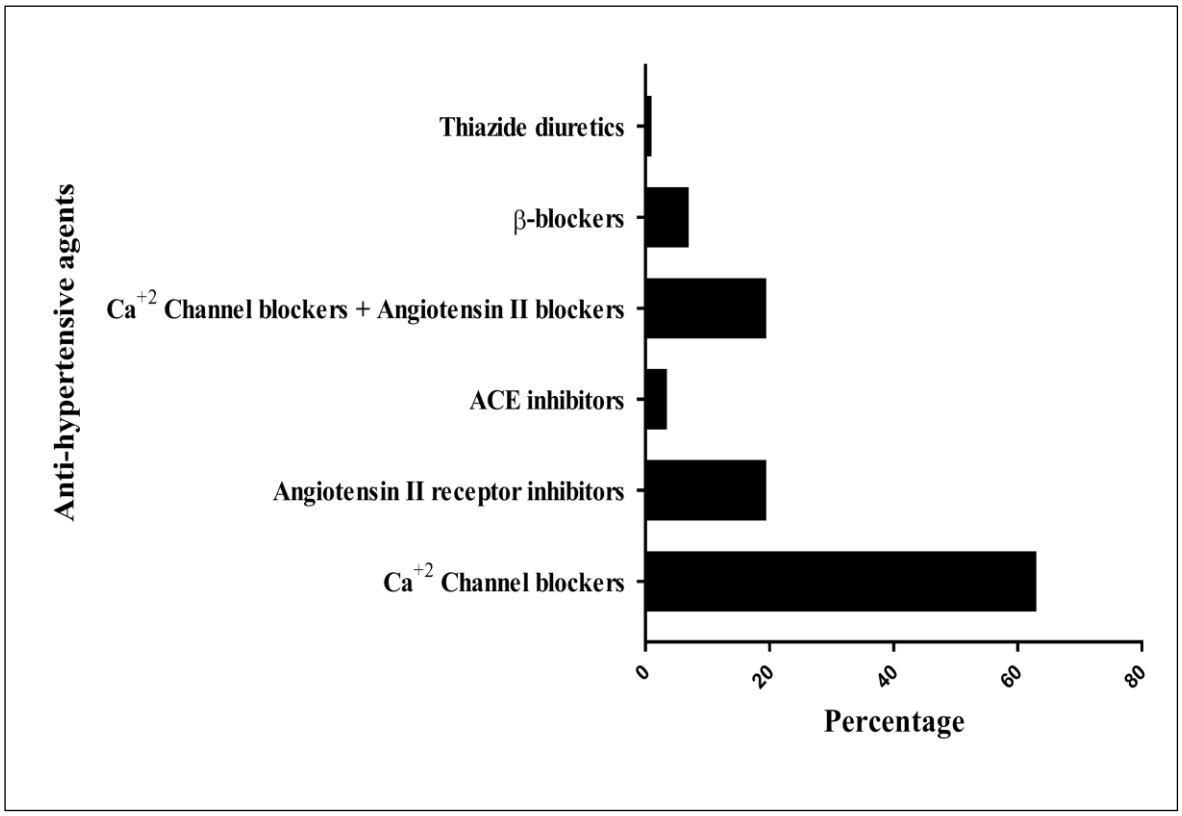

Figure 3.16: Percentage of stroke patients receiving anti-hypertensive agents

Among different types of anti-platelet drugs, aspirin (18.5%) was found to use more commonly than clopidogrel (1.5%) or combination of aspirin and clopidogrel (1%) shown in figure 3.17A. Anti-platelet drugs were received by 21% patients and among them, 20% anti-platelet drugs were received by ischemic stroke patients shown in figure 3.17B.

In case of cholesterol lowering agents, atorvastatin (25.5%) was found to be used most commonly. Fenofibrate was prescribed to 1% patients and cerivastatin was prescribed to 0.5% patients which have been shown in figure 3.18.

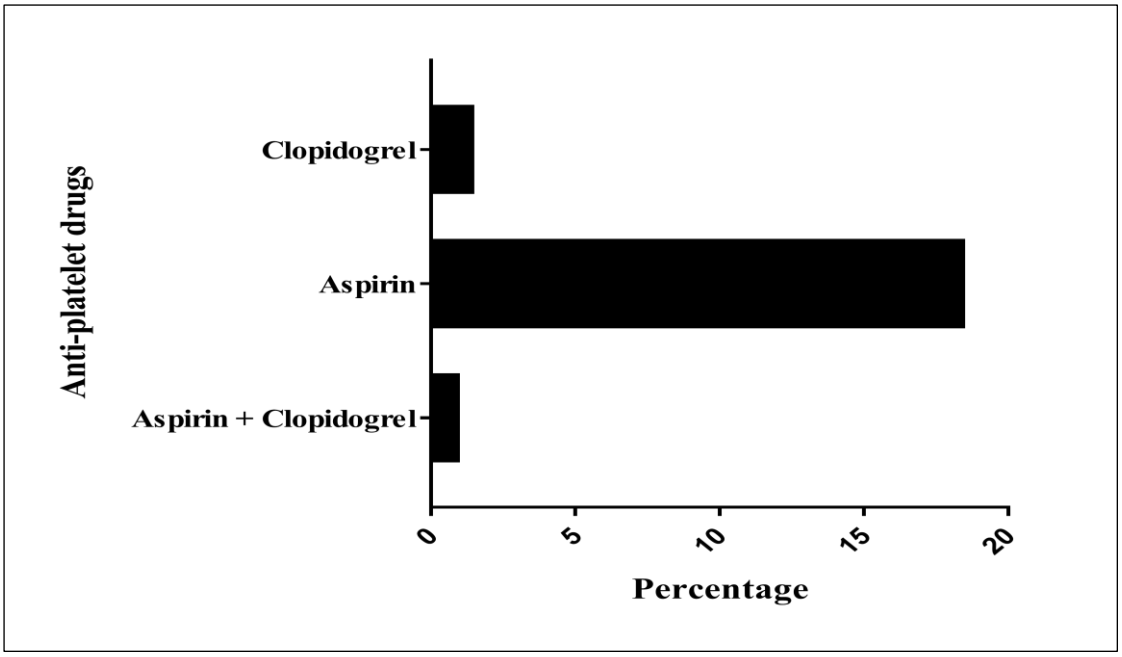

Figure 3.17A: Percentage of stroke patients receiving anti-platelet drugs

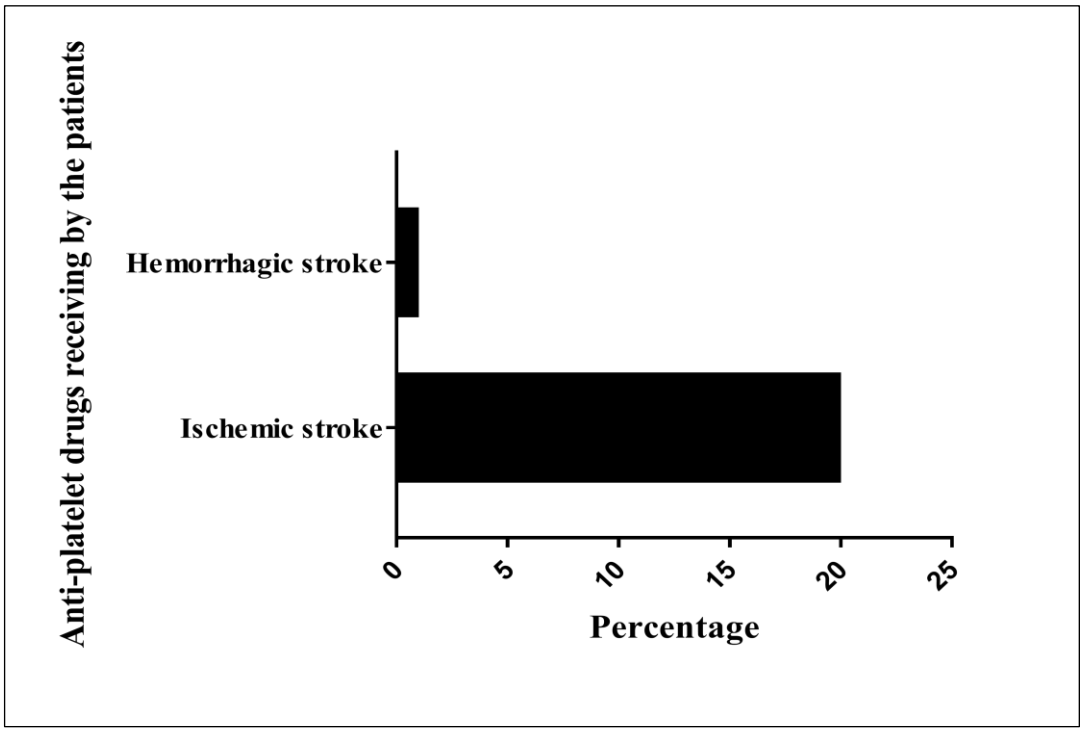

Figure 3.17B: Percentage of stroke patients receiving anti-platelet drugs in terms of stroke types

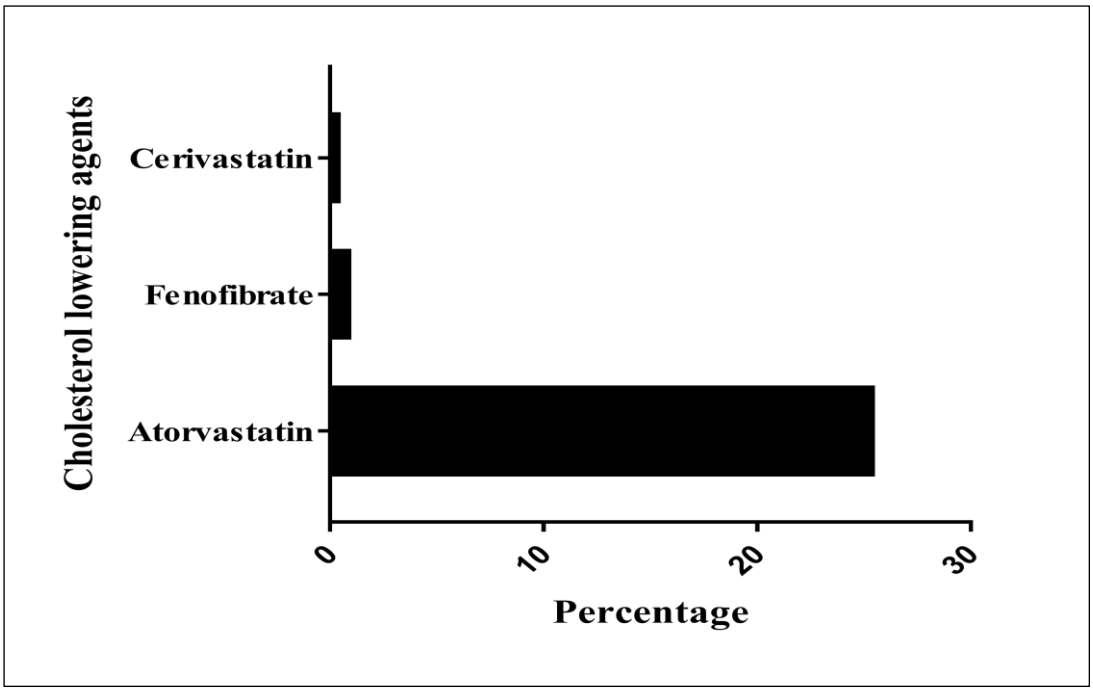

Figure 3.18: Percentage of stroke patients receiving cholesterol lowering agents

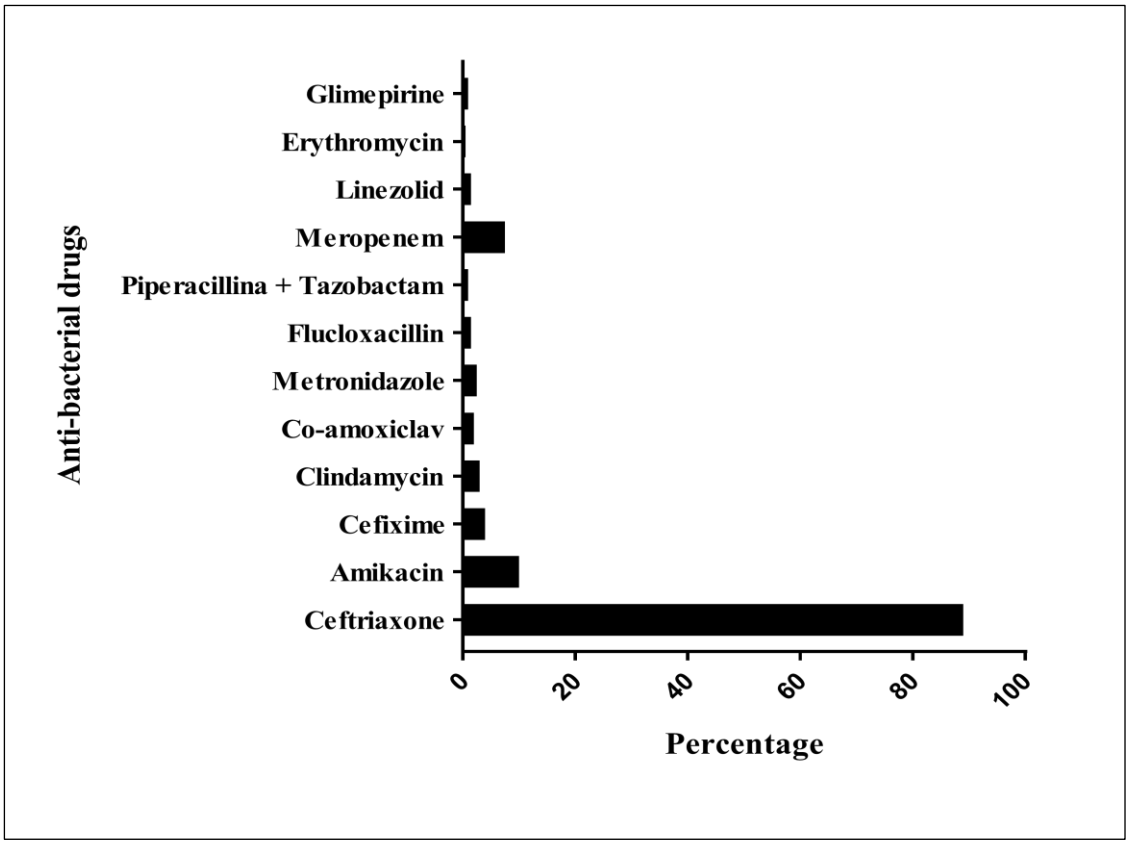

Figure 3.19: Percentage of stroke patients receiving anti-bacterial drugs

In terms of anti-bacterial drugs, ceftriaxone was received individually by 89% patients, amikacin was received by 10% patients, meropenem was received by 7.5%, cefixime was prescribed to 4% patients. Clindamycin (3%), co-amoxiclav (2%), metronidazole (2.5%), flucloxacillin (1.5%), linezolid (1.5%) and combination of piperacillina and tazobactam (1%) which has been shown in figure 3.20.

An adequate number of anti-epileptic drugs were prescribed. Among them, phenytoin (33%) was the mostly prescribed anti-epileptic drug and clonazepam (6.5%) was second-common prescribed anti-epileptic drug. Diaazepam, vinpocetin, phenobarbitol, levetiracetam were also received by 5.5%, 4.5%, 4%, 3% patients respectively. Lorazepam and valproic acid were received by only one patient as shown in figure 3.20. In terms of corticosteroids, dexamethasone and hydrocortisone were received by 74.5% and 2% patients respectively as shown in figure 3.21A. Among them 63% patients were hemorrhagic stroke patients and rests of the 13.5% patients were ischemic stroke patients, shown in figure 3.21B.

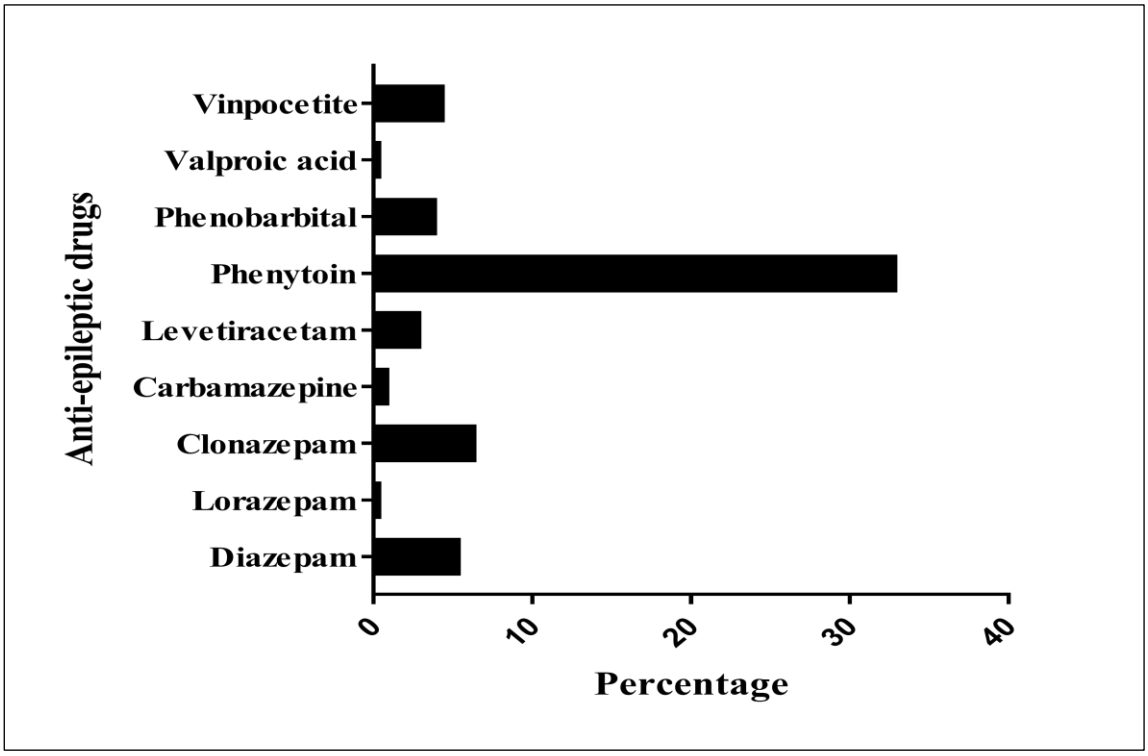

Figure 3.20: Percentage of stroke patients receiving anti-epileptic drugs

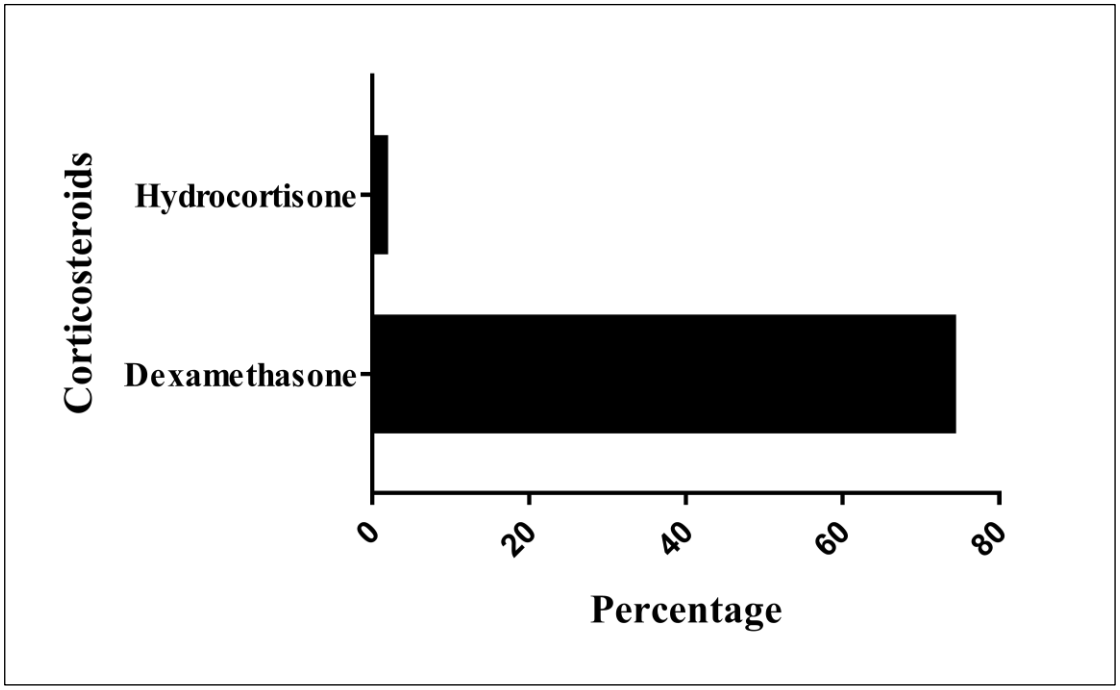

Figure 3.21A: Percentage of stroke patients receiving corticosteroids

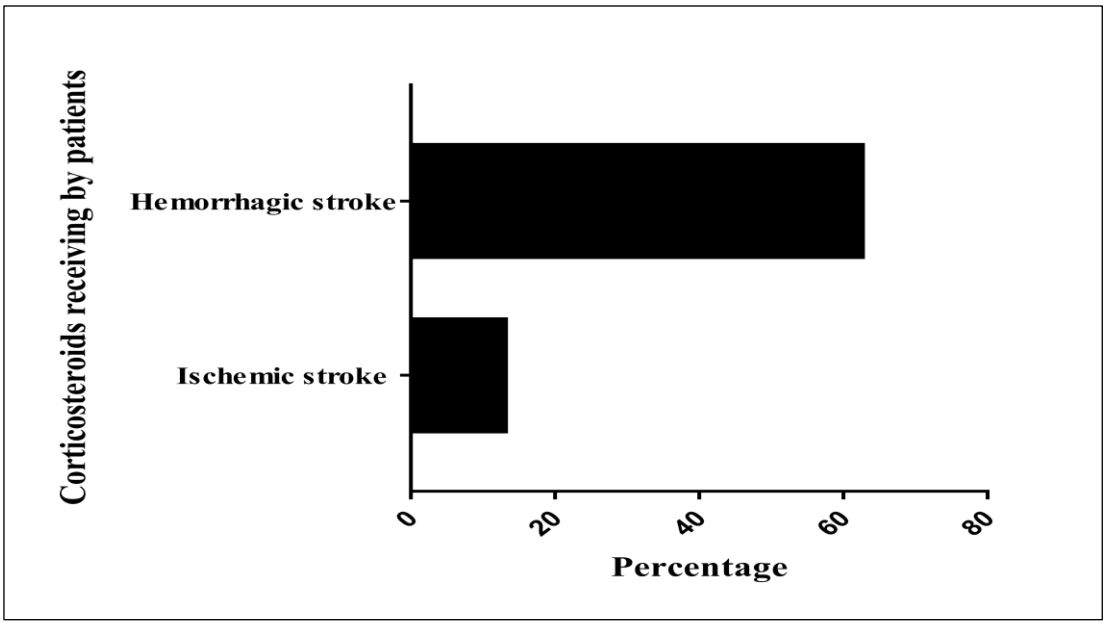

Figure 3.21B: Percentage of stroke patients receiving corticosteroids in terms of stroke types

Among the anti-psychotic drugs, haloperidol was prescribed to 14% patients and quetiapine was prescribed to 12.5% patients and olanzapine was received by only patient shown in figure 3.22. Anti-pyretic drugs were also prescribed to many patients. Among them, paracetamol was prescribed to 50%, tramadol was prescribed to 6.5% and combination of paracetamol and tramadol was also prescribed to 7.5% patients shown in figure 3.23.

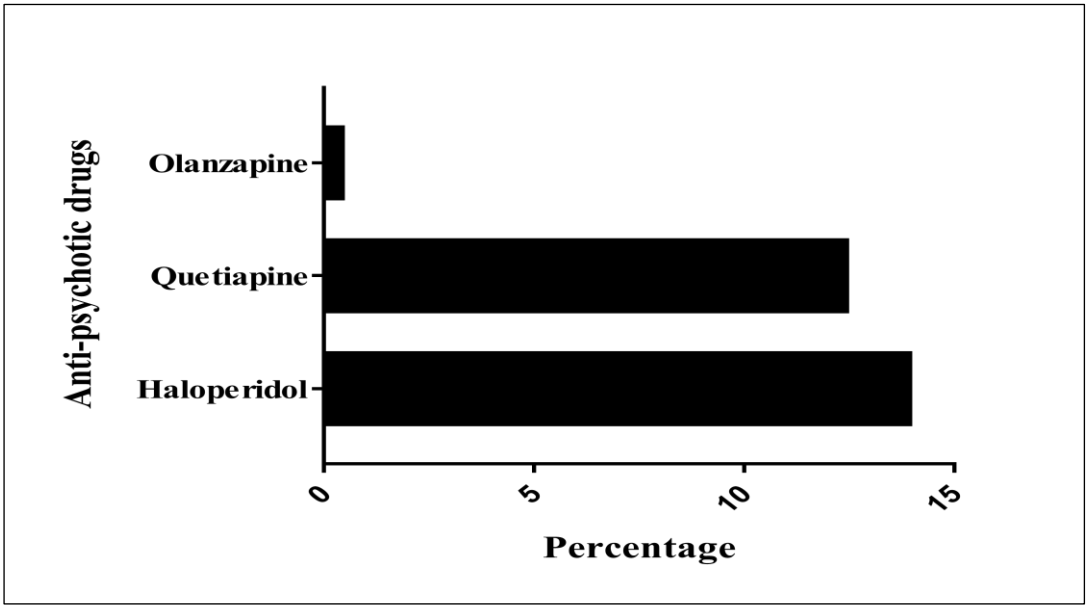

Figure 3.22: Percentage of stroke patients receiving anti-psychotic drugs

Nitroglycerine was also prescribed as a vasodilator agent to 16.5% patients and lactulose syrup was prescribed to 64.5% patients as a treatment of constipation. As a neurotransmitter agent, procyclidine hydrochloride was prescribed to 5% patients. Domperidone was prescribed to 9% patients and ondansetron was also prescribed to 17.5% patients as anti-emetic drugs shown as figure 3.24. To correct electrolyte imbalance, 5.5% patients were receiving sodium chloride (NaCl) syrup and 17.5% patients were receiving potassium chloride (KCl) syrup.

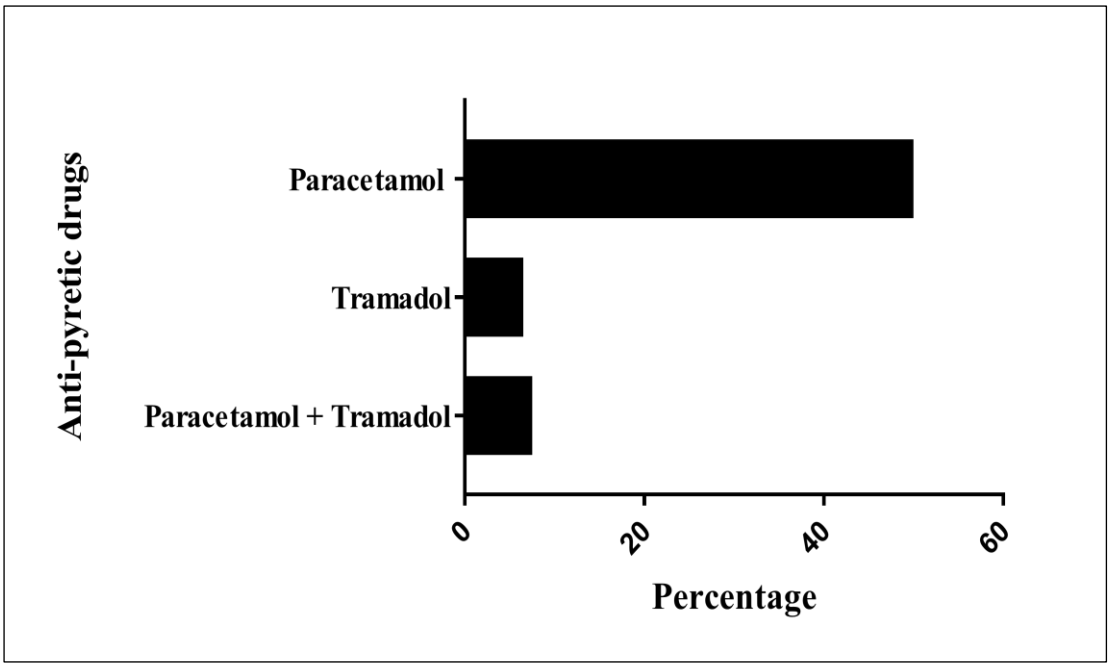

Figure 3.23: Percentage of stroke patients receiving anti-pyretic drugs

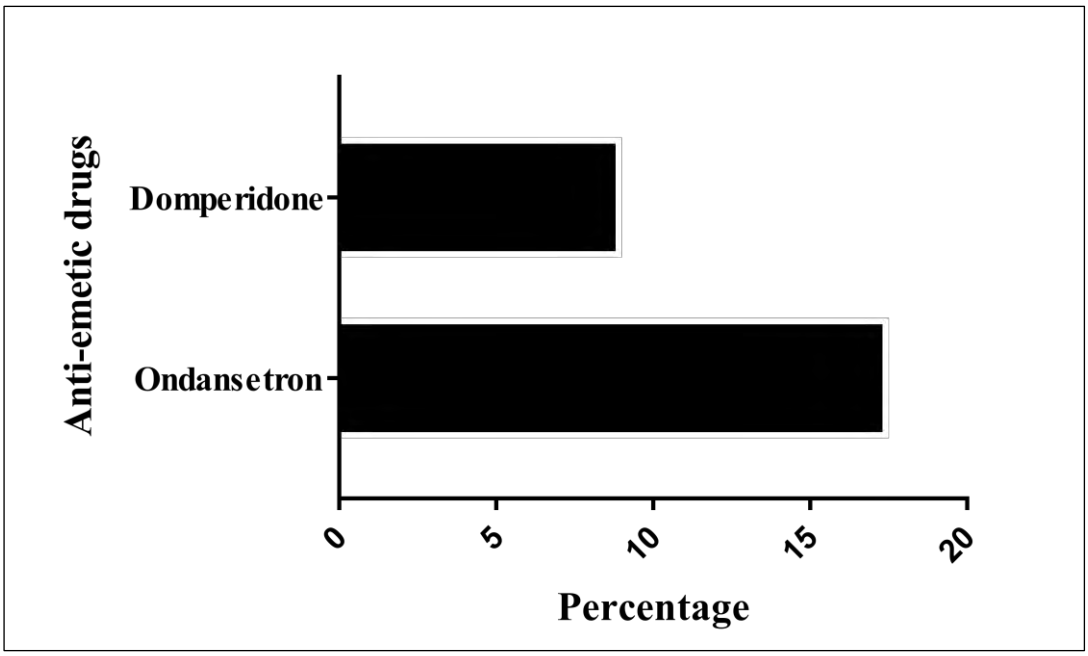

Figure 3.24: Percentage of stroke patients receiving anti-emetic drugs

3.2 Discussions

After India and Pakistan, Bangladesh is the third biggest South-Asian country with 160 billion populations. Asian countries are contributing 40% of developing countries and 22% of world population. An adequate amount of mortality takes place in Bangladesh due to stroke and become third leading cause of mortality. From 2006 to 2011, stroke related mortality increased from 6%-9%. Stroke prevalence is 0.3% in case of age 40 or more than 40 years old and its prevalence elevated to 1% for age group 70 or more than 70 years old (Bhowmik et al., 2016). The socio-demographic profile of this study reflects that stroke was more prevalent among male (57.5%) compared to female (42.5%) and stroke prevalence was comparatively high after 30 years old and greater prevalence was found in age group 61-70 which was 28% and details information has been shown in table 3.1. Stroke percentage was significantly high for the patients who lived in rural areas (66.5%) and in case of education levels, most of the stroke patients were medium level educated (37%). A similar study was conducted by Li et al. (Li et al., 2017) in China shown similar findings in terms of gender, residential status and education levels. But in terms of age group, there was a slight difference. In our study, most of the stroke patients were between 31-70 years old and our study findings were matched with Bhowmik et al. (Bhowmik et al., 2016) study conducted in Bangladesh. In terms of working status, we found that 33% stroke patients were working persons and among them 42.4% patients were worked for more than 10 hours and in terms of housewives, 40% patients were housewives and we did not calculate any working hours for housewives. Working hazards were found in 65.15% stroke patients. So, it is quite clear that working hazards and working hours could be mild contributors to stroke. One fifth percent (22.5%) patients were liked to have spicy foods, 20.25% patients were liked to have salty foods and 18.5% patients were liked to have sweet dishes. Taking salty foods and sweet dishes increased the risk of having hypertension and diabetes mellitus respectively which ultimately leaded towards stroke but these findings were not matched so far with any study findings. In terms of smoking, 18% patients were smokers and 10% patients were previously habituated to smoking. As cigarette smokers are more prone to stroke than non-smokers even after reconciliation of all the risk factors. At the year 2011, a review study exposed the dose-response relationship of stroke and cigarette smoking. The study stated that comparative risk for stroke could be raised from 1.16 for smoking five cigarettes per day to 1.56 for smoking 40 cigarettes per day. So, there is no minimum limit of smoking which can be indicated as safe lower limit (WHO, 2016). In our study, we observed that more than 50% of the patients

were habituated to betel. Smoking habit of female was also found but most of them were habituated to betel. Among the risk factors, hypertension was the most dominant risk factor among both male and female which were correlated with Pandian & Sudhan (Pandian & Sudhan, 2013) and Sridharan et al. (Sridharan et al., 2009) study findings. Another study conducted by Mehndiratta, Wasay, & Mehndiratta and they also marked hypertension as a dominant risk factor of stroke in Asian women (Mehndiratta, P., Wasay, & Mehndiratta, M., 2015). Another study conducted by Appleton, Sprigg, & Bath found that for both ischemic and hemorrhagic stroke, hypertension is one of the leading negative determinant which accounts for 100 crore people across the world. In case of acute stroke, blood pressure raised in 75% people and among them 50% patients have the previous history of hypertension (Appleton et al., 2016). In our study, we observed that 76% patients had elevated blood pressure at arrival of hospital and 63.50% patients had previous history of hypertension shown in figure 3.1 and figure 3.9. Diabetes mellitus was found in 17% patients and a study conducted by Saha et al. in 2016 (Saha et al., 2016) also found similar result. In terms of history of IHD (13%) and dyslipidemia (5%), our findings did not match with the study conducted by Saha et al. Dyslipidemia was previously considered as a fatal risk factor of cardiovascular disease but recently this risk factor established a strong relation with cerebrovascular disease like stroke. One of the dominant facts for hemorrhagic stroke is low density lipoprotein cholesterol level (LDL-C) rather than lacunar and cardio-embolic stroke (A, Ks, & R, 2014). One-fifth patients (33.5%) had previous history of TIA and 19.5% patients had previous history of stroke and 24%, 22.5% patients had family history of heart disease and stroke respectively. A study conducted by Bhowmik et al. (Bhowmik et al., 2016) found similar findings. Among these 200 patients, vomiting (53%) was most appeared symptom on stroke onset and second common symptom was sensory loss found in 38% patients. Dysphasia was found in 32.5% patients shown as figure 3.4. Similar studies were conducted by Saha et al. 2016 (Saha et al., 2016) in Faridpur medical college and Siddique et al. (Siddique et al., 2009) in Chittagong medical college hospital found hemiplegia as the most familiar symptom for both ischemic and hemorrhagic stroke and vomiting and headache was dominant symptom of hemorrhagic stroke. In our study, we also found vomiting as a most appeared symptom and 74.5% patients were account for hemorrhagic stroke as shown in figure 3.4 and figure 3.13. From these findings we can also assume vomiting as a dominant symptom of hemorrhagic stroke. In accordance with American stroke association (ASA) stroke guideline, one third admitted stroke patients will be hypothermic ($>37.6^0$ C) in one hour of stroke onset. But our study findings indicate that most of the patients had normal

body temperature (figure 3.10). It could be due to patients' late hospital admission after stroke onset. Hypertension is the most common outcome during stroke. An observational study conducted by Qureshi et al. (Qureshi et al., 2008) found that 53% of patients' systolic blood pressure was above 139 mmHg and 10.5% were above 184 mmHg and these findings also matched with our study shown in figure 3.9. To establish clinical diagnosis, ASA recommended these tests to all patients like CT scan or MRI of brain, blood glucose test, serum electrolyte, serum creatinine, ECG, CBC, PT and APTT and Directorate general of health service recommended CT scan of brain, CBC, blood glucose, ECG, serum electrolyte, fasting lipid profile, chest x-ray, and urine examination as a first line investigation. Our findings showed that CT scan was conducted to 100% patients, serum electrolyte test was done for 94% patients; serum creatinine test was done for 89.5% patients, CBC was done for 79.5% patients and the detailed information has been shown in Figure 3.12. In our study, 72% stroke was hemorrhagic stroke and 19% was ischemic stroke and rest of the 7.50% were recurrent ischemic and hemorrhagic stroke and 1.5% patient had both ischemic & hemorrhagic stroke. A similar study conducted by Venketasubramanian & Chen (Venketasubramanian & Chen, 2008) in Singapore. As a part of emergency department based care, there are some steps recommended by ASH after stroke onset such as door to physician ≤10 minutes, door to stroke team ≤15 minutes door to CT initiation ≤25 minutes, door to CT interpretation ≤45 minutes, door to drug (≥80% compliance) ≤60 minutes and door to stroke unit admission ≤3 hour. Our study found that only 17% patients were presented to physician within one hour of stroke onset and 41.5% patients were presented to physician within 3 hours of stroke onset which has been shown in figure 3.7. Our study also found that 41.5% cases were recognized by patients' family member(s) or patients itself (figure 3.6). Despite of symptoms recognition, they made many hours delay (highest 73 hours delay) before contacting physician for the first time after stroke onset which has been shown in figure 3.8A. CT scan of 85% patients were done within 24 hours of stroke onset and 14.50% patients took more than 24 hours for CT scanning after stroke onset and 0.50% patient's CT scan timing was after 7 days of stroke onset. As an initial treatment strategy, ASH class I recommendations are to control blood pressure of patient (systolic >220mmHg and diastolic >120mmHg), treatment of hypoglycemia (blood glucose <60mg/dL), correction of hypovolemia with IV normal saline & cardiac arrhythmias. In our study we observed that most of the patients were given anti-hypertensive agents in order to control elevated blood pressure. Among 200 patients, 81% patients were infused normal saline and 8% patients were infused dextrose normal saline. ASA class I recommendation for ischemic stroke is to use

aspirin as an anti-platelet drug within 24 to 48 hours to alleviate death rate after acute ischemic stroke. This NSAID also moderately alleviates the chance of early recurrent stroke as well as long term disablement but it might elevates the chance of having intracranial hemorrhage (Sandercock et al., 2003) and class II recommendation is to use clopidogrel in case of emergency. Our study found that only 18.5% patients were prescribed aspirin and 1.5% patients were prescribed clopidogrel and 1% patients were prescribed combination of aspirin and clopidogrel. In total, 21% patients were receiving anti-platelet drugs and among them, 20% were ischemic stroke patients shown in figure 3.17A and figure 3.17B. The use of anti-platelet drugs in hemorrhagic stroke is still controversial. Some studies like Salman & Dennis, Ferguson & Body showed that anti-platelet drugs like aspirin could be continued after ICH as well as other types of hemorrhagic stroke (Salman & Dennis, 2014); (Ferguson & Body, 2006). In our study, no record was found regarding use of anti-coagulant drugs like heparin, low molecular weight warfarin (LMWH). American heart association categorized aspirin, clopidogrel as anti-coagulant drugs. On the other hand, American stroke association considered aspirin, clopidogrel as anti-platelet drugs. For our study purpose, we are following ASA guideline. The panel of stroke council of American heart association reviewed that there is no effectiveness in using anti-coagulants for ischemic stroke treatment. An adequate number of clinical trials become unsuccessful to bring out any helpfulness of anti-coagulant in the primary treatment of ischemia. Several investigations have been done to see the effectiveness of anticoagulant over antiplatelet medications by giving them within 12-24 hours of the initial event but found that there is no benefit of low molecular weight heparin over aspirin (Smith, English & Johnston, 2013). In our study, we found that most of the patients were receiving calcium channel blockers as an anti-hypertensive agent. β-blockers, angiotensin II receptors, ACE inhibitors were also received by the patients shown in figure 3.16. Hypertension is a major complication after stroke. To prevent hypertension after stroke, calcium channel blockers are proven to be effective in several studies (Inzitari & Poggesi, 2005); (Tomassoni, Lanari, Silvestrelli, Traini, & Amenta, 2008); (Chen & Yang, 2013). Anti-epileptic drugs (AEDs) are commonly used to control seizure. About 70% seizures could be control by using anti-epileptic drugs but it is also used to treat or control convulsions causes by other brain diseases such as trauma, tumors and stroke (Rang, Dale, Ritter, Flower & Henderson, 2007). In accordance with epilepsy foundation of America, with stroke as well as with other neurologic lesions, neuronal damage could alter the balance between excitation and inhibition which ultimately lead to stroke. To prevent seizure or convulsion, we found that 33% patients were receiving phenytoin, 6.5% patients were receiving clonazepam, 5.5%

patients were receiving diazepam, 4.5% were receiving vinpocetite, 4% were receiving phenobarbital, levetiracetam were receiving by 3% patients and other anti-epileptic drugs like carbamazepine, valproic acid were receiving less than 2% patients shown in figure 3.20. A similar cross-sectional survey study was conducted in 2011 among British physicians to know the use of anti-epileptic drugs in post-stroke by Illsley (Illsley, 2011) found that valproate and lamotrigine were most prescribed AED for stroke patients. Steroids alleviate ischemic edema formation by reducing permeability of blood brain barrier. A study conducted by Betz & Coester (Betz & Coester, 1990) found that dexamethasone is beneficial to reduce permeability of blood brain barrier in order to reduce ischemic edema formation. Another prospective double-blind placebo-controlled study was conducted in West-Africa to find out the effectiveness of short-course of elevate dose dexamethasone therapy on death rate and neurological recovery in stroke patients. They did not found any benefits of using dexamethasone in reducing death rate and neurologic recovery (Ogun & Odusote, 2001). Some other studies also concluded their study that there was not enough evidence to establish the benefit of corticosteroids in ischemic stroke patients because corticosteroid reduce vasogenic cerebral edema which is result from leaky vessels rather broken vessels (Qizilbash, Lewington, & López-Arrieta, 2002); (Sandercock & Soane, 2011). Another study conducted by Feigin et al. (Feigin et al., 2006) to evaluate the effect of corticosteroids specially dexamethasone in hemorrhagic stroke (ICH and SAH). This study also does not found any evidence that support the routine use of corticosteroids. In our study, 74.5% patients were hemorrhagic stroke patients and in total 75.5% patients were receiving corticosteroids shown in figure 3.21A and most of the corticosteroid receivers were hemorrhagic stroke patients (63%) shown in figure 3.21B. This finding indicates that corticosteroids are more beneficial for hemorrhagic stroke patients rather than ischemic stroke patients. Delirium, a disturbed state of mind in the acute stage of stroke are varies from 13% to 48%, depending its definition and study populations. Prolonged hospitalization and poorer prognosis are the reasons of delirium. For the treatment purpose of delirium, sedative and anti-psychotic drugs are used. Haloperidol is the traditional treatment of choice but due to its adverse symptoms, it could be replaced by quetiapine, olanzapine, resiperidone. These atypical anti-psychotic drugs are as effective as haloperidol. An observational study conducted in Taiwan found the rate of mortality among acute stroke patients treated with anti-psychotic drugs were significantly low (Wang et al., 2014). In our study, we observed that 14% were receiving conventional anti-psychotic (haloperidol) and 12.5% patients were receiving atypical anti-psychotics like quetiapine, olanzapine in order to get relieve from delirium as well as from

various psychiatric illness shown in figure 3.22. Almost two-third patients were prescribed anti-bacterial drugs to prevent pneumonia and urinary tract infection as well as other infections related diseases among them ceftriaxone (89%) and amikacin (10%) were used mostly. As a result, we found that only 9% patients were suffered from pneumonia and 6.5% patients were suffering from urinary tract infections shown in figure 3.15 and figure 3.19. A study conducted by Vermeij et al. (Vermeij et al., 2016) found that ceftriaxone has positive effect in reducing infections in stroke patients through death rate remain unchanged. Electrolyte imbalance were also found in 2% patients and 5.50% patients were receiving sodium chloride (NaCl) and 17.5% patients were receiving potassium chloride (KCl) syrup. Anti-pyretic drugs were received by a lots of patients in order reduce fever, as fever is a poor outcome of stroke (Grau et al., 1999); (Dorhout Mees, Luitse, Van Den Bergh, & Rinkel, 2008) and vomiting was a frequent outcome after stroke (Lee & Shin, 2012) and 31.5% patients were receiving anti-emetic drugs in order to prevent vomiting shown in figure 3.23 and figure 3.24 respectively.

Chapter 4: Conclusion

Chapter 4: Conclusion

Stroke is one of the significant contributors of mortality and morbidity throughout the world. It is particularly true for Bangladesh. Our study indicated that most of the stroke patients were above 30 years old and patients above 90 years old were not found significantly. In our study, we identified many risk factors, among them, hypertension marked as a major risk factor of stroke, then diabetes mellitus and dyslipidemia. Targeting these risk factors will help us to alleviate the burden of stroke in our country. For the proper clinical diagnosis establishment, patients need to do a number of tests including CT scan of brain, MRA, MRV, CTA, MRI, CBC, ECG, ECHO, X-ray, different types of blood tests etc. but many a times patients financial conditions become barrier in treatment procedures. Most of the times, patients' family are not capable to continue the costs and an adequate number of surgery procedures do not take place due to patients' economic conditions. In terms of treatment strategies, we found that anti-hypertensive agents, anti-bacterial drugs, anti-psychotic drugs, anti-platelet drugs, corticosteroids etc. are used. Intravenous thrombolytic agents were not used so far. Bangladesh like other low and middle income countries is in the midst of stroke pestilence. There is a huge burden of stroke with different regional variations. Stroke units and rehabilitation centers are not available in rural areas though WHO has taken efforts to reduce risk factors and mortality from low and middle income countries by 2025. Organized stroke care including evidence-based clinical practice guidelines and adoption of quality improvement program could reduce death rate and disabilities after stroke. Proper recognition of stroke symptoms and contacting the physicians without making many hours delay also reduce the rate of death and disability.

Chapter 5: Future work

Chapter 5: Future work

To the best of our knowledge, this is the first study which reflects patients' medical history and prescription based medications which were receiving by the patients. Due to certain limitations, we could not follow up the patients. Our future plan is to conduct another study to study about the medications which are receiving by the patients after discharge. Tissue plasminogen activator is an important treatment strategy in terms of stroke treatment. We are eagerly waiting to conduct another survey to observe the effect of tissue plasminogen activator on different types of stroke and we can do that once it is introduced in the treatment strategy of stroke.

References

A, C., Ks, Y., & Arunachalam R. (2014). Dyslipidemia in stroke. *IOSR Journal of Dental and Medical Sciences Ver. VI*, *13*(4), 2279–861.

Adams, H. P., Bruno, A., Connors, J. J. B., Demaerschalk, B. M., Khatri, P., Mcmullan, P. W., … Wang, D. Z. (2013). AHA / ASA guideline. Guidelines for the early management of patients with acute ischemic stroke. https://doi.org/ 10.1 161/STR .0b 013e 318284056a

Adnan I. Qureshi, MD, Mustapha A. Ezzeddine, MD, Abu Nasar, MS, M. Fareed K. Suri, MD, Jawad F. Kirmani, MD, Haitham Hussein, MD, and Afshin A. Divani, P. (2008).

Ahasan, H. A. M. N., Hossain, Y., Das, A., Minnat, B., & Chowdhury, M. K. (2013). Review article Thrombolytic therapy in acute stroke : Outcome , barriers & how to overcome, 65–69.

Alam, B. (2015). Neurological disease burden : Bangladesh perspective, *1*(2), 31–32.

Alawneh, J. A., Clatworthy, P. L., Morris, R. S., & Warburton, E. (2011). Stroke management. *Clinical Evidence*, *6*, 201.

Albers, G. W., & Amarenco, P. (2001). Combination therapy with clopidogrel and aspirin: Can the cure results be extrapolated to cerebrovascular patients? *Stroke*, *32*(12), 2948–2949. https://doi.org/10.1161/hs1201.100829

Aminoff, M. J., Greenberg, D. A., & Simon, R. P. (2015). *Clinical neurology: Ninth Edition* (9th ed.). New York: McGraw-Hill Education.

Appleton, J. P., Sprigg, N., & Bath, P. M. (2016). Blood pressure management in acute stroke. https://doi.org/10.1136/svn-2016-000020

Bastos Conforto, A., & Conforto, A. B. (2013). Lacunar strokes : does shape matter ? *Arquivos de Neuro-Psiquiatra*, *71*(10), 753–754. https://doi.org/10.1590/0004-282X20130166

Benjamin, E. J., Blaha, M. J., Chiuve, S. E., Cushman, M., Das, S. R., Deo, R., … Muntner, P. (2017). *Heart disease and stroke Statistics—2017 Update: A report from the American heart association*. *Circulation* (Vol. 135). https://doi.org/10.1161/

CIR.0000000000000485

Bhowmik, N. B., Abbas, A., Saifuddin, M., Islam, M. R., Habib, R., Rahman, A., … Wasay, M. (2016). Ischemic Strokes: Observations from a hospital based stroke registry in Bangladesh. *Stroke Research and Treatment*, *2016*. https://doi.org/10.1155/2016/5610797

Bolwar, A. C. (2015). Sickle cell anemia in Washim district , Maharashtra, *4*(1), 1320–1326.

Betz, A. L., & Coester, H. C. (1990). Effect of steroids on edema and sodium uptake of the brain during focal ischemia in rats. *Stroke; a Journal of Cerebral Circulation*, *21*(8), 1199–204. https://doi.org/10.1161/01.STR.21.8.1199

Bousser, M.-G., & Kittner, S. J. (2000). Oral contraceptives and stroke. *Cephalalgia*, *20*(3), 183–189. https://doi.org/10.1046/j.1468-2982.2000.00040.

Bernstein, R. A. (2011). Cerebrovascular disease: Hemorrhagic stroke. In J. C. Brust (Eds.), *Current diagnosis and treatment neurology* (pp. 128-148). New York: McGraw- Hill Education.

Caicoya, M., Corrales, C., & Rodriguez, T. (1999). Family history and stroke: A community case-control study in Asturias, Spain. *Journal of Epidemiology and Biostatistics*, *4*(4), 313–20.

Choi, J. C., Lee, J. S., Kang, S.-Y., Kang, J.-H., & Bae, J.-M. (2009). Family history and risk for ischemic stroke: Sibling history is more strongly correlated with the disease than parental history. *Journal of the Neurological Sciences*, *284*(1–2), 29–32. https:// doi.org /10.1016/j.jns.2009.03.015

Chen, G. J., & Yang, M. S. (2013). The effects of calcium channel blockers in the prevention of stroke in adults with hypertension: A meta-analysis of data from 273,543 participants in 31 randomized controlled trials. *PloS One*, *8*(3), e57854. https://doi.org/10.1371/ journal .pone. 0057854

Chamorro, Á., Meisel, A., Planas, A. M., Urra, X., van de Beek, D., & Veltkamp, R. (2012). The immunology of acute stroke. *Nature Reviews Neurology*, *8*(7), 401–410. https://doi.org/10.1038/nrneurol.2012.98

Dorhout Mees, S. M., Luitse, M. J. A., Van Den Bergh, W. M., & Rinkel, G. J. E. (2008).

Fever after aneurysmal subarachnoid hemorrhage: Relation with extent of hydrocephalus and amount of extravasated blood. *Stroke*, *39*(7), 2141–2143. https://doi.org/10.1161/ STROKE AHA.107.509851

De Schryver, E., Algra, A., & van Gijn, J. (2003). Dipyridamole for preventing stroke and other vascular events in patients with vascular disease. In A. Algra (Ed.), *Cochrane Database of Systematic Reviews* (p. CD001820). Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/14651858.CD001820

Egeto, P., Fischer, C. E., Ismail, Z., Smith, E. E., & Schweizer, T. A. (2014). Lacunar stroke, deep white matter disease and depression: A meta-analysis. *International Psychogeriatrics*, *26*(7), 1101–1109. https://doi.org/10.1017/S1041610214000568

Engels, T., Baglione, Q., Audibert, M., Viallefont, A., Mourji, F., Faris, M. E. A., … Aidi, S. (2014). Socioeconomic status and stroke prevalence in morocco:results from the rabat-casablanca study. *PLoS ONE*, *9*(2).https://doi.org/ 10.1371 /jour nal. pone. 008 9271

Finsterer, J. (2010). Management of cryptogenic stroke. *Acta Neurologica Belgica*, *110*(2), 135–47.

Fitzsimmons, B. M., & Lazzaro, M. (2011). Cerebrovascular disease: Ischemic stroke. In J. C. Brust (Eds.), (2011). *Current diagnosis and treatment neurology* (pp.102-127). New York: McGraw-Hill Education.

Grau, A. J., Buggle, F., Schnitzler, P., Spiel, M., Lichy, C., & Hacke, W. (1999). Fever and infection early after ischemic stroke. *Journal of the Neurological Sciences*, *171*(2), 115–20.

Garcy, J. S., Elkind, M. S.V. (2015). Global burden of neurologic disease. In E. D. Louis, S. A. Mayer & L. P. Rowland (Eds.). *Merritt's neurology* (pp. 1-7).

Haeusler, K. G., Laufs, U., & Endres, M. (2011). Chronic heart failure and ischemic stroke. *Stroke*, *42*(10), 2977–2982. https://doi.org/ 10.1161/STROKE AHA. 111. 628 479

Haley, M. J., & Lawrence, C. B. (2016). Obesity and stroke: Can we translate from rodents to patients? *Journal of Cerebral Blood Flow & Metabolism*, *36*(12), 2007–2021. https://doi.org/10.1177/0271678X16670411

Harmsen, P., Rosengren, A., Tsipogianni, A., & Wilhelmsen, L. (1973). Risk factors for stroke in middle-aged men in Goteborg, Sweden, *51*.

Hart, R. G., Diener, H. C., Coutts, S. B., Easton, J. D., Granger, C. B., O'Donnell, M. J., … Connolly, S. J. (2014). Embolic strokes of undetermined source: The case for a new clinical cons truct. *The Lancet Neurology*, *13*(4), 429–438. https://doi.org/10. 1016/S1474-4422(13)70310-7

Hering, D., Coca, A., Cunha, P., Gasecki, D., Lovic, D., Sierra, C., & Zaninnelli, A. (2016). Update on hypertension management hypertension and stroke subtypes : A causative role or simple association ?

Howard, V. J., & McDonnell, M. N. (2015). Physical activity in primary stroke prevention: Just Do It! *Stroke*, *46*(6), 1735–1739. https://doi.org/10.1161 /STROKE AHA. 11 5.006317

Ionita, C. (2011). Lacunar infarction. *Neurology Medlink.*

Islam, M. N., Moniruzzaman, M., Khalil, M. I., Basri, R., Alam, M. K., Loo, K. W., & Gan, S. H. (2013). Burden of stroke in Bangladesh. *International Journal of Stroke*, *8*(3), 211–213. https://doi.org/10.1111/j.1747-4949.2012.00885.

Illsley, A. (2011). Use of Anti-epileptic drugs in post-stroke seizures : A Cross-sectional Survey Among, *10*(6), 27–29.

Inzitari, D., & Poggesi, A. (2005). Calcium channel blockers and stroke. *Aging Clinical and Experimental Research*, *17*(4 Suppl), 16–30.

Jahirul, M. S., Choudhury, H., Chowdhury, T. I., & Nayeem, A. (2015). Modifiable and non-modifiable risk factors of stroke : A review update, *1*(1), 22–26.

Kappelle, L. J., Visseren, F. L. J., & Graaf, Y. Van Der. (2013). Asymptomatic carotid artery stenosis and the risk of ischemic stroke according to subtype in patients with clinical manifest arterial disease, 1002–1008. https://doi.org/10.1161/ strokeaha. 111. 66 9267

Kim, H., Friedlander, Y., Longstreth, W. T., Edwards, K. L., Schwartz, S. M., & Siscovick, D. S. (2004). Family history as a risk factor for stroke in young women. *American Journal of Preventive Medicine*, *27*(5), 391–396. https:// doi.org/ 10.1016/ j.am epre.2004.08.008

Kulshreshtha, A., Vaccarino, V., Goyal, A., McClellan, W., Nahab, F., Howard, V. J., & Judd, S. E. (2015). Family history of stroke and cardiovascular health in a national cohort. *Journal of Stroke and Cerebrovascular Diseases*, *24*(2), 447–454. https://doi.org /10.1016 /j.jstrokecerebrovasdis.2014.09.017

Lindey, K. W, Bone, I. & Fuller, G. (2010). *Neurology and neurosurgery illustrated (*5th ed.). Churchill Livingstone Elesevier.

Li, Q., Wu, H., Yue, W., Dai, Q., Liang, H., Bian, H., … Shen, Y. (2017). Prevalence of stroke and vascular risk factors in china: A nationwide community-based study. https://doi.org/10.1038/s41598-017-06691-1

Lee, K. L., & Shin, J. I. (2012). Cyclic vomiting syndrome developed after stroke. *Annals of Rehabilitation Medicine*, *36*(1), 141–3. https://doi.org/10.5535/arm.2012.36.1.141

Liu, L., Xiong, X.-Y., Zhang, Q., Fan, X.-T., & Yang, Q.-W. (2016). The efficacy of prophylactic antibiotics on post-stroke infections: An updated systematic review and meta-analysis. *Scientific Reports*, *6*(1), 36656. https://doi.org/10.1038/srep36656

Lo, E. H., Dalkara, T., & Moskowitz, M. A. (2003). Mechanisms , challenges and opportunities in stroke. https://doi.org/10.1038/nrn1106

Masood, C. T., Hussain. M., Rehman. A., Abbasi. S. (2016). Clinical presentation , risk factors and outcome of stroke at a district level teaching hospital.

Mehndiratta, M. M., Khan, M., Mehndiratta, P., & Wasay, M. (2014). Stroke in Asia: Geographical variations and temporal trends. *Journal of Neurology, Neurosurgery, and Psychiatry*, *85*, 1308–1312. https://doi.org/10.1136/jnnp-2013-306992

Mehndiratta, M. M., Mehndiratta, P., Gulati, N. S., & Wasay, M. (2014). Global perspectives. *Neurology*, *83*(9), 1022–1025. https://doi.org/10 .1212/WN L.0000000 000000728

Mehndiratta, P., Wasay, M., & Mehndiratta, M. M. (2015). Implications of female sex on stroke risk factors, care, outcome and rehabilitation: An Asian perspective. *Cerebrovascular Diseases*, *39*(5–6), 302–308. https://doi.org/10.1159/000381832

Miah, M., Azhar, M., Rahman, A., Halder, D., Akteruzzaman, M., & Kundu, N. (2012). Risk Factors of stroke in young and old age group - A comparative study. *Journal of Medicine*, *13*(2), 138–142. https://doi.org/10.3329/jom.v13i2.12741

Moulin, S., & Cordonnier, C. (2015). Prognosis and outcome of intracerebral haemorrhage. *Frontiers of Neurology and Neuroscience*. https://doi.org /10.1 159 / 0 004 37122

Mehta, S. L. (2014). Mechanisms of stroke induced neuronal death: Multiple therapeutic opportunities. *Advances in Animal and Veterinary Sciences*, *2*(8), 438–446. https://doi.org/10.14737/journal.aavs/2014/2.8.438.446

Mozaffarian, D., Benjamin, E. J., Go, A. S., Arnett, D. K., Blaha, M. J., Cushman, M., … Turner, M. B. (2016). *Heart disease and stroke statistics-2016 update a report from the American heart association*. *Circulation* (Vol. 133). https://doi. org/10. 1161/ CIR.0000000000000350

Okada, Y. (2013). Transient ischemic attack as a medical emergency. In *Frontiers of neurology and neuroscience* (Vol. 33, pp. 19–29). https://doi.org/10.1159/000351889

Ogun, S. A., & Odusote, K. A. (2001). Effectiveness of high dose dexamethasone in the treatment of acute stroke. *West African Journal of Medicine*, *20*(1), 1–6.

Pandian, J. D., & Sudhan, P. (2013). Stroke epidemiology and stroke care services in India. *Journal of Stroke*, *15*(3), 128–34. https://doi.org/10.5853/jos.2013.15.3.128

QD, M. (2003). Management of stroke. *Bangladesh Med J*, *42*(1), 34–37.

Qizilbash, N., Lewington, S., & López-Arrieta, J. (2002). Corticosteroids for acute ischaemic stroke. In N. Qizilbash (Ed.), *Cochrane Database of Systematic Reviews* (p. CD000064). Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10.1002/14 651858.CD000064

Rabinstein, A. A. (2013). Subarachnoid hemorrhage. *Neurology*, *80*(5), e56–e59. https://doi.org/10.1212/WNL.0b013e3182834b22

Raman, G., Kitsios, G. D., Moorthy, D., Hadar, N., Dahabreh, I. J., O'Donnell, T. F., … Lau, J. (2012). Management of asymptomatic carotid stenosis.Neurol Clinic.; 33(2):443-57. https:// doi: 10.1016/j.ncl.2014.12.008

Rang, H. P., Dale, M. M., Ritter, J. M., Flower, R.J., Henderson, G. (2007). *Rang and Dale's pharmacology* (7th ed.). Elsevier Churchill Livingstone.

Rothwell, P. M. (2007). Transient ischaemic attacks: Time to wake up. *Heart (British*

Cardiac Society), *93*(8), 893–4. https://doi.org/10.1136/hrt.2007.121111

Sridharan, S. E., Unnikrishnan, J. P., Sukumaran, S., Sylaja, P. N., Nayak, S. D., Sarma, P. S., & Radhakrishnan, K. (2009). Incidence, types, risk factors, and outcome of stroke in a developing country the trivandrum stroke registry. *Stroke*, *40*(4), 1212–1218. https://doi.org/10.1161/STROKEAHA.108.531293

Smith, W. S., English, J. D., & Johnston, S. C. (2013). Cerebrovascular diseases. In S. L. Hauser (Eds.), *Harrison's neurology in clinical medicine* (pp. 256-293). New York: Mc Graw-Hill Education.

Sacco, R. L., Kasner, S. E., Broderick, J. P., Caplan, L. R., Connors, J. J., Culebras, A., … Vinters, H. V. (2013). An updated definition of stroke for the 21st century: A statement for healthcare professionals from the American heart association/American stroke association. *Stroke*, *44*(7), 2064–2089. https://doi.org/10.1161 /STR. 0b013 e3182 96aeca

Saha, R., Islam, M., Hossain, A. M., Mamun, A. A., Saha, S. K., Mondal, S. K., & Alam, M. J. (2016). Clinical presentation and risk factors of stroke-a study of 100 hospitalized stroke patients in Bangladesh, *11*(July 2014), 23–25.

Sandercock, P., Gubitz, G., Foley, P., & Counsell, C. (2003). Antiplatelet therapy for acute ischaemic stroke. In P. Sandercock (Ed.), *Cochrane Database of Systematic Reviews* (p. CD000029). Chichester, UK: John Wiley & Sons, Ltd. https://doi. org/10 .1002/14651858.CD000029

Saver, J. L. (2016). Cryptogenic stroke. *New England Journal of Medicine*, *374*(21), 2065–2074. https://doi.org/10.1056/NEJMcp1503946

Semplicini, A., Calo, L., Calò, L., A., S., & L., C. (2005). Administering antihypertensive drugs after acute ischemic stroke: Timing is everything. *Canadian Medical Association Journal*, *172*(5), 625–626. https://doi.org/10.1503/cmaj.1041393

Sandercock, P. A., & Soane, T. (2011). Corticosteroids for acute ischaemic stroke. In P. A. Sandercock (Ed.), *Cochrane Database of Systematic Reviews* (p. CD000064). Chichester, UK: John Wiley & Sons, Ltd. https://doi.org/10 .1002 /1465 1858. CD0 0006 4.pub2

Shahpouri, M. M., Mousavi, S., Khorvash, F., Mousavi, S. M., & Hoseini, T. (2012). Anticoagulant therapy for ischemic stroke: A review of literature. *Journal of Research in Medical Sciences : The Official Journal of Isfahan University of Medical Sciences*, *17*(4), 396–401. Retrieved from http://www.ncbi.nlm.nih.gov/pubmed/23267405

Siddique, A. N., Nur, Z., Mahbub, S., Alam, B., & Miah, T. (2009). Clinical presentation and epidemiology of stroke - a study of 100 cases. *Journal of Medicine*, *10*(1), 86–89. https://doi.org/10.3329/jom.v10i2.2820

Spence, J. D. (1986). Antihypertensive drugs and prevention of atherosclerotic stroke, 808–811.

Salman, R. A. S., & Dennis, M. S. (2014). Antiplatelet therapy may be continued after intracerebral hemorrhage. *Stroke*, *45*(10), 3149–3150. https://doi. org/10.116 1/ stroke aha.114.005786

State of the nation. (2017). Annual statistics of stroke association, United Kingdom.

Talahma, M., Strbian, D., & Sundararajan, S. (2014). Sickle cell disease and stroke. *Stroke*, *45*(6), 114–117. https://doi.org/10.1161/Strokeaha.114.005144

Tegeler, C. H., Shi, F., & Morgan, T. (1991). Carotid stenosis in lacunar stroke. *Stroke; a Journal of Cerebral Circulation*, *22*(9), 1124–1128. https://doi.org/ 10.1161/ 01. ST R.22.9.1124

Tomassoni, D., Lanari, A., Silvestrelli, G., Traini, E., & Amenta, F. (2008). Nimodipine and its use in cerebrovascular disease: Evidence from recent preclinical and controlled clinical studies. *Clinical and Experimental Hypertension*, *30*(8), 744–766. https://doi.org /10.1080 /10641960802580232

The National Collaborating Centre for Chronic Conditions. (1990). *National clinical guideline for diagnosis and initial management of acute stroke and transient ischaemic attack (TIA)*. *BBA - General Subjects* (Vol. 1035). https://doi.or g/10.10 16/0304-4165(90)90085-B

Truelsen, T., Begg, S., & Mathers, C. (2000). The global burden of cerebrovascular disease. *Global Burden of Disease*, 1–67.

Uchiyama, S. (2009). Tischemic attack, a medical emergency. *Brain and Nerve*, *61*(9), 1013–

22.

Van de Beek, D. (2009). Preventive antibiotics for infections in acute stroke. *Arch Neurol*, *66*(9), 1076–1081. https://doi.org/10.1161/Strokeaha.111.643726

Venketasubramanian, N., & Chen, C. L. H. (2008). Burden of stroke in Singapore. *International Journal of Stroke*, *3*(1), 51–54. https://doi.org/10.1111/j.1747-4949.2008.00181.

Vermeij, J.-D., Westendorp, W. F., Roos, Y. B., Brouwer, M. C., Van de Beek, D., Nederkoorn, P. J., & PASS Investigators, for the P. (2016). Preventive ceftriaxone in patients with stroke treated with intravenous thrombolysis: Post hoc analysis of the preventive antibiotics in stroke study. *Cerebrovascular Diseases (Basel, Switzerland)*, *42*(5–6), 361–369. https://doi.org/10.1159/000446160

Wardlaw, J. M. (2005). What causes lacunar stroke? *Journal of Neurology, Neurosurgery, and Psychiatry*, *76*(5), 617–619. https://doi .org/10.11 36/jnnp .2004. 039 982

Westendorp, W. F., Vermeij, J.-D., Vermeij, F., Hertog, H. M. D., Dippel, D. W. J., van de Beek, D., & Nederkoorn, P. J. (2012). Preventive antibiotics in acute stroke: Summary of a cochrane systematic review and meta-Analysis. *Stroke*, *43*(11), e113–e114. https:// doi. org/10.1161/STROKEAHA.112.671420

Wasay, M., Khatri, I. A., & Kaul, S. (2014). Stroke in South Asian countries. *Nature Publishing Group*, *10*(3), 135–143. https://doi.org/10.1038/nrneurol.2014.13

WHO. (2016). *Tobacco & Stroke. World Health Organization*, (6), 33–36.

WHO. (2010). *Diabetes mellitus. World Health Organization*.

WHO. (2016). *Managing acute stroke in low-resource settings. World Health Organization*.

Wolf, P. A. (1985). Risk factors for stroke. *A Journal of Cerebral Circulation,16(3)*.

Wolf, P. a, Abbott, R. D., & Kannel, W. B. (1991). Atrial fibrillation as an independent risk factor for stroke : The Framingham Study. *Stroke*, *22*, 983–988. https://doi.org/ 10.1 161/01.STR.22.8.983

Woodruff, T. M., Thundyil, J., Tang, S.-C., Sobey, C. G., Taylor, S. M., & Arumugam, T. V. (2011). Pathophysiology, treatment, and animal and cellular models of human

ischemic stroke. *Molecular Neurodegeneration*, *6*(1), 11. https://doi.org/10 .1186/1 75 0-1326-6-11

World Health Organization. (2013). A global brief on hypertension - World Health Day 2013. *World Health Organization*,1–40. https://doi.org/10.1136/bmj.1.4815.882-a

Wang, J.-Y., Wang, C.-Y., Tan, C.-H., Chao, T.-T., Huang, Y.-S., & Lee, C.-C. (2014). Effect of different antipsychotic drugs on short-term mortality in stroke patients. *Medicine*, *93*(25), e170. https://doi.org/10.1097/MD.0000000000000170

Zahra, F., Kidwai, S. S., Siddiqi, S. A., & Khan, R. M. (2012). Frequency of newly diagnosed diabetes mellitus in acute ischaemic stroke patients. *Journal of the College of Physicians and Surgeons Pakistan*, *22*(4), 226–229. https://doi.org/04.2012/ JCPSP .226229