# A STUDY OF PLASMA FIBRINOGEN LEVELS IN STROKE

**Dissertation submitted to**

**THE TAMILNADU DR.M.G.R MEDICAL UNIVERSITY**

**CHENNAI- TAMILNADU**

**In partial fulfillment for the Degree of**

**DOCTOR OF MEDICINE**

**BRANCH I –M.D., (General Medicine)**

**APRIL-2015**

**DEPARTMENT OF MEDICINE**

**TIRUNELVELI MEDICAL COLLEGE**

**TIRUNELVELI- 627011**

**TAMILNADU**

# CERTIFICATE

This is to certify that the Dissertation entitled "**A STUDY OF PLASMA FIBRINOGEN LEVELS IN STROKE"** is a bonafide original work of Dr.S.BALACHANDAR**,** in partial fulfillment of the requirement for M.D., BRANCH- I General Medicine Examination of The Tamilnadu Dr.M.G.R. Medical university, Chennai to be held in April 2015

The bonafide work is carried out by him under my guidance and supervision. This dissertation partially or fully has not been submitted for any other degree or diploma of this university or other.

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# DECLARATION

I**, Dr. S.BALACHANDAR**, solemnly declare that, I carried out this work on **"A STUDY OF PLASMA FIBRINOGEN LEVELS IN STROKE"** at, Department of General medicine, Tirunelveli Medical College and Hospital during the period of August 2013 to August 2014.

I also declare that this bonafide work or a part of this work was not submitted by me or any others for any award, degree, diploma to any university, found either in India or abroad.

This is submitted to The Tamilnadu Dr.M.G.R.Medical University, Chennai, in partial fulfillment of the rules and regulations for the MD Degree Branch I General Medicine Examination, to be held on April 2015.

Place : TIRUNELVELI

**DR.S.BALACHANDAR ,**

POST GRADUATE,

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PROTOCOL TITLE: A Study of Plasma Fibrinogen Levels in Stroke

NAME OF PRINCIPAL INVESTIGATOR: Dr.S.Balachandar

DESIGNATION OF PRINCIPAL INVESTIGATOR: Post Graduate Resident

DEPARTMENT & INSTITUTION: Department of General Medicine, Tirunelveli Medical College

*Dear Dr* Dr.S.Balachandar, *the Tirunelveli Medical College Institutional Ethics Committee (TIREC) reviewed and discussed your application during the IEC meeting held on* 29.03.2013.

**THE FOLLOWING DOCUMENTS WERE REVIEWED AND APPROVED**

| | | |
|---|---|---|
| 1. | TIREC Application Form | ☑ |
| 2. | Study Protocol | ☑ |
| 3. | Department Research Committee Approval | ☑ |
| 4. | Patient Information Document and Consent Form in English and Vernacular Language | ☑ |
| 5. | Investigator's Brochure | ☑ |
| 6. | Proposed Methods for Patient Accrual Proposed | ☑ |
| 7. | Curriculum Vitae of the Principal Investigator | ☑ |
| 8. | Insurance /Compensation Policy | ☐ |
| 9. | Investigator's Agreement with Sponsor | ☐ |
| 10. | Investigator's Undertaking | ☑ |
| 11. | DCGI/DGFT approval | ☐ |
| 12. | Clinical Trial Agreement (CTA) | ☐ |
| 13. | Memorandum of Understanding (MOU)/Material Transfer Agreement (MTA) | ☑ |
| 14. | Clinical Trials Registry-India (CTRI) Registration | ☐ |

**THE PROTOCOL IS APPROVED IN ITS PRESENTED FORM ON THE FOLLOWING CONDITIONS**

1. The approval is valid for a period of 2 year/s or duration of project whichever is later
2. The date of commencement of study should be informed
3. A written request should be submitted 3weeks before for renewal / extension of the validity
4. An annual status report should be submitted.
5. The TIREC will monitor the study
6. At the time of PI's retirement/leaving the institute, the study responsibility should be transferred to a person cleared by HOD
7. The PI should report to TIREC within 7 days of the occurrence of the SAE. If the SAE is Death, the Bioethics Cell should receive the SAE reporting form within 24 hours of the occurrence.
8. In the events of any protocol amendments, TIREC must be informed and the amendments should be highlighted in clear terms as follows:
   a. The exact alteration/amendment should be specified and indicated where the amendment occurred in the original project. (Page no. Clause no. etc.)
   b. The PI must comment how proposed amendment will affect the ongoing trial. Alteration in the budgetary status, staff requirement should be clearly indicated and the revised budget form should be submitted.
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   f. The amendment is unlikely to be approved by the IEC unless all the above information is provided.
   g. Any deviation/violation/waiver in the protocol must be informed

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**State of Tamilnadu, South India**

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# *CONTENTS*

# A STUDY OF PLASMA FIBRINOGEN LEVELS IN STROKE


## ABSTRACT

## INTRODUCTION

Increased plasma fibrinogen is a risk factor for vascular diseases related to atherosclerosis. Its predictive value in stroke is not well established. We conducted this study to establish the significance of hyperfibrinogenemia with severity and functional outcome of acute stroke.

## METHODS

We studied 100 patients who got admitted with stroke within 24 hours of symptom onset. We noted the history regarding risk factors and assessed the severity of stroke by Scandinavian stroke scale and functional outcome of stroke by modified Rankin scale at the time of admission and discharge. Plasma fibrinogen was measured in all patients. The values computed and analysed with pearson correlation and chi-square tests.

## RESULTS

The mean fibrinogen was 405.6 mg/dl. The mean value was increased in patients having ischemic stroke. Patients having hyperfibrinogenemia at the time of admission has increased severity of stroke ($p<0.01$) as assessed by Scandinavian stroke scale (mean-29.91) and similarly has poor functional outcome as evidenced by increased scores of modified Rankin scale ($p<0.01$) at

the time of admission and discharge.12 patients were expired during the course of stay in hospital. The mean fibrinogen among the dead patients was significantly higher (439.58) as compared to overall mean fibrinogen value.

Among the risk factors, although the mean value was increased in smokers, hypertension and diabetes, we could establish a significant relation only with diabetes.

## CONCLUSION

Increased plasma fibrinogen shortly after ischemic stroke predicts the severity and poor functional outcome of stroke.

**Key words:** fibrinogen, stroke severity, Scandinavian stroke scale, modified Rankin scale.

# INTRODUCTION

Stroke is a common neurological illness causing significant morbidity and mortality among all hospital admissions in both developing and developed countries. The prevalence of stroke in India ranges from 84 to 262 per lakh in rural areas and 334 to 424 in urban areas .The case fatality rate is highest in Kolkata which corresponds to 42%. In urban India stroke accounts for 1% mortality of all hospital admissions, 4% in all medical cases and about 20% in all disorders of central nervous system [1].

Important Risk factor for stroke includes Diabetes, Hypertension, smoking and dyslipidemia.

Fibrinogen is a soluble plasma glycoprotein that consists of three non-identical pairs of polypeptide chains Aα, Bβ and γ chains [2].

In the first phase of thrombus formation, thrombin converts soluble fibrinogen into insoluble fibrin. Thrombin cleaves Aα and Bβ chains thereby releasing fibrinopeptides . These fibrinopeptides initiate a process in which fibrin monomers begin to gel. These fibrin monomers polymerise to form fibrin polymers. This process continues and elongation of polymers causes formation of protofibrils. Once a critical [1] mass of long protofibrils is established, the protofibrils form lateral contacts with other protofibrils thereby forming fibrin clot. Fibrin clot thereby potentiates formation of thrombosis.

Epidemiological observations indicate that high plasma fibrinogen levels strongly correlate with two major thrombotic complications of atherosclerosis, stroke and myocardial infarction. Thrombosis is increasingly recognized as a central mechanism in stroke as well as in myocardial infarction. Fibrinogen is involved in events thought to play a major role in thrombosis [3].

At the beginning of stroke the elevated level of inflammatory markers such as C-reactive protein (CRP) or fibrinogen may reflect the underlying burden of atherosclerosis and/or the association of concomitant risk factors (e.g. Diabetes mellitus, Hypertension, Obesity)[4]. In addition, the blood level of these markers could rise during stroke as a part of the acute phase reaction [1].

There is a significant inter individual variability in inflammatory response after stroke. In Scottish heart health study it was found that plasma fibrinogen level was elevated in smokers, premature heart disease, known hypertensive patients, Diabetics and patients with intermittent claudication.

In another study it was found that sustained increase in fibrinogen value during an acute stroke episode predicts the worse outcome irrespective of the baseline fibrinogen value. In this study, the fibrinogen was measured at day 1,7, and 14 and compared with stoke outcome scales NIHSS (National Institute of Health Stroke Scale) and Modified Rankin Scale.

The relationship between fibrinogen and thrombosis may strengthen the predictive value of this protein and suggest new treatment in management of stroke. It remains uncertain whether this rise in inflammatory marker is an epiphenomenon to stroke severity or it contributes independently to functional stroke outcome.

Many case control studies done previously proven that plasma fibrinogen levels was elevated in smokers, hypertensives and dyslipidemia patients.

Hence this study is designed to investigate mainly the association between plasma fibrinogen levels and acute stroke outcome [5] .

# AIMS AND OBJECTIVES

1. To study plasma fibrinogen levels in patients with stroke.
2. To correlate fibrinogen level with other major risk factors for stroke.
3. To find out immediate prognosis of patients (during hospital stay) with stroke who have abnormal fibrinogen level.

# REVIEW OF LITERATURE

The brain receives a constant supply of glucose and oxygen from the blood for its normal functioning. The blood perfuses at a rate of 55 to 70 ml per 100 g of brain tissue per minute. The principal source of energy for this brain tissue is derived exclusively from oxidation of glucose. If the blood perfusion is reduced below 15 ml per 100 g per minute , ischemia develops due to hypoxia and when it is prolonged , it will lead on to death of neurons and glia.

“Stroke” is defined as an acute neuronal injury that occurs as a result of diseases of cerebral vasculature and its contents [6].The severity of stroke varies from complete recovery over a few days to persistent disability or death.

Transient ischemic attack (TIA) is defined as a transient episode of neurologic deficit caused by brain, spinal cord, or retinal ischemia, which recovers within 24 hours of duration[7]. During a 5 year follow up of this TIA patients 30% of these patients are more prone to develop a full-fledged stroke.

“RIND” (Reversible ischaemic neurological deficit) refers to the resolution of symptoms within a period of seven days.

Approximately 80 percentage of strokes are due to ischaemic cerebral infarction and 20 percentage are due to brain haemorrhage. Stroke is the 3rd most common cause of death in developed nations. In India the prevalence rate is in the range of 200 per 1 lakh persons.

**Historical Review**

Hippocrates was probably the first to write about the medical aspects of stroke.

Hippocrates wrote in his aphorisms on apoplexy,

"Persons are most subject to apoplexy between the ages of forty and sixty", and attacks of numbness might reflect "impending apoplexy".

A few hundred years after Hippocrates, Galen (131-201 AD) described the anatomy of the brain and its blood vessels from dissections of animals.

During the last half of the seventeenth century, two important physicians Johann Jakob Wepfer and Thomas Willis made important contributions to understand the anatomy of blood circulation and clinical features of stroke.

Wepfer was the first to show clearly that bleeding into the brain was an important cause of apoplexy.

Thomas Willis, a Neuroanatomist best known for his CEREBRI ANATOME, which contained a description of a circle of anastomotic

vessels at the base of the brain. Willis recognized transient ischemic attacks and the phenomenon of embolism, as well as existence of occlusion of the carotid artery.

During the eighteenth century, one of the giants in medical history, Giovanni Battista Morgagni (1682-1771) was able to focus attention on pathology and the[8] cause of disease. Morgagni also described cases of intracerebral haemorrhage and recognized that paralysis was on the side of the body opposite to the brain lesion.

John Abercrombie contributed a more detailed clinical classification of apoplexy in his general text published in 1828. Abercrombie used the presence of headache, stupor, paralysis and outcome to separate apopletics into three clinical groups.

Detailed observation of the distribution of the arteries and veins in the cranium were made by Duret a French neurosurgeon, by Stopford in Britain and later by Foix.

During the twentieth century, especially in the 1970's and 1980's, there was an explosive growth in knowledge about stroke. Advances in technology allowed better visualization of the anatomy and the functional aspects of the brain and of vascular lesions during life.

The technological revolution probably began with the work of the Portuguese neurosurgeon Moniz (1874-1955). Moniz surgically exposed and temporarily

ligated the internal carotid artery in the neck and then injected by hand a 30% solution of sodium iodide, taking skull films later at regular intervals. Hounsfield of the research laboratories of Electrical musical instruments in Britain originated the concept of computed tomography (CT) during the mid 1960's.

The instrument was first tried at the Atkinson-Morley hospital in London. CT Scanners were first introduced to North America in 1973. Films from first generation scanners were quite primitive, but by the late 1970'sthird generation scanners had made CT a useful, almost indispensable, diagnostic tool.

CT allowed clear distinction between the brain ischemia and haemorrhage and allowed definition of the size and location of most brain infarcts and haemorrhages.

The advent of Magnetic Resonance Imaging (MRI) in clinical medicine in the mid 1980's was a further major advance. MRI proved superior to CT in showing old hemosiderin containing haemorrhages and in imaging vascular malformations, lesions abutting on bony surfaces, and posterior fossa structures.

Ultrasound was introduced to medicine in 1961 by Franklin and colleagues.

B Mode Ultrasound was soon used to provide images of the extra cranial carotid arteries non-invasively.

In 1982, Aaslid and colleagues introduced a high energy bidirectional pulsed Doppler system that used low frequencies to study intracranial arteries, termed Transcranial Doppler ultrasound (TCD). TCD made possible the non-invasive detection of severe occlusive disease in the major intracranial arteries during life as well as sequential study of these lesions.

Introduction of Echocardiography and ambulatory cardiac rhythm monitoring in the 1970's and 1980's greatly improved cardiac diagnoses and detection of cardiac sources of embolism.

By the end of twentieth century, advanced brain imaging with CT, MRI, and newer MR modalities, diffusion, perfusion and functional MRI, MR Spectroscopy, were able to show clinicians the localization, severity and potential reversibility of brain ischemia. Vascular lesions could be quickly and safely defined using spiral CT angiography, MR angiography, extracranial and transcranial ultrasound.

**STROKE**

Stroke can be broadly classified into two types:

- Ischemic stroke.
- Haemorrhagic stroke.

This type of stroke occurs due to occlusion of the arteries supplying brain either by thrombosis or embolism. This results in decreased perfusion to the affected brain tissue thereby causing cell death.

**Causes of ischemic stroke**

**Thrombosis**

- Small / large vessel disease
- Dehydration

**Embolism**

- Atrial fibrillation
- Paradoxical emboli
- Artery to artery embolism
- Dilated cardiomyopathy
- Left atrial myxoma/ thrombus
- Valvular pathology
- Ischemic heart disease
- Valvular vegetations
- Inter atrial septal aneurysm

**Rare causes**

- Coagulation factor deficiency like protein C,S

- OCP use
- Antiphospholipid antibody syndrome
- Cancer associated
- Pregnancy
- Polycythemia vera
- Inflammatory bowel disease
- Fibro muscular dysplasia
- MoyaMoya disease
- Nephrotic syndrome
- Leukoaraiosis
- Trauma to vessel
- Irradiation
- Migraine
- Systemic lupus erythematoses
- Post-operative period
- Snake bite
- Hanging
- Vasculitis
- Disseminated intravascular coagulation

**Causes of Intracerebral haemorrhage**

- Systemic hypertension

- Trauma
- Haemorrhagic transformation of old infarct
- Bleeding in space occupying lesion
- Bleeding diathesis
- Aneurysmal rupture
- AV malformations
- Cerebral amyloid angiopathy
- Telangiectasis
- Post thrombolysis
- Use of anticoagulants
- Renal failure
- Thrombotic Thrombocytopenic Purpura
- Tumours
- Drug abuse
- Snake bite
- Thrombocytopenia
- Antiplatelets
- Cortical vein thrombosis
- Liver cell failure

# PATHOPHYSIOLOGY OF STROKE

## CEREBRAL AUTOREGULATION

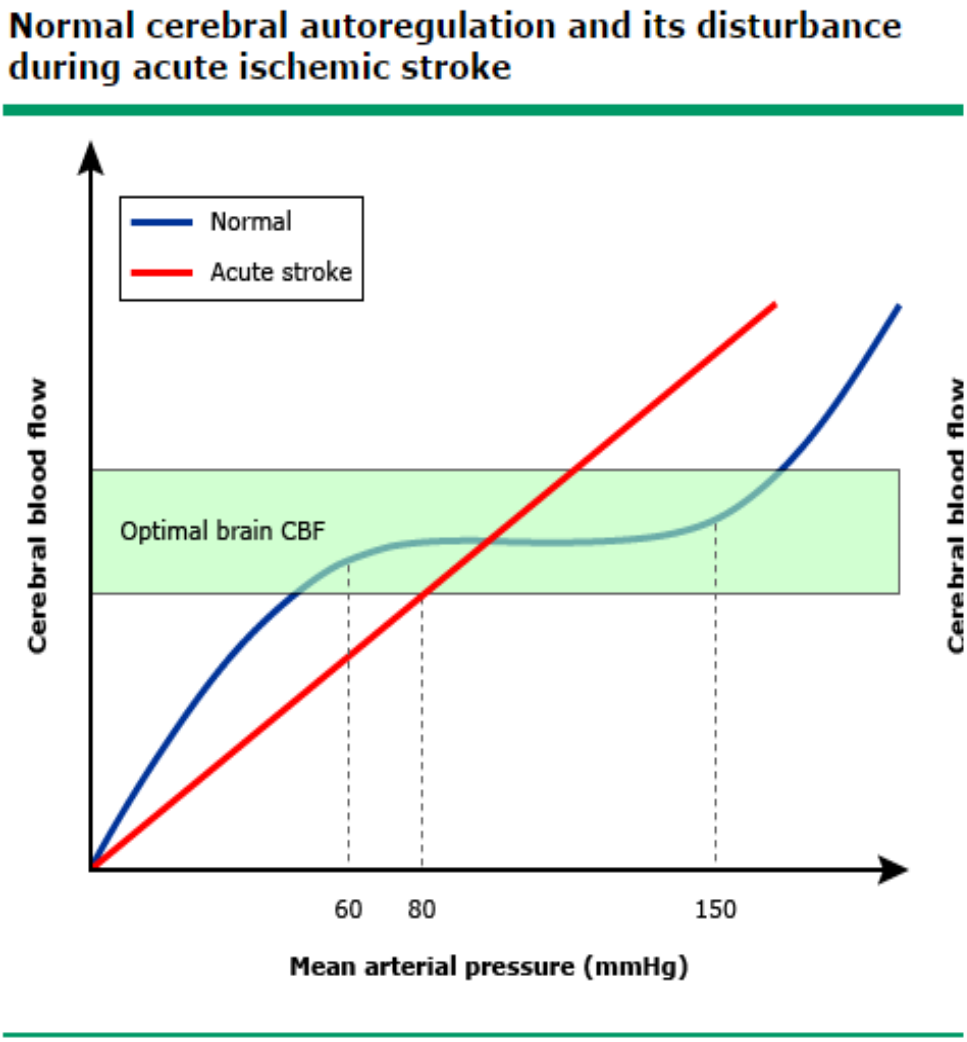
Under normal circumstances, cerebral blood flow mainly depends upon the amount of vascular resistance within cerebral blood vessels, which is related to their diameter[9]. Dilatation of blood vessels leads to increased cerebral blood flow, whereas constriction of vessels has the opposite effect. Cerebral perfusion pressure also determines the cerebral blood flow.

Cerebral autoregulation maintains the cerebral blood flow at a relatively constant rate despite [9-11] variations in perfusion pressure. The mechanism by which autoregulation occurs is not well understood, which may involve multiple pathways. There are evidences which suggest that the smooth muscle in cerebral vessels can respond directly to changes in perfusion pressure, contracting when pressure increases and relaxing when pressure decreases. Reductions in cerebral blood flow may lead to cerebral vasodilatation due to release of vasoactive substances, although the substance responsible for this has not been identified. Nitric oxide which released from vascular endothelium appears to play a role in autoregulation.

Cerebral blood flow is maintained by autoregulation which typically occurs within a range of 60 to 150 mmHg of mean arterial pressure. The upper and lower limits vary between individuals, However beyond this range, the brain is unable to compensate for changes in perfusion pressure,

and the cerebral blood flow increases or decreases passively with corresponding changes in pressure, resulting in the risk of ischemia at low pressures and edema at high pressures.

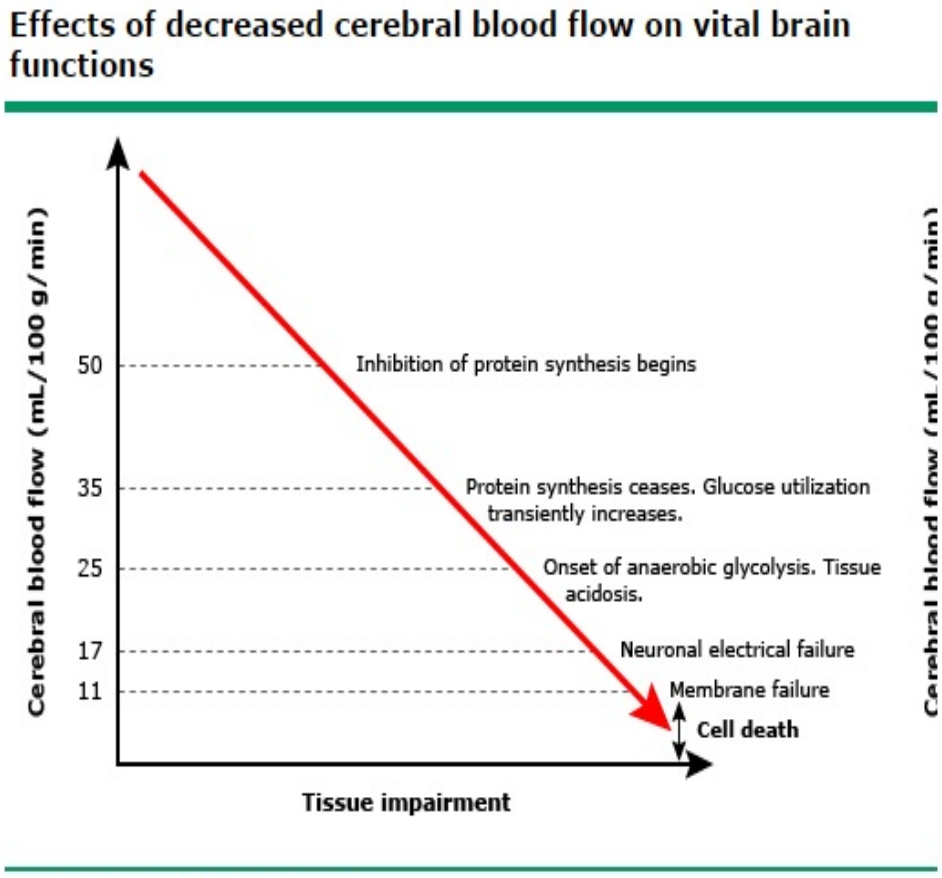
**FIGURE-1**



## CEREBRAL AUTOREGULATION DURING STROKE

Cerebral auto regulation is impaired due to some disease conditions, which includes ischemic stroke also. When cerebral perfusion pressure decrease there will be cerebral vascular dilatation and when it falls below the compensatory capacity of the brain it will lead to decrease in the cerebral blood flow. Initially, the oxygen extraction fraction is increased in order to maintain levels of oxygen delivery to the brain. As the cerebral blood flow continues to fall, other mechanisms come into play.

**FIGURE-2**



In patient with hypertension autoregulation usually occurs at higher arterial pressures. Reduction of blood pressure to normal levels could actually exacerbate the derangement to autoregulation that occurs during stroke and lead to a further decrease in cerebral blood flow.

## CONSEQUENCES OF REDUCTION IN BLOOD FLOW DURING STROKE

The human brain is very much sensitive to even a short duration of ischemia. Even though brain is only 2 to 3% of total body weight, the blood flow it receives is 20 to 25% of the total cardiac output. The brain has no energy stores of its own, and therefore it depends on the blood for their delivery. So even a brief deprivation can lead to death of the affected brain tissue. During stroke, reduction of blood flow to brain results in deprivation of glucose and oxygen.

Commonly strokes are due to ischemia, which affects the small part of the brain mainly affecting a single blood vessel and its branches. Region which is commonly involved is the area supplied by the same vessel which is immediately surrounding the vessel. If the ischemia is prolonged in this area, cells will die by necrosis and the peripheral area which receives nutrients and oxygen by collateral vessel will not die immediately, which can be revived by timely intervention and restoration of blood flow. This area which

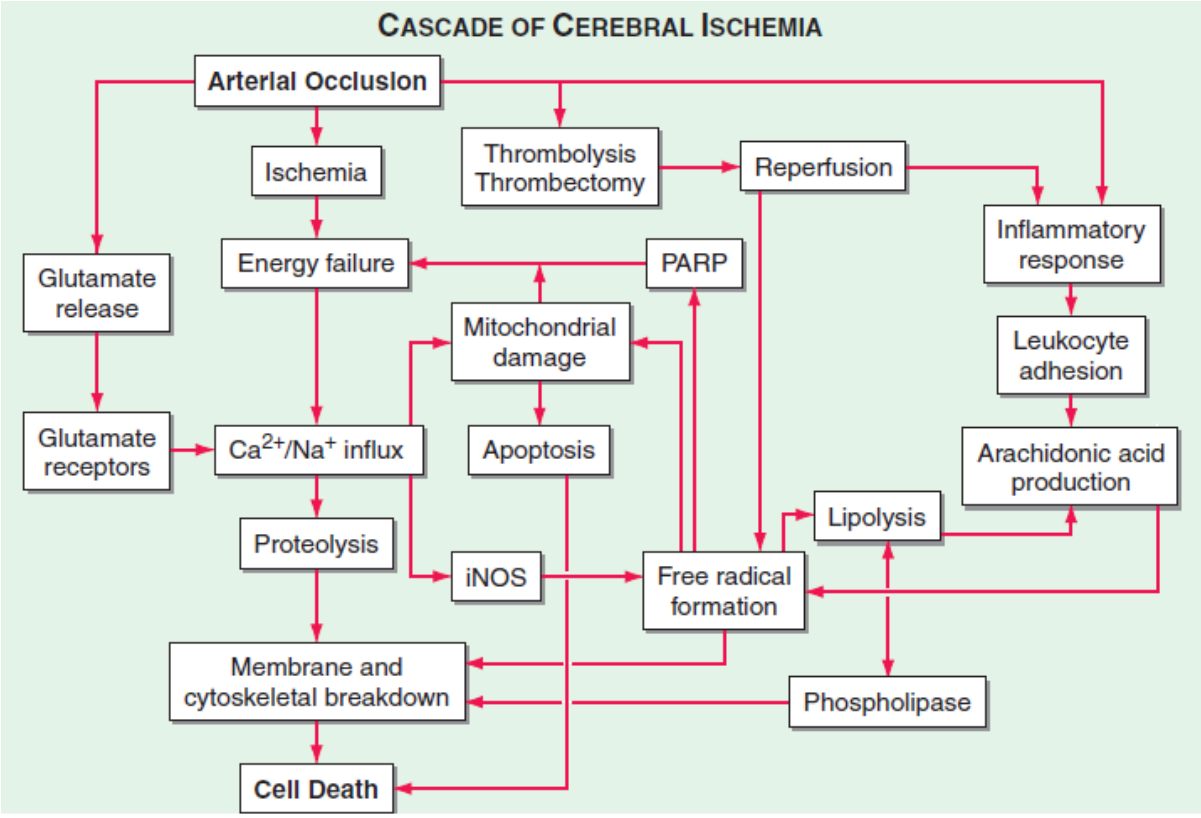
surrounds the dead cells is known as ischemic penumbra and the area underwent necrosis is known as infarct.

## MECHANISMS OF ISCHEMIC CELL INJURY AND DEATH

A sequence of events occurs following brain ischemia leading to brain cell death. The possible mechanisms [12-13]are

1. ATP depletion
2. Na+ ,K+ and Ca2+ ionic concentration changes
3. Increase amount of lactic acid which leads to acidosis
4. Oxygen free radicals
5. Proteolytic enzymes
6. Accumulation of water inside the cell

**FIGURE-3**




As a consequence of the electrical failure that occurs as a result of ischemia, there will be increased secretion of excitatory Neurotransmitter at the synapse will cause the glutamate [14] receptor activation and lead to out flow of the potassium and inflow of the sodium [15-18] and calcium ion. It will lead to variety of effects. The main subtypes of glutamate receptors involved are

1. N-methyl-D-aspartate (NMDA) receptor (main)
2. The alpha-amino-3-hydroxy-5-methyl-4-isoxazoleproprionic acid (AMPA)

3. Metabotropic glutamate receptors. Activation of these receptors leads to membrane depolarization and increased calcium influx.

Another effect of NMDA receptor activation is the production of nitric oxide[19]. The activity of nitric oxide synthase (NOS) and the total amount of nitric oxide present in the brain are increased following exposure to hypoxia[20].

Nitric oxide is an important signalling molecule within the body and can be beneficial at normal physiologic levels. As an example, endothelial nitric oxide synthase (eNOS) leads to the production of low levels of nitric oxide that cause vasodilation and increase blood flow [21]. However, neuronal nitric oxide synthase (nNOS) and inducible nitric oxide synthase (iNOS) result in larger amounts of nitric oxide that may lead to brain injury. Nitric oxide is a free radical and reacts directly with cellular components to damage them. Nitric oxide can also react with another free radical, Superoxide, to produce the highly reactive peroxynitrite. Peroxynitrite causes single strand breaks in DNA [22]. This results in the activation of DNA repair enzymes, which consume vital energy needed for other processes. DNA damage also may activate the process of apoptosis, leading to cell death.

The production of reactive oxygen species, a normal by product of oxidative metabolism, is also increased during ischemia. Like nitric oxide, they can react with and damage cellular components. Injury to the plasma

membrane of a cell can lead to inability to control ion flux, resulting in mitochondrial failure. Reactive oxygen species, as well as calcium influx and other factors, can also permeabilize the mitochondrial membrane [23].This leads to metabolic failure as well as release of initiators of apoptosis and DNA damage. Metabolic failure results in the depletion of cellular ATP levels. ATP is required for nuclear condensation and DNA degradation in the final stages of apoptosis [24]. In the absence of ATP, cell death occurs by necrosis rather than apoptosis.

The release of by products from cellular damage and death by necrosis activates components of the inflammatory pathway [25]. The role that inflammation plays during ischemia is mixed, having both positive and negative effects[26]. On way the surrounding inflammation results in proliferation of blood vessels and thereby increasing the blood flow to affected region, this will deliver more oxygen and glucose to the tissues. On the other hand, increased blood flow may also deliver more calcium to the area where the damage will be more.

Inflammation also results in the migration of activated leukocytes to damaged tissues[27]. Although these leukocytes may remove damaged and necrotic tissues, they also release cytokines to attract additional inflammatory cells. Under severe inflammatory conditions, these cytokines can accumulate to toxic levels.

## NECROSIS AND APOPTOSIS

Cell death following cerebral ischemia or stroke can occur by two way either by necrosis or apoptosis.

The process of necrosis is not well understood. The changes include

1) Condensation of chromatin

2) Swelling of endoplasmic reticulum

3) Ribosomal dispersion[28]

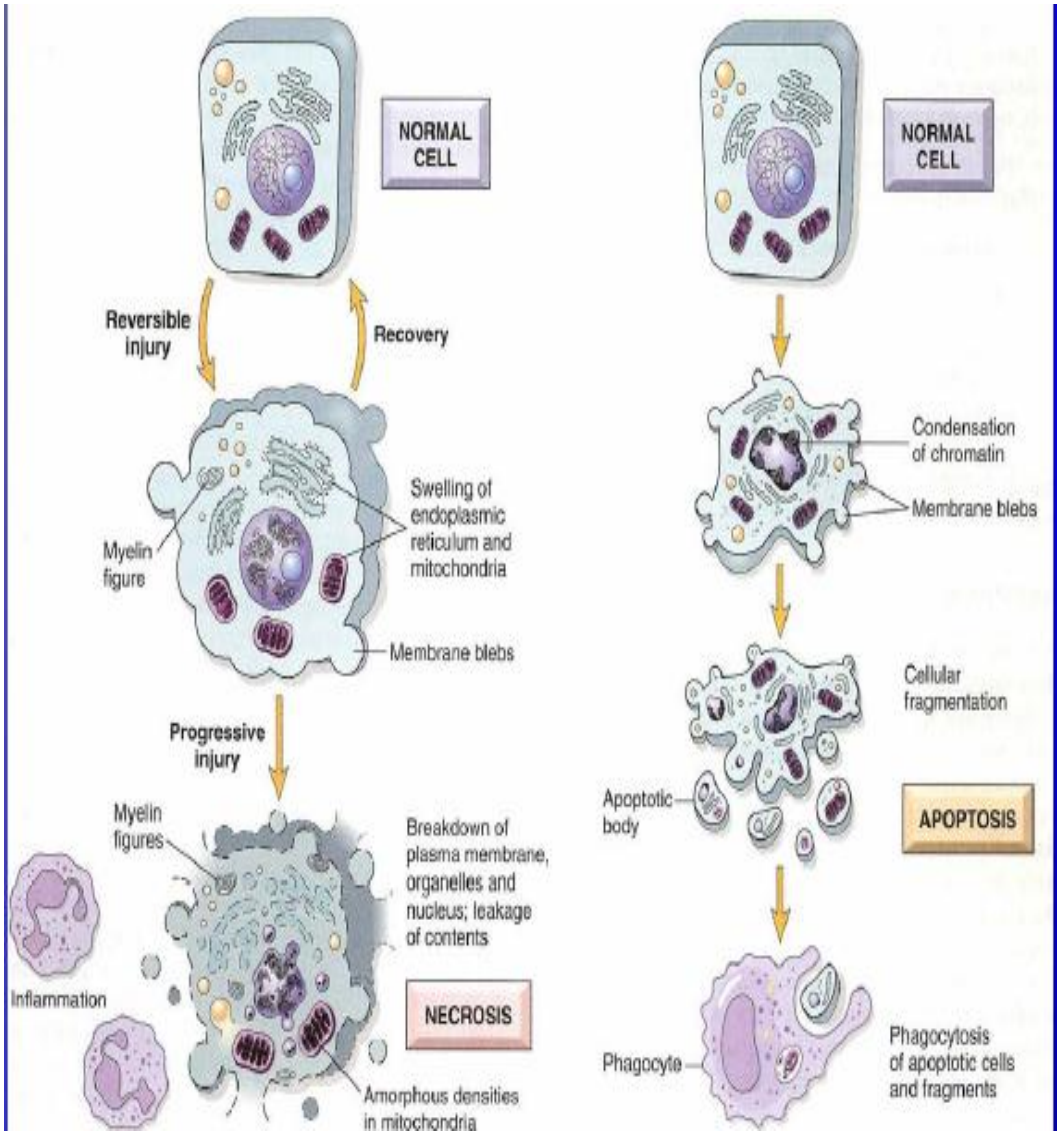
There will be swelling of the entire cell and plasma membrane and mitochondria after chromatin condensation. Eventually this cell leaks out the materials into the adjacent tissues and triggers the inflammation in the surrounding areas.

Apoptosis is nothing but a programmed cell death. Here also chromatin condensation takes place similar to necrosis in early stages. But in later stages the cell shrinks and the nucleus fragments into pieces and activates caspases and leads to destruction of the cell. This apoptosis is highly regulated by various enzymes like caspases and p53 gene.

There are three known pathways by which apoptosis can be initiated [ 29 ]:

- Mitochondrial permeabilization
- Death receptor (Fas) pathway
- Endoplasmic reticulum stress

**FIGURE-4 APOPTOSIS VS NECROSIS**



The most important pathway is permeabilization of the mitochondria and release of cytochrome C into the cytoplasm. Activation of membrane-bound Fas, the so called "death receptor," and the accumulation of misfolded proteins at the endoplasmic reticulum during stress, can also lead to apoptosis. These initiators all lead to the activation of caspases that cleave cellular proteins and eventually cause cell death. Caspase independent mechanisms of apoptosis have also been proposed.

The pattern of cell death after cerebral ischemia, as seen in animal models, depends on the nature of the insult to cerebral tissue [30]. In global cerebral ischemia that occurs after cardiac arrest and resuscitation or transient severe systemic hypotension, the entire brain is exposed to ischemia. Formation of infarct is not immediate, but rather occurs after a delay of 12 hours to several days. Cell death is limited to those regions of the brain that are particularly susceptible to ischemic damage, such as the CA1 and CA4 regions of the hippocampus, the striatum, and cortical layers two and five. Cell death in these regions occurs primarily by apoptosis.

Focal cerebral ischemia is a more common pattern than global ischemia in human stroke. In animal models of focal ischemia, changes in cell morphology are visible microscopically as early as two to three hours after the insult, and the infarct develops rapidly over a period of 6 to 24 hours. Cell death occurs by necrosis in the core, with apoptotic cells located

at the periphery. In addition to the type of insult, the duration of ischemia also affects the pattern by which cell death occurs. Longer ischemic insults produce greater damage to cerebral tissue, resulting in an increased proportion of necrosis and decreased proportion of apoptosis.

There have been few studies of apoptosis in the brain following stroke in human patients. However, accumulating evidence suggests that apoptosis is involved [31-34], as illustrated by the following observations:

- In a neuropathology study that compared specimens from 27 patients who had cerebral infarction with specimens from rat brains subjected to experimental transient forebrain ischemia, the patterns of cell death were similar in human and animal brain tissue and included both morphologic and histochemical findings typical of apoptosis [31]. In the human stroke specimens, apoptosis was apparent during the subacute stage, but was not seen in acute or chronic stages.
- In another neuropathology report that compared 13 cases of fatal ischemic stroke with three patients who died of non-neurologic causes, histochemical and morphologic changes indicative of apoptosis were seen in cells throughout the brain of both patients and controls [34] .The morphologic changes were more advanced in the peri-infarct region and infarct core of the patients with stroke. Apoptotic cells were located primarily within the peri-infarct region, consisting of up to

26% of all cells. Increased ischemic damage and neuronal necrosis was associated with a decrease in the percentage of apoptotic cells.

The deciding factor in determining whether cells undergo necrosis or apoptosis seems to be the level of energy available in the form of ATP, which is required for formation of the apoptosome. Apoptosis is unable to proceed in its absence. When energy levels are limiting, cell death occurs by necrosis rather than by apoptosis. The role of ATP in the mechanism of cell death has been investigated primarily using cell culture models. Cultured neurons depend on the presence of serum in the culture medium for survival. If the serum is removed, the cells die by necrosis. In serum-free media with added glucose, however, the cells die by apoptosis.

ATP levels are decreased in acute stroke because of decreased blood supply. Glucose metabolism is decreased by about 50% in both global and focal ischemia models of stroke. As a consequence, ATP levels may fall to 10% of normal in global models or 25% in the infarct core in focal ischemia models. ATP levels in the penumbra, however, only drop to 50% to 70% of normal [35].

ATP levels in the brain may also be decreased by mitochondrial damage or failure, activity of DNA repair enzymes, such as PARP, and neuronal depolarization related to glutamate excitotoxicity. In stroke, in the central area of infarction where the ATP level is least, necrosis takes place

whereas in the penumbra ATP levels will be slightly more than the central area and thereby apoptosis occurs. Hence the duration of ischemia directly related to the area of necrosis.

## LOSS OF BRAIN STRUCTURAL INTEGRITY

Cerebral ischemia and infarction leads to loss of the structural integrity of the affected brain tissue and blood vessels. This process of tissue destruction and neurovascular disruption is mediated by the release of various proteases, like the Matrix Metalloproteases (MMP) that degrade collagens and laminin in the basal lamina [36]. The loss of vascular integrity leads to breakdown of the blood-brain-barrier and development of cerebral edema. Catastrophic loss of vascular integrity is postulated to cause haemorrhagic conversion of ischemic infarction by allowing extravasation of blood constituents into the brain parenchyma [37 ].

## CEREBRAL EDEMA

Cerebral edema complicating stroke can cause secondary damage by several mechanisms, including increased intracranial pressure, which may decrease cerebral blood flow, and mass effect causing displacement of brain tissue from one compartment to another (ie, herniation), a process that can be life-threatening.

Two types of cerebral edema can occur as a consequence of ischemic stroke .

1. Cytotoxic edema is caused by the failure of ATP-dependent transport of sodium and calcium ions across the cell membrane. The result is accumulation of water and swelling of the cellular elements of the brain, including neurons, glia, and endothelial cells.
2. Vasogenic edema is caused by increased permeability or breakdown of the brain vascular endothelial cells that constitute the blood-brain barrier [38-39]. This allows proteins and other macromolecules to enter the extracellular space, resulting in increased extracellular fluid volume.

About 10% of ischemic stroke may be massive because of the presence of space-occupying cerebral edema that may be severe enough to produce elevated intracranial pressure and brain herniation.

## RISK FACTORS ASSOCIATED WITH STROKE

Atherosclerosis is the common basic cause in both cerebrovascular and cardiovascular related morbidity and mortality. The major risk factors associated with stroke and myocardial infarction include [40-44] .

- Systemic Hypertension
- Diabetes mellitus
- Smoking
- Dyslipidemia

As we all know the risk increases more with combination of two or more risk factor. This was proved by a study conducted in 3998 subjects and assessed the severity of carotid stenosis and found that the carotid stenosis increased as the number of risk factors increased. This study also founded that this incidence was more among men than women.[45]:

- Without any risk factors the incidence of a severe stenosis was 2.4 and 0.6 % in men and women respectively.
- With single risk factor it was 6.7 and 1.5 %.
- With two risk factors it was 10.7 and 2.7 %
- With three risk factors it was 18.6 and 5 %.

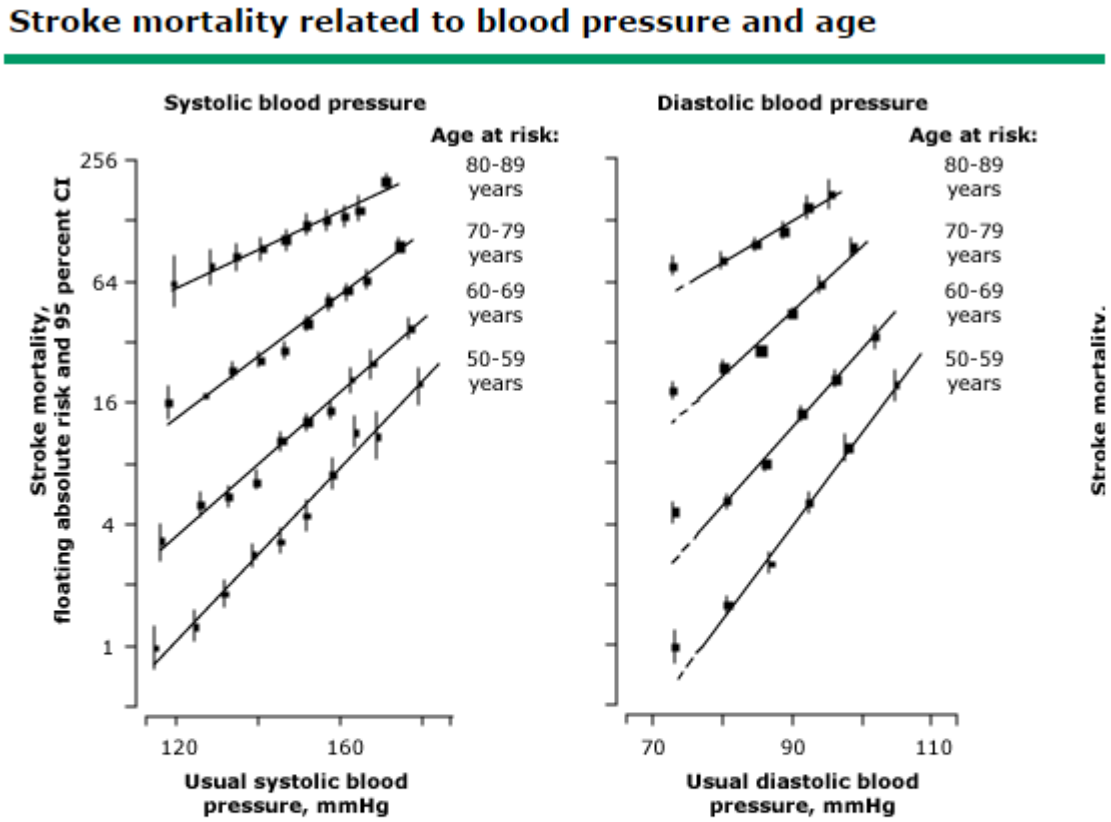
Therefore control of these risk factors will provide an additional benefit as this risk factor control also reduces the risk of cardiovascular events, a common comorbidity in patients with cerebrovascular disease.

## HYPERTENSION

Hypertension, which has a crucial role in the formation of atherosclerotic lesions, is an important as well as treatable risk factor for cerebrovascular accident.

- Hypertension is present in approximately 60 % of men and women in all age groups.
- Hypertension can cause either a silent or subclinical stroke and it is also one of the important risk factor for recurrent stroke and dementia due to vascular pathology. [46-48]
- Mean blood pressure is an important risk factor for stroke. In addition to that there is evidence to say that visit to visit variability in systolic blood pressure is also a risk factor for stroke.[49,50]

**FIGURE-5**




Stroke mortality rate, pictured on a log scale with 95 percent confidence intervals, in each decade of age in relation to the estimated usual systolic and diastolic blood pressure at the start of that decade. Stroke mortality increases with both higher pressures and older ages. For diastolic pressure, each age-specific regression line ignores the left-hand point (ie, at slightly less than 75 mmHg), for which the risk lies significantly above the fitted regression line (as indicated by the broken line below 75 mmHg).

ASA/AHA Guidelines 2011 includes antihypertensive regimen andlife style modifications viz. [51]

1.Salt restriction

2.Weight loss

3.Vegetables

4.Diet rich in fruits

5.Regular aerobic physical activity

6.Low-fat dairy products

7.Limited alcohol consumption.

Scottish heart health study was a random population survey conducted among Scottish people.10359 men and women participated, out of which plasma fibrinogen was measured in 8824 patients.

The result from that study confirms that plasma fibrinogen is not only a risk factor for stroke and coronary heart disease, this plasma fibrinogen value was also increased in patients with family history of premature heart disease , Smokers , Diabetes, Hypertension and intermittent claudication.

**SMOKING**

Smoking is an important risk factor for all stroke subtypes. In various studies it was found that there exists a dose response relationship for both subarachnoid haemorrhage and ischaemic stroke.[52-57]

Both males and females are affected equally among smokers but as the age progresses the association seems to become weaker. There is perhaps an association with passive smoking also.

Up to one half of all smokers are expected to die from a tobacco-related mortality [1]. In one population-based cohort study which involves

about 50,000 people aged between 40 to 70 years in Norway, the total years of life lost were 2.7 years in men and 1.4 years in women, among those who smoked ≥20 cigarettes daily, compared to those who never smoked.

In the Nurses' Health Study, it was found to have that smokers had a relative risk of stroke of 2.58 compared with patients those who never smoked[53] .

- Another interesting fact found in this study was that the excess risk disappeared within two to four years among the former smokers after cessation of smoking.
- In the Framingham Heart Study, it was found that the odds ratio was 1.08 for moderate carotid stenosis, for each five pack-years of smoking [55] .
- 10,938 normotensive subjects were studied in a prospective Swedish cohort study, and found to have about 39% of strokes were attributable to smoking [56].

Though there is no randomized controlled trials relating both smoking cessation and stroke prevention, few observational studies have shown that the increased risk of stroke due to smoking declines after quitting and is eliminated by five-years of smoking cessation[57-58]. Hence smoking

cessation is recommended, for patients with transient ischemic attack (TIA) and stroke.

In addition to cigarettes, tobacco is also smoked in the form of pipes, cigars, and water pipes. Tobacco products get absorbed through mucosal membranes after tobacco chewing and snuffing. Electronic cigarettes (e-cigarettes) use a liquid nicotine cartridge, rather than tobacco.

In two Nottinghamshire studies which compares smokers with non-smokers, chronic smokers had a significantly elevated absolute rate of fibrinogen synthesis. Moreover, abstinence from smoking for a period of only 2 weeks results in significant decrease in fibrinogen synthesis by the liver, thereby concomitantly reduces the plasma fibrinogen concentration.

**DIABETES MELLITUS**

When compared to those who are non-diabetic the risk of stroke is double in patients with diabetes[59-62]. Endothelial dysfunction, Dyslipidemia, platelet and other coagulation abnormalities promotes the development of carotid atherosclerosis in diabetics.

Studies also proved that impaired glucose tolerance and increased HbA1c are associated with carotid plaque development [64,65].

## GLYCEMIC CONTROL

Strict glycemic control reduces the risk of microvascular complications such as nephropathy, retinopathy and neuropathy in patients with diabetes mellitus.

However, randomized controlled trials failed to demonstrate a consistent beneficial effect of lifestyle modification or intensive glucose lowering therapy on macrovascular outcomes such as cardiovascular events and death in patients with Type 2 Diabetes.

In contrast, the results of the UKPDS post-trial observation follow-up study suggest that initial intensive control of Hb A1C to7.0 % in individuals who was newly diagnosed diabetes has long-term benefit in decreasing the risk of stroke, myocardial infarction, diabetes related mortality, and overall mortality.

In one study by Ang et al there was a significant interaction between fibrinogen and diabetes mellitus and they also established lower platelet inhibition when treated with clopidogrel if diabetes and elevated plasma fibrinogen coexist. [63]

## METABOLIC SYNDROME

The metabolic syndrome was defined as three or more of the following factors.

1. Hypertension ,
2. High fasting glucose,
3. Abdominal obesity ,
4. Low high-density lipoprotein,

The available evidence will not satisfactorily explain that metabolic syndrome is an independent risk factor for stroke

- A prospective cohort study which includes 14,284 patients with coronary heart disease found that the risk for TIA or stroke was independently associated with the presence of metabolic syndrome as with frank diabetes as well as patients without diabetes, corresponds to odds ratios 2.3 and 1.5, respectively[64].
- Another population-based prospective cohort study followed 3298 stroke-free subjects in which 44 % of whom had metabolic syndrome for a mean of 6.4 years [65]. After adjusting for age, sex, ethnicity, socioeconomic status, and other risk factors, the metabolic syndrome was associated with a high risk of ischemic stroke.

- In the prospective ARIC study which includes 14,993 middle-aged subjects who were stroke-free at baseline, metabolic syndrome was present in 39%[66]. There was a dose-response relationship between the number of metabolic syndrome components and risk of ischemic stroke. Elevated fasting glucose and Elevated blood pressure were the two components that conveyed the highest risk.

The utility of the metabolic syndrome to predict stroke risk does not appear to improve upon more conventional assessments such as the Framingham Risk Score (FRS). In a prospective study of 5128 middle-aged men with no history of stroke or coronary heart disease, presence of the metabolic syndrome was associated with a significant increase in stroke risk, but the FRS was significantly more effective for predicting stroke rather than the number of metabolic abnormalities [67].

**DYSLIPIDEMIA**

Hyperlipidemia is an important risk factor for myocardial infarction. But the relation between blood lipids and stroke is not well established.

## OTHER FACTORS INFLUENCING RISK

### ALCOHOL INTAKE

Depending upon the type of stroke, level of consumption, and ethnicity, alcohol affects the risk of stroke in contradictory directions. Patients having binge drinking or consuming large amount periodically is associated with an increased risk of stroke as compared to patients who take alcohol occasionally or in smaller amounts. AHA/ASA guidelines 2011 recommends that patients with previous history of stroke should eliminate or reduce their alcohol consumption to avoid the alcohol based morbidity and mortality.

In one study which was conducted in French population as a part of DESIR study, fibrinogen value was found to be higher in subjects who are non-alcoholic or who consume more than 60g of alcohol per day. And another fact found in this study was increased value in subjects consuming beer and spirits than those who consume wine or cider. And moderate amount of drinking lowers the fibrinogen value. Hence this can be attributed to protective effect of alcohol on cardiovascular disease.

### APOLIPOPROTEIN- E

The role of apolipoprotein E (APOE) phenotypes in cerebrovascular disease and ischemic stroke is unsettled. This apolipoprotein helps in clearance of VLDL and chylomicron remnants from the circulation. The

APOE e4 allele has been reported to be a stroke risk factor in some studies[68].

## HYPERHOMOCYSTEINEMIA

Increased serum homocysteine concentrations are associated with an increased risk of coronary and cerebrovascular disease.

Homocysteine has prothrombotic and primary atherogenic properties. The pathologic features of vessel wall include intimal thickening, disruption of elastic lamina, smooth muscle proliferation, platelet aggregation, and the formation of platelet rich thrombi.

Elevated homocysteine seems to be associated with an increased risk of the atherosclerosis in large artery, and possibly in small artery and it does not appear to be associated with cardioembolic or other stroke subtypes [69].

Unfortunately, there is no evidence that treating hyperhomocysteinemia with folic acid and vitamins will prevent the recurrent events.

For patients with hyperhomocysteinemia, the AHA/ASA guidelines of 2011 states that folic acid can be given to reduce the homocysteine levels. However, there is no clear cut data or evidence to prove that reducing homocysteine level prevents stroke recurrence.

## INFLAMMATORY MARKERS

Mounting data suggest that inflammation plays a role in atherosclerosis and contributes to stroke risk.

## C-REACTIVE PROTEIN

C-reactive protein (CRP) concentration is associated with the long-term risk of atherosclerotic vascular events, including ischemic stroke and myocardial infarction, as confirmed by a meta-analysis of 54 prospective studies and individual records from over 160,000 subjects without a history of vascular disease[70].

While elevated CRP levels could be used as an additional marker of increased stroke risk, there are no randomized clinical trial data to support the hypothesis that lowering CRP levels will lead to reduced stroke risk. Furthermore, appropriate critical thresholds of CRP elevation and optimal timing of CRP measurements in the setting of acute cerebral ischemia have not been established. Hence routine checking of CRP levels are not recommended for primary or secondary ischemic stroke prevention.

## FIBRINOGEN

Plasma fibrinogen is associated with the increased risk of stroke and cardiovascular disease. This fibrinogen acts by several possible mechanisms, including promotion of atherogenesis and inflammation, elevation of blood

and plasma viscosity, increased platelet aggregation, and increased tendency to form fibrin within thrombus.

Elevated fibrinogen levels appear to correlate with vulnerable atherosclerotic plaque characteristics, including thinning of the fibrous cap of atheroma predisposing to rupture, and to increased plaque inflammation [71]. However, it is not established that elevated fibrinogen is an independent risk factor for carotid atherosclerosis progression, as some evidence suggests it is rather a nonspecific marker of inflammatory activity.

Due to the lack of clinical trial data, measuring plasma fibrinogen is not recommended routinely in all stroke patients. Still more studies are needed to study about the drug therapy specifically aimed at lowering the fibrinogen concentrations for patients at risk of ischemic stroke or progressive carotid disease.

## LEUKOCYTES

Leukocyte counts and neutrophil counts were associated with ischemic events including stroke, myocardial infarction, and vascular death in a high-risk population. In the week before the recurrent event, the leukocyte count was significantly increased over the baseline value. However, treatment with aspirin or clopidogrel did not modify the predictive effects of elevated leukocyte counts.

An independent association of leukocyte count elevation with increased ischemic stroke risk was also found among stroke-free participants in a prospective, longitudinal, cohort study (the Northern Manhattan Study).

## RADIOTHERAPY

Head and neck radiotherapy for cancer treatment may lead to a delayed vasculopathy of large and small vessels mediated by endothelial damage, fibrosis, and accelerated atherosclerosis. Radiotherapy-related occlusive disease is often diffuse and occurs in uncommon locations, in contrast to the typical focal lesions that develop at vessel bifurcations from atherosclerosis in the absence of radiation.

Depending on the site and dose of radiation, the involved vessels may include the extracranial carotid and vertebral arteries and the intracranial circle of Willis vessels. This process may lead to symptomatic carotid disease, moyamoya syndrome, and ischemic stroke.

## ANATOMY OF CEREBRAL CIRCULATION

At rest, the brain which is only 2% of total body weight, receives 20% of the cardiac output and consumes 20% of the total inspired oxygen. This rich blood supply is delivered by the two internal carotid and two vertebral arteries, which anastomose at the base of the brain to form the circle of Willis. The carotid arteries supply the anterior, and the vertebra basilar arterial system supplies the posterior portions of the brain.

There is individual variation in the branches of the main cerebral arteries and also there is considerable variation between the individuals in the usual brain territories of supply of the various major arteries, and these territories can be asymmetrical and even change with time, depending in part on the availability of functional collaterals.

The Internal Carotid artery (ICA) starts from bifurcation of the common carotid artery (CCA) at the level of upper border of thyroid cartilage. The artery gives no branches in the neck to the skull base. The artery then passes into foramen lacerum. This artery enters into carotid canal which is present in the petrous part of temporal bone. It then traverses cavernous sinus and enter the duramater. This artery exits just medial to the anterior clinoid process, and then divides into the anterior cerebral artery and the larger middle cerebral artery.

The external carotid artery also starts at the CCA bifurcation and supplies the jaw, face, scalp, neck and meninges .The ophthalmic artery supplies the eye and orbit.

The Posterior communicating artery arises from internal carotid artery. This artery runs backwards and joins with posterior cerebral artery thereby closing the circle of Willis. The branches from this artery supply the thalamus, midbrain and radiations for visual pathway.

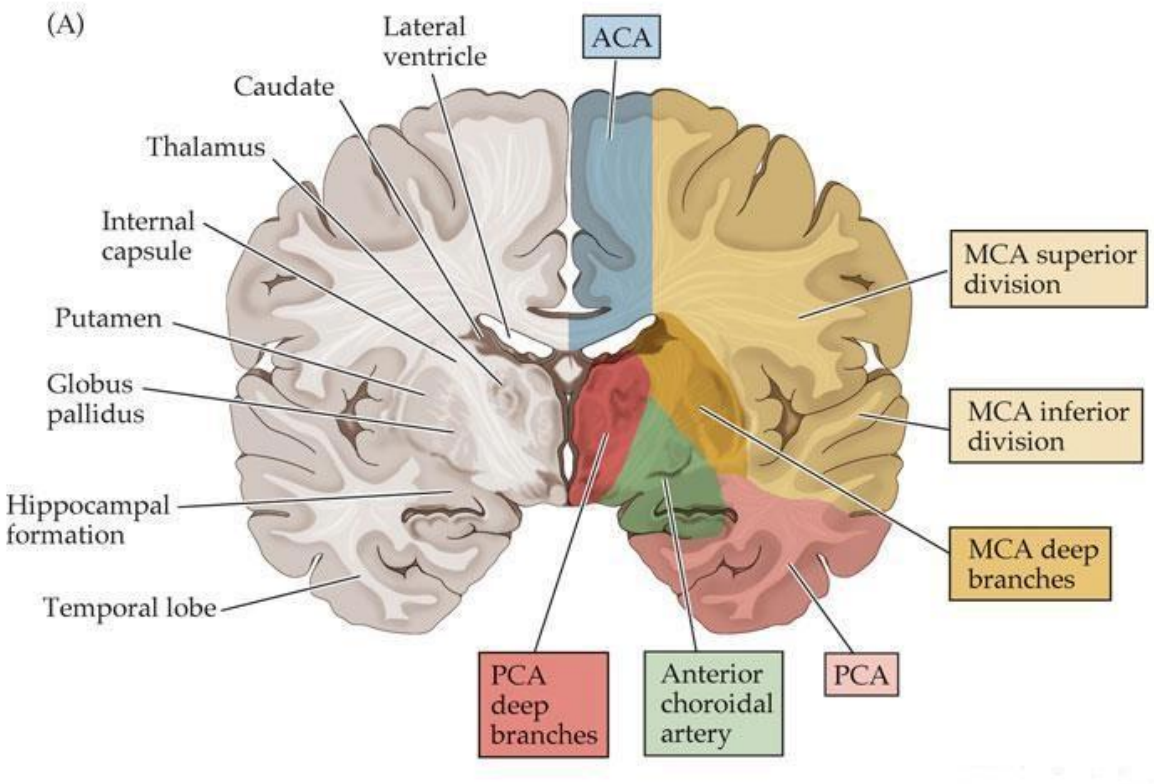



**FIGURE-6 BLOOD SUPPLY OF BRAIN**

The anterior choroidal artery is the final branch from internal carotid artery that supplies the capsulo-ganglionic region, optic radiations and temporal lobes.

Anterior cerebral artery (ACA) passes horizontally and medially to enter the interhemispheric fissure, anastomoses with its counterpart of the opposite side via the anterior communicating artery (ACoA), curves up around the genu of the corpus callosum, and supplies the anterior and medial parts of the cerebral hemisphere. Small branches also supply parts of the optic nerve and chiasma, hypothalamus, anterior basal ganglia, and internal capsule.

The ACA is divided into two segments-

1.The pre communal (A1) segment, or the stem which connects the internal carotid artery to the anterior communicating artery and

2.The post communal (A2) segment distal to the anterior communicating artery.

The middle cerebral artery (MCA) enters the sylvian fissure and divides into 2-4 branches which supply the lateral parts of the cerebral hemisphere.

The proximal MCA (M1 segment) gives rise to penetrating branches (lenticulostriate arteries) that supply the putamen, outer globus pallidus, posterior limb of internal capsule, the adjacent corona radiata and most of the caudate nucleus. In the Sylvian fissure, the MCA in most patients divides

into superior and inferior divisions (M2 branches). Branches from the inferior division supply the inferior parietal and temporal cortex, and those from the superior division supply the frontal and superior parietal cortex.

The vertebral artery arises from the proximal subclavian artery and ascends to pass through the transverse foramina of the sixth to second vertebrae. It unites with the opposite vertebral artery on the ventral surface of the brain stem at the pontomedullary junction to form the basilar artery. The vertebral artery gives rise to the anterior and posterior spinal arteries, the posterior inferior cerebellar artery and small penetrating arteries to the medulla. The posterior inferior cerebellar artery supplies the inferior vermis, inferior and posterior surfaces of the cerebellar hemispheres and brain stem.

The basilar artery ascends ventral to the pons to the pontomidbrain junction in inter peduncular cistern where it divides into the two posterior cerebral arteries (PCA).Numerous small branches penetrate the brainstem and cerebellum. The basilar artery also gives rise to the anterior inferior cerebellar artery which supplies the rostral cerebellum, brainstem, inner ear, and the superior cerebellar artery which supplies the brainstem, superior half of cerebellar hemisphere, vermis and dentate nucleus.

The posterior cerebral artery (PCA) encircles the midbrain close to the oculomotor nerve at the level of the tentorium and supplies the inferior parts of the temporal lobe and the occipital lobe. Many small perforating arteries arise from the P1 segment of posterior cerebral artery to supply the midbrain.

There is an anatomic variant in which both the medial surface of thalamus receive a common blood supply from single arterial trunk called ARTERY OF PERCHERON. The posterior cerebral artery also supplies thalamus, hypothalamus and geniculate bodies. In about 15% of individuals the PCA is a direct continuation of the PoCA, its main blood supply then coming from ICA rather than the basilar artery.

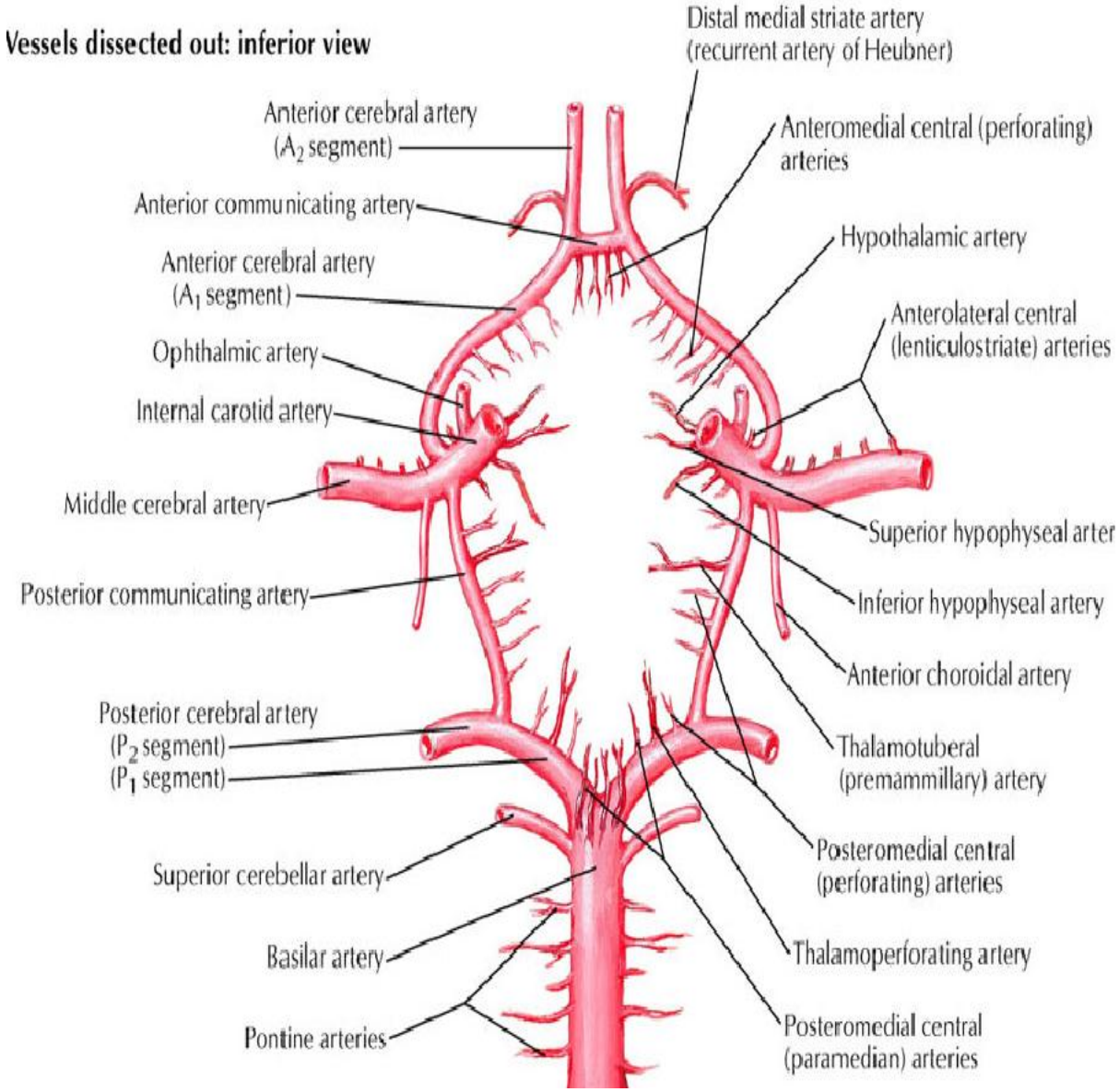
**COLLATERAL BLOOD SUPPLY TO THE BRAIN**

Normally the ICA provides blood to the anterior two-thirds of the ipsilateral cerebral hemisphere. There is rather little mixing of blood via the PoCA and so the posterior circulation is usually supplied by the vertebral, basilar and posterior cerebral arteries. However there are several ways in which collateral blood supply to the brain can develop distal to the occlusion of major arteries in the neck or head. The actual pattern of collateral blood flow depends on where the major vessels are stenosed or occluded, and on which collateral channels are anatomically available in a particular individual, and free from disease. Collateral blood flow may develop from the circle of Willis, which is formed by the proximal part of the two ACA's connected by the ACoA, and the proximal part of the two PCA's, which are connected to the distal ICA's by the PoCA.

Other areas of collateral blood flow are:

1. Around the orbit
2. Leptomeningeal anastomoses
3. Parenchymal anastomoses

**FIGURE-7 CEREBRAL CIRCULATION**




## VENOUS DRAINAGE

Venous blood flows centrally via the deep cerebral veins and peripherally via the superficial cerebral veins into the dural venous sinuses which drain into the internal jugular veins. The cerebral veins are thin

walled, have no valves and the blood flow is often in the same direction as in neighbouring arteries [72].

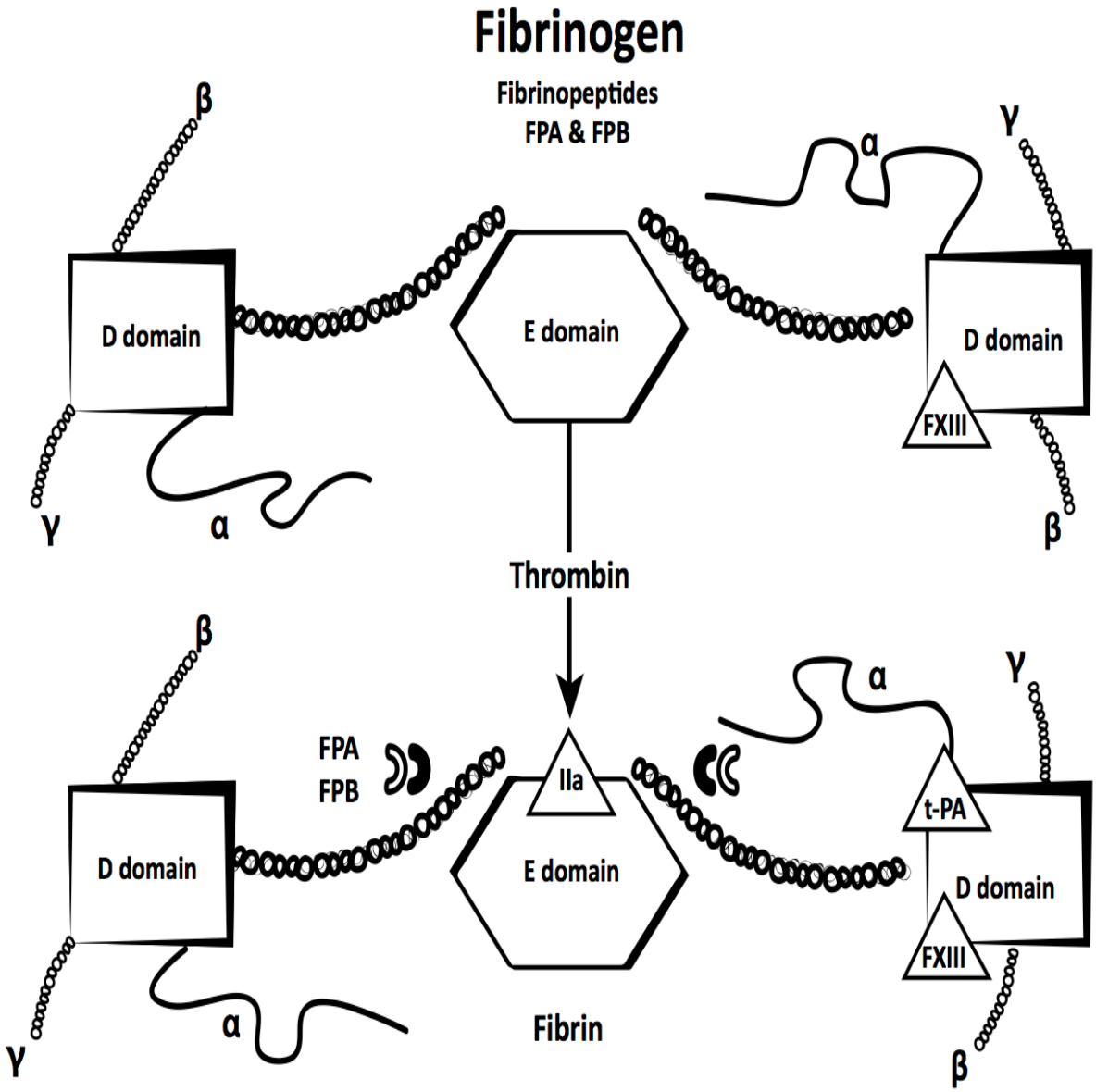
## FIBRINOGEN

### STRUCTURE [73-74]

The fibrinogen is synthesized by liver and secreted in plasma. The fibrinogen molecule is a large trinodular di sulphide bonded glycoprotein composed of two symmetric half molecules. Each half molecule contains three distinct polypeptide chains called Aα, Bβ and γ chains. The entire molecule has a molecular mass of 3,40,000 Dalton and is 45nm long and 9nm in diameter. The central nodule or E-domain is 5nm in diameter and contains the NH-2 terminal of all six polypeptide chains forming the NH-2 terminal disulphide knot. The outer two D-domain nodules are composed of the C-terminal two thirds of both the Bβ and γ chains. X-ray diffraction studies suggest that the Bβ and γ chain each form an independent subdomain within the D-domain. These two subdomains are located diagonally along the long axis of the molecule. Between the E- and D- domains, there is a stretch of approximately 120 amino acids from each of the three chains that forms an α- helical structure known as the "coiled coil domain". This region of the molecule is supported on both the sides by a set of disulphide bonds called disulphide rings. These rings play an important role in making fibrin mechanically strong and resistant to proteolysis.

The Aα chain is a 610 amino acid polypeptide. It is divided into three distinct domains. The first section of Aα chain (residues 1-194) contains a region (residues 45-161) linked to the Bβ and γ chains by disulfide bonds. This section

**FIGURE - 8**



forms part of the α-4helix or coiled coil domain. This first section also contains fibrinopeptide-A (residues 1-16) and the polymerization site in the E-domain.

The middle third of the molecule (residues 240-424) is extremely rich in a polar amino acids and contain 10 tandem repeats each 13 amino acids long. The region bridging these first two sections (residues 195-239) is composed of a protease sensitive domain containing a high content of pralines as well as several plasmin cleavage sites. There are two glutamine residues in the midsection that serve as important cross-linking receptor sites for factor XIIIa. Within the hydrophilic C-terminal third molecule (residues 425-610) are the cross-linking sites for both fibronectin and α-2 antiplasmin. There are also two RGD (arginine, glycine and aspartic acid) sequences (residues 95-97 and 572-574) located in the Aα chain which play a role in cellular adhesion events.

The Bβ chain is a polypeptide composed of 461 amino acids and is also divided into three sections. The first 80 residues contain the fibrinopeptide B sequence (residues 1-15) and a site that supports endothelial cell spreading and proliferation (residues 15-42) The middle section (residues 81-192) is linked to the Aα and γ chains through disulphide rings and forms part of the coiled-coil domain. The C-terminus of the Bβ chain forms one of the independently folded sub domains of the D-domain.

The γ chain is only 411 amino acids long and is also divided into three distinct sections. Unlike the Aα and Bβ chains, there is no fibrinopeptide at the NH2- terminus of the γ chain. The first 18 amino acids of the γ chain form part of the NH2-terminal disulfide knot. The middle segment of this polypeptide consists of amino acids 19-135. This section contains the disulfide rings that link this region to the Aα and Bβ chains in the coiled-coil domain. The C-terminal section containing amino acids 136-411 forms a globular sub domain of the D-domain. Within this region is the D-domain polymerization site, the factor XIIIa cross-linking sites, and the binding domain important for platelet aggregation (residues 400-411)

There are 2 distinct forms of the γ chains in the human plasma fibrinogen. Approximately 15% of the γ chain contain an extended C-terminal and are designated γ1 chains. The γ1 chain is produced by alternative polyadenylation of the last intron of the γ chain gene. Although fibrin polymerization and cross linking of γ1 proceed normally, the γ1 chain does not support platelet aggregation. The clinical significance of the γ1 chain remains unknown; however, recent studies suggest that γ1 is a carrier for zymogen of factor XIII in circulating blood.

The Bβ and γ chains of fibrinogen contain asparagine residues that serve as N-glycosidic linkages for carbohydrate attachment. In a variety of diseases involving hepatic injury, a fetal form of fibrinogen is produced that has increased amounts of sialic acid attached to the carbohydrate side chains.

This results in defective fibrin polymerization, and is associated with hepatomas and cirrhosis. The polymerization defect in fetal fibrinogen does not cause any bleeding disorder, although it can produce a significant prolongation of clotting time when assayed in vitro.

Electron microscopic examination has revealed a trinodular structure with a central nodule (fragments E) linked through 2 thin rods (fragments D) to two peripheral nodules.

**SYNTHESIS**

Plasma fibrinogen is synthesized exclusively by the hepatocyte, and the synthesis of the three chains is under the coordinated control of three separate genes localized on chromosome 4(ch4q23-q32). Subsequent to the assembly of the constituent polypeptide chains and the addition of carbohydrate side chain (3%), the mature molecule is secreted into the circulation, where it manifests the half-life of 72-108 hours and fractional catabolic rate of 25% per day. The turnover rate of fibrinogen is about 1.7-5 gm/day (30-60mg/kg/day).

**FUNCTION**

Fibrinogen plays the central role in three major functional processes.

1. The soluble fibrinogen molecule is converted into insoluble fibrin during the process of blood coagulation.

2. The polymerized fibrin serves as a template for the localized assembly and activation of the fibrinolytic system, which modulates fibrin deposition and

clot dissolution.

3. Fibrinogen binds to vascular cells such as platelets, where it supports platelet aggregation by binding to platelet GP IIb-IIIa receptors and to endothelial cells, where it participates in tissue repair

The conversion of fibrinogen into insoluble fibrin can be divided into three distinct phases.

1. Enzymatic cleavage of fibrinopeptide by thrombin.

2. Fibrin polymerization.

3. Fibrin stabilization, via covalent cross-linking by factor XIIIa.

**FIBRINOGEN ABNORMALITIES**

Classified as congenital or acquired, with both groups manifesting quantitative defects or qualitative differences of fibrinogen molecules. In few instances, both quantitative and qualitative abnormalities can be present in the same patient.

**a) CONGENITAL DISORDERS**

**i. Congenital Afibrinogenemia and Hypofibrinogenemia**

They are familial and cause bleeding disorders of varying severity from birth. Sometimes low fibrinogen may be an abnormal molecule then it is called hypodysfibrinogenemia. CT, PT and aPTT are abnormal.

**ii. Congenital dysfibrinogenemia.**

It is characterized by biosynthesis of a structurally abnormal fibrinogen

molecule that exhibits altered functional properties and commonly exhibits an abnormal thrombin mediated conversion to fibrin. The various mutants described carry the name of the city of origin of the patient initially affected with a particular dysfibrinogenemia. Functional abnormalities are usually reflected as abnormalities in one or more phases of fibrinogen to fibrin conversion.

These include:

1. Impaired release of fibrinopeptides.

2. Defects in fibrin polymerization.

3. Failure of polymerized fibrin to undergo normal covalent stabilization by factor XIIIa.

4. Abnormal interaction with platelets, endothelial cells or calcium.

Most patients are asymptomatic. Prothrombin time is prolonged. Plasma fibrinogen concentration is normal when measured immunologically and the discrepancy between clotable protein and immunologically measured fibrinogen is a characteristic feature of dysfibrinogenemia.

**b.) ACQUIRED DISORDERS**

**HYPERFIBRINOGENEMIA**

Various causes for elevated fibrinogen level are,

1. **Advanced age:** It has been observed in various epidemiological studies that plasma fibrinogen level increases with increasing age.

2. **Gender:** Males have a higher fibrinogen levels than females.

3. **Race:** Fibrinogen is about 0.2gm/L higher in blacks than in whites.

4. **Smoking:** Smoking is a very important influencing factor for fibrinogen levels. There is a positive correlation between smoking and plasma fibrinogen levels; fibrinogen level begins to fall soon after smoking is discontinued. The consistent observation of higher plasma fibrinogen levels in heavy smokers, independent of age, may be explained by two hypothesis;

a) Smoking may lead to endothelial damage resulting in activation of the coagulation system.

b) Smoking activates lung macrophages which release interleukin-6 increasing liver synthesis of fibrinogen[75].

**5. Physical inactivity:** There is an inverse relationship between physical activity and fibrinogen concentration.

6. **Diet:** Diet rich in carbohydrates and fat and diet poor in ω-3 and ω-6 PUFA's and fibre are associated with raised fibrinogen levels.

7. **Excess body weight:** In obese patients, plasma viscosity and fibrinogen levels are increased.

8. **Hyperlipidemia:**

9. **Diabetes Mellitus**.

10. **Hypertension**

11. **Ischemic heart disease:**

12. **Left ventricular dysfunction:** There is an increased risk of intracardiac thrombus and systemic thromboembolism in patients with poor cardiac function, especially in those with ventricular aneurysm and dilated cardiomyopathy. The increased risk of thrombosis in patients with left ventricular dysfunction is increased because of increased fibrinogen levels as compared to patients with normal left ventricular function[76].

13. **Atrial fibrillation-** Plasma fibrinogen levels are elevated in patients with chronicatrial fibrillation.

14. **Psychological and mental stress-** It has been shown to increase plasma fibrinogen concentration.

15. **Cerebrovascular disease-** Increased fibrinogen was correlated with stroke and TIA incidence and progression of carotid atherosclerotic lesion[77]. Peripheral vascular disease is associated with increased fibrinogen concentration. Fibrinogen levels have been found to be higher in those women who are taking oral contraceptives and in postmenopausal age.

16.**Social class-** Fibrinogen has been found to be higher in lower socioeconomic class.

17. **Family history of IHD** -Fibrinogen is raised in individuals with family history of ischemic heart disease.

18. **Genetic factors-** There is a significant genetic influence on plasma fibrinogen formation and genetic inheritability may account for up to 51% of variance of the plasma fibrinogen level. Variation at the beta fibrinogen

locus has been thought to affect fibrinogen concentration, because the beta gene control formation of Bβ chains, the rate limiting step in fibrinogen synthesis. Individuals with B1B2 genotype who have high fibrinogen levels are at increased risk of atherosclerosis[76].

19. **Dental disease-** Chronic inflammatory gingival and periodontal infection causes elevation in the levels of plasma fibrinogen.

20. **Elevated leukocyte count-** It is associated with increase in fibrinogen concentration.

21. **Acute inflammation and infections-** Fibrinogen increases by three fold in response to acute inflammation as an acute phase response.

**HYPOFIBRINOGENEMIA**

Hypofibrinogenemia occurs in,

i. Decreased hepatocyte biosynthesis due to fulminant hepatic failure, decompensated liver cirrhosis.

ii. Disseminated intravascular coagulation due to increased consumption.

iii. Use of drugs like L-asparaginase, valproic aced.

iv. Alcohol consumption has a small but significant effect on decreasing plasma fibrinogen. A decrease of approximately 0.78% per 10gm of alcohol consumed has been noted.

v. Fibrinolytic therapy reduced fibrinogen levels for a day or two.

## DYSFIBRINOGENEMIA:

### Dysfibrinogenemia of liver disease

About 50% of patients with cirrhosis or hepatitis or hepatoma exhibit dysfibrinogenemia characterized functionally by impaired polymerization of fibrin. Similar changes have also been observed in hypernephroma as a part of paraneoplastic syndrome.

Antibodies against fibrinogen can cause functional abnormalities of fibrinogen as seen in SLE, ulcerative colitis and post-necrotic cirrhosis or sometimes can be idiopathic. Inhibition of fibrin monomer polymerization is seen in multiple myeloma.

# MATERIALS AND METHODS

This study was conducted in our medical college hospital. Patients were recruited from medicals wards and IMCU. A total of about 110 patients were selected and 10 of them were excluded as per exclusion criteria used. The remaining 100 patients were included in the study. Informed consent was obtained from all patients. Plasma fibrinogen value was estimated in all 100 patients admitted with stroke who got admitted within 24 hours of stroke onset.

## INCLUSION CRITERIA

Patients who got admitted in our hospital within 24 hours of the onset of stroke.

## EXCLUSION CRITERIA

1. Patients admitted with stroke more than 24 hours from onset.
2. Patients refused to give consent for the study,
3. Patients having renal failure,
4. Inflammatory disease,
5. Active viral hepatitis,
6. Infection,
7. Severe dehydration
8. History of myocardial infarction or

9. Surgery in 3 months.
10. Patients having space occupying lesions,
11. Subdural hematoma.

**METHODOLOGY**

For all the 100 cases admitted, detailed clinical examination done and history was taken regarding smoking, alcohol, diabetes, hypertension, coronary heart disease, renal disease, any infection, surgery, trauma. Blood sugar, ECG and routine investigation was done. CT BRAIN was done in all patients to classify ischemic or haemorrhagic stroke. And for all the patients in our study Scandinavian stoke scale was calculated at the time of admission. Also modified Rankin score was calculated in all the patients during the time of admission and discharge.

Plasma fibrinogen was measured in all these 100 patients who are included in the study and the values interpreted.

## PLASMA FIBRINOGEN

### MEASUREMENT OF FIBRINOGEN [78-79]

There are many fibrinogen assays available in various laboratories. Out of all, the clauss method is the one that is most commonly used to determine plasma fibrinogen value in most of the laboratories. Few of the tests are designed for an emergency situation where we need only to know whether the value is elevated or decreased. The exact fibrinogen value is not needed at certain times.

### PREREQUISITE

WHO recommends tri-sodium citrate to be used as an anticoagulant for determining plasma fibrinogen value. The strength most commonly used is 0.105 to 0.109m.

The sample to be used should contain 1 part of anticoagulant and 9 parts of blood. Under strict aseptic precautions the blood should be drawn rapidly from the venepuncture site with minimal stasis and transferred to citrated container.

This sample should be inverted gently to look for any clots. In the presence of clot or hemolysis the sample should not be used and discarded as this may interfere with fibrinogen value. The blood sample collected can be stored at room temperature.

## PREPARATION OF PLASMA

The sample collected should be subjected to centrifuge to remove the platelets. This centrifugation can be performed in room temperature. The resultant plasma can be used immediately or stored in deep freeze at -70$^0$C for maximum of 18 months. The photo optical methods used in determination of fibrinogen may interfere with the samples that are lipaemic or icteric and hence these samples should be avoided.

In case of frozen plasma the sample should be thawed for 5 minutes at 37$^0$C and mixed by inversion before doing analysis.

## FIBRINOGEN ASSAYS [80]

1. CLAUSS ASSAYS

It is the most commonly performed method to determine plasma fibrinogen value. This test based on the rate of clot formation in dilute citrated plasma following the addition of thrombin. The clotting of dilute plasma is inversely proportional to the plasma fibrinogen concentration when high concentration of thrombin is used. In this procedure a high concentration of thrombin say 100μ/ml is added to platelet poor plasma and the clotting time is measured.

The high concentration of thrombin that is added to plasma ensures that wide fibrinogen values are independent of thrombin concentration. . The clotting end point is measured by either mechanical or photo-optical means, as these methods have shown excellent cross correlation and precision.

The results are plotted in a calibration curve made from clotting times with serial dilution and fibrinogen concentration. The result obtained will be in mg/dl.

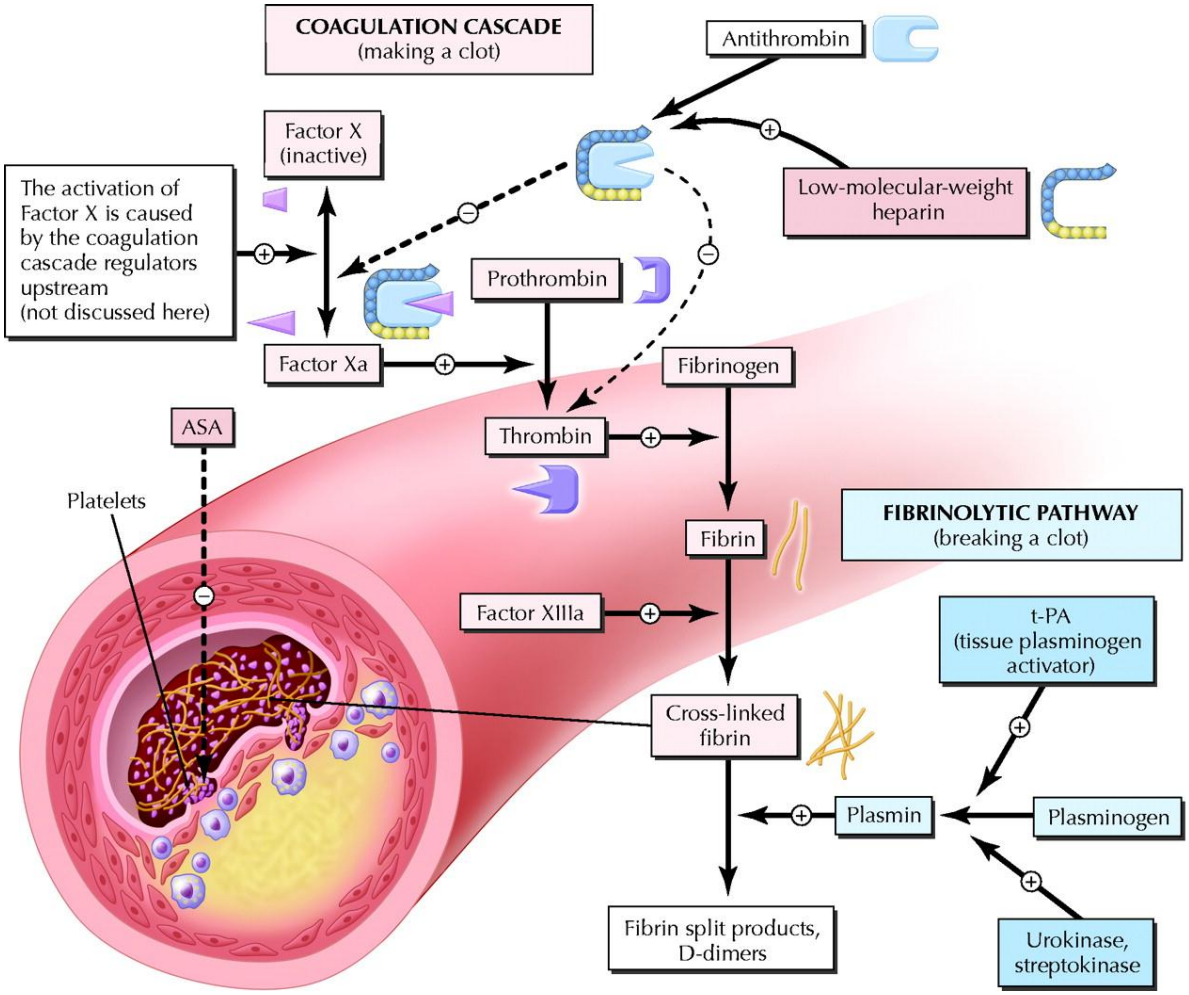
As this type of assay measures the time to formation of a detectable clot, the presence of inhibitors of fibrin polymerization, such as fibrinogen and14 fibrinogen degradation products results in under estimation of the actual fibrinogen concentration.

The normal reference value is 200 to 400 mg/dl.

**PT - BASED TESTS**

In this method prothrombin time is determined by optical density change in platelet poor plasma and compared with derived fibrinogen in a calibration curve.

## FIGURE-9 COAGULATION CASCADE




The other methods to determine fibrinogen include;

1. Gravimetric method

2. Immunological

3. Salting out.

**SCANDINAVIAN STROKE SCALE (SSS)**

CONCIOUSNESS

- Fully conscious - 6
- Somnolent, awaked to full conscious level-4
- Not fully conscious, but reacts to verbal commands-2
- Coma-0

Eye movement

- Without gaze palsy-4
- With gaze palsy-2
- Conjugate eye deviation-0

Speech

- Without aphasia-10
- Limited expression or comprehension-6
- More than yes or no, but no longer sentences-3
- Only yes or no or less than that-0

Orientation

- Oriented to person place and time-6
- Any two present-4
- Any one present-2

- ❖ Fully disoriented-0

Gait

- ❖ Walks 5 or more meter without aid-12
- ❖ Can walk with aid-9
- ❖ Can walk with another person help-6
- ❖ Sits without any support-3
- ❖ Wheelchair bound or bedridden-0

Facial palsy

- ❖ Absent-2
- ❖ Present-0

Arm, motor power (tested on affected side)

- ❖ Can lift the arm with normal power-6
- ❖ Can lift the arm with reduced power-5
- ❖ Raises the arm with flexion in elbow-4
- ❖ Able to move but not against gravity-2
- ❖ Total paralysis-0

Hand, motor power (tested on affected side)

- ❖ Normal strength-6
- ❖ Reduced strength in full range-4

- ❖ Some movement, without fingertip reaching the arm-2
- ❖ Total paralysis-0

Leg motor power (tested on affected side)

- ❖ Normal strength-6
- ❖ Raises leg with decreased strength-5
- ❖ Raises leg with flexion of knee-4
- ❖ Can move, but not against gravity-2
- ❖ Total Paralysis-0

**MODIFIED RANKIN SCORE (MRS)**

- ❖ No symptoms-0
- ❖ No disability despite of the symptoms-1
- ❖ Slight disability present, but does not require any assistance-2
- ❖ Moderate disability, patient can walk without assistance-3
- ❖ Moderately severe disability, not able to walk without assistance-4
- ❖ Severe disability, bedridden and incontinent-5
- ❖ Dead-6.

# OBSERVATIONS AND RESULTS

## AGE DISTRIBUTION

Out of 100 patients participated in the study 53 were aged less than 60 years and 47 were aged more than 60 years.

The mean age comes around 59.

| Age in years | Number of patients | Percentage |
|---|---|---|
| Less than 60 | 53 | 53% |
| More than 60 | 47 | 47% |

## SEX DISTRIBUTION

Out of 100 patients 58 were male patients and 42 were female patients.

| Sex | Number of patients | Percentage |
|---|---|---|
| Male | 58 | 58% |
| Female | 42 | 42% |

**SMOKERS**

| | Number of patients | Percentage |
|---|---|---|
| Smokers | 37 | 37% |
| Non smokers | 63 | 63% |

Out of 100 persons 37 were known smokers and 63 were non smokers.

Alcoholics constitute about 19% among the total patients.

Both the alcoholic and smoking are seen only in men.

**ALCOHOLICS**

| | Number of patients | Percentage |
|---|---|---|
| Alcoholics | 19 | 19% |
| Non alcoholics | 81 | 81% |

Both smoker and alcoholic were 12% of the patients.

## SYSTEMIC HYPERTENSION

40 % of the patients in our study are known case of systemic hypertension.

| | Number of patients | Percentage |
|---|---|---|
| Known SHT | 40 | 40% |
| Non Hypertensives | 60 | 60% |

## DIABETES

25% of patients are diabetics in our study.

| Diabetes | Number of patients | Percentage |
|---|---|---|
| Present | 25 | 25% |
| Absent | 75 | 75% |

Both diabetes and hypertensive patients were 5% in our study.

**TYPE OF STROKE**

Ischemic stroke comprises about 88% and haemorrhagic stroke constitutes about 12%

| Stroke | Number of patients | Percentage |
|---|---|---|
| Ischaemic | 88 | 88% |
| Haemorrhagic | 12 | 12% |

Out of 100 cases 12 cases were expired. In most of the cases the infarct is within the middle cerebral artery territory.

**AGE**

In our study the minimum age recorded is 30 years and the maximal age is 85 years and the mean age comes 58.87 with standard deviation of 12.152.

| | N | Minimum | Maximum | Mean | Std. Deviation |
|---|---|---|---|---|---|
| Age in years | 100 | 30 | 85 | 58.87 | 12.154 |

**SYSTOLIC BLOOD PRESSURE**

The mean systolic blood pressure is 144.4 with lowest recording of 110 and highest 200 with standard deviation of 21.896.

| | Number | Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|---|---|
| SBP | 100 | 110 | 200 | 144.40 | 21.896 |

**DIASTOLIC BLOOD PRESSURE**

In our study the diastolic blood pressure recorded to the lowest was 60 and highest was 110 with mean 83.45 and standard deviation 11.38

| | Number | Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|---|---|
| DBP | 100 | 60 | 110 | 83.45 | 11.38 |

**SSS**

Scandinavian stroke scale (SSS) is a measure of severity of stroke. Total score is 58. Out of which the Scandinavian stroke scale for our patients ranges from 4 to 44 with mean value of 29.91 and standard deviation of 10.107.

| | Number | Minimum | Maximum | Mean | Standard Deviation |
|---|---|---|---|---|---|
| SSS | 100 | 4 | 44 | 29.91 | 10.107 |

## MODIFIED RANKIN SCALE (MRS)

Modified Rankin scale (MRS) is the one which is used to measure the functional outcome of patient in our study. This score ranges from 0 to 6 which varies from no symptoms to death. This modified Rankin scale is calculated at the time of admission and discharge.

At the time of admission this values varied from 2 to 5 with mean 3.96 and standard deviation of 0.984.

During discharge the scale ranges from 1 to 5 with a mean of 2.85 and standard deviation of 1.209. This scale is calculated only in 88 patients out of 100 as 12 patients were expired during the period of hospital stay.

| | Number | Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|---|---|
| MRS-admission | 100 | 2 | 5 | 3.96 | 0.984 |
| MRS-discharge | 88 | 1 | 5 | 2.85 | 1.209 |

**FIBRINOGEN**

Plasma fibrinogen was measured for all the patients in our study as soon as they got admitted. It is noted that lowest value seen in our patients is 179 and highest value 530. The mean value is 405.46 and standard deviation is 83.459.

| | Number | Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|---|---|
| Plasma fibrinogen | 100 | 179 | 530 | 405.6 | 83.459 |

**RANDOM BLOOD SUGAR**

The random blood sugar was estimated in all patients and the results are summarised below.

| | Number | Minimum | Maximum | Mean | Standard deviation |
|---|---|---|---|---|---|
| Random blood sugar | 100 | 82 | 402 | 207.63 | 83.459 |

Then we analysed the correlation coefficient using pearson method. We compared fibrinogen value with Scandinavian stroke scale, modified

Rankin scale at admission and discharge, systolic blood pressure, diastolic blood pressure and random blood sugar.

The correlation coefficient is more in MRS-admission and discharge and Scandinavian stroke scale.

The correlation between fibrinogen value and Scandinavian stroke scale was assessed and found to be statistically significant.

The P value obtained is <0.01 where the relation is highly significant.

**LEVELS OF CORRELATION WITH PLASMA FIBRINOGEN**

| FACTORS | CORRELATION COEFFFICIENT |
|---|---|
| SBP | 0.083 |
| DBP | 0.054 |
| BLOOD SUGAR | 0.231 |
| SSS | 0.506 |
| MRS-ADMISSION | 0.594 |
| MRS-DISCHARGE | 0.582 |

Similarly modified Rankin scale at the time of admission and discharge also correlated with fibrinogen value and found to be statistically significant with P value <0.01.

And also we correlated fibrinogen value with the four important risk factors like Diabetes, Smoking, Hypertension and alcoholism.

Even though the mean value is increased in smokers compared to non-smokers, in our study we could not establish a statistically significant relationship.

| | Mean fibrinogen | Standard deviation |
|---|---|---|
| Smokers | 412.86 | 73.364 |
| Non smokers | 401.22 | 89.197 |

## CHARTS AND GRAPHS

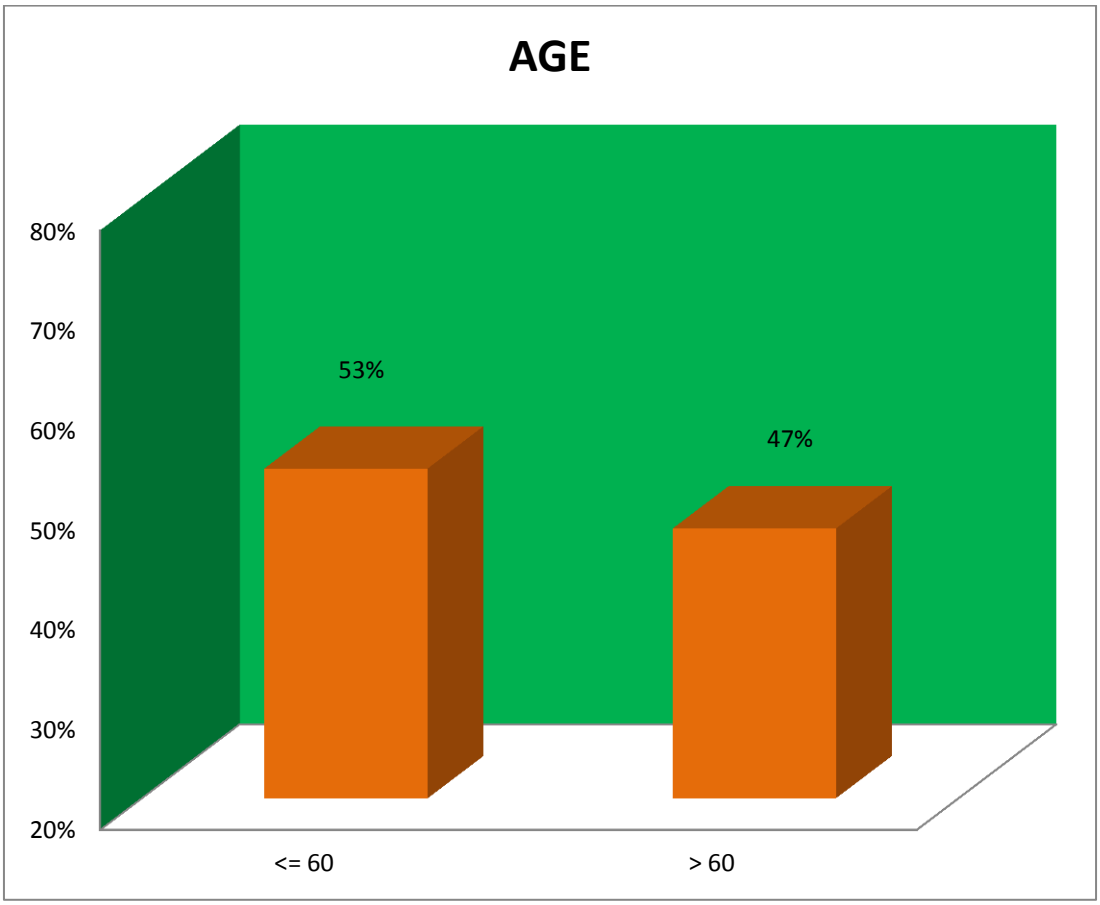



**FIGURE-10 AGE DRISTIBUTION**

This figure depicts that 53 percentage of stroke patients from our study are aged less than 60 and 47 percentage above 60.

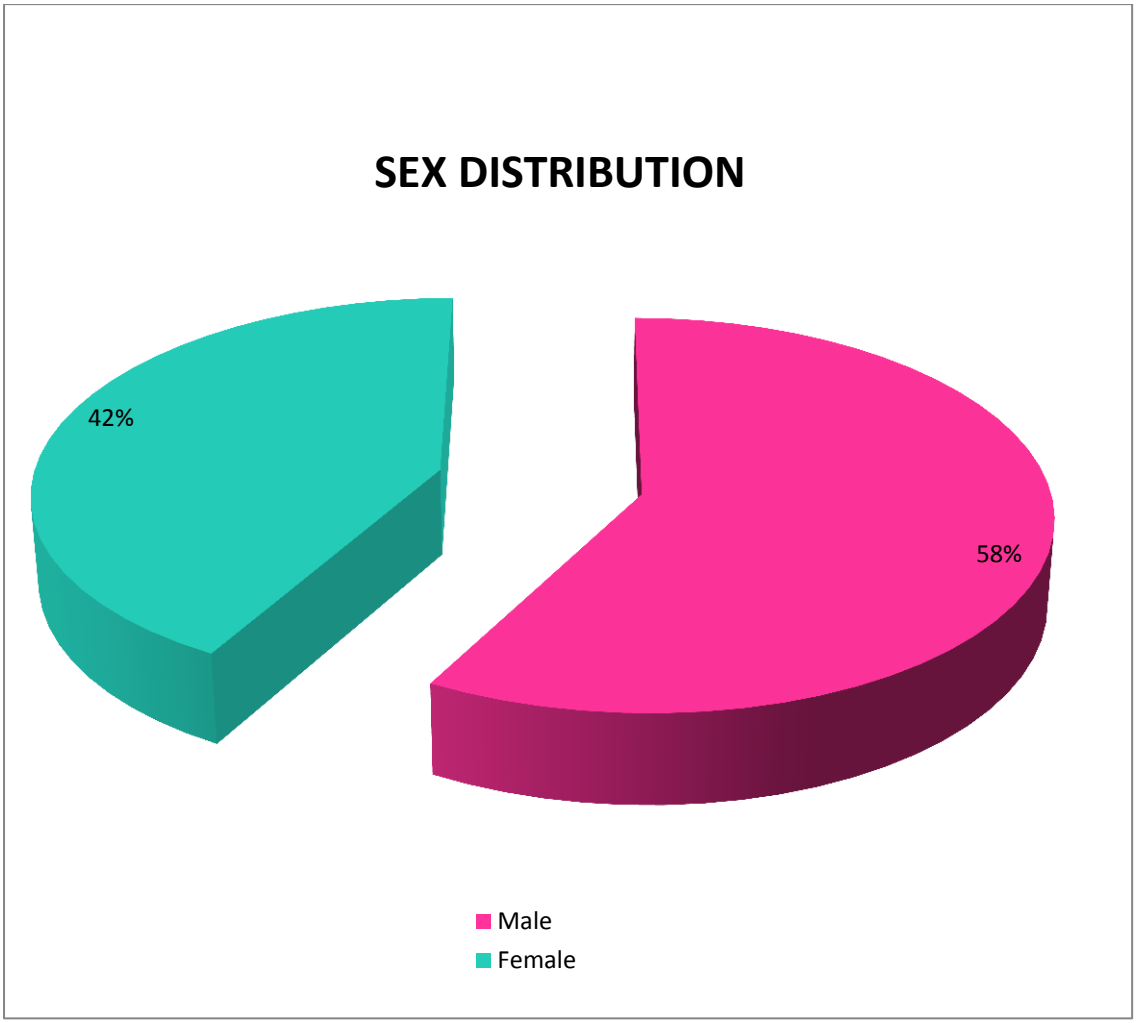



**FIGURE-11 SEX DISTRIBUTION**

This graph depicts the male and female distribution among stroke. The prevalence among male is more in this study which comes around 58%.The important risk factors like smoking and alcohol is exclusively seen in males.

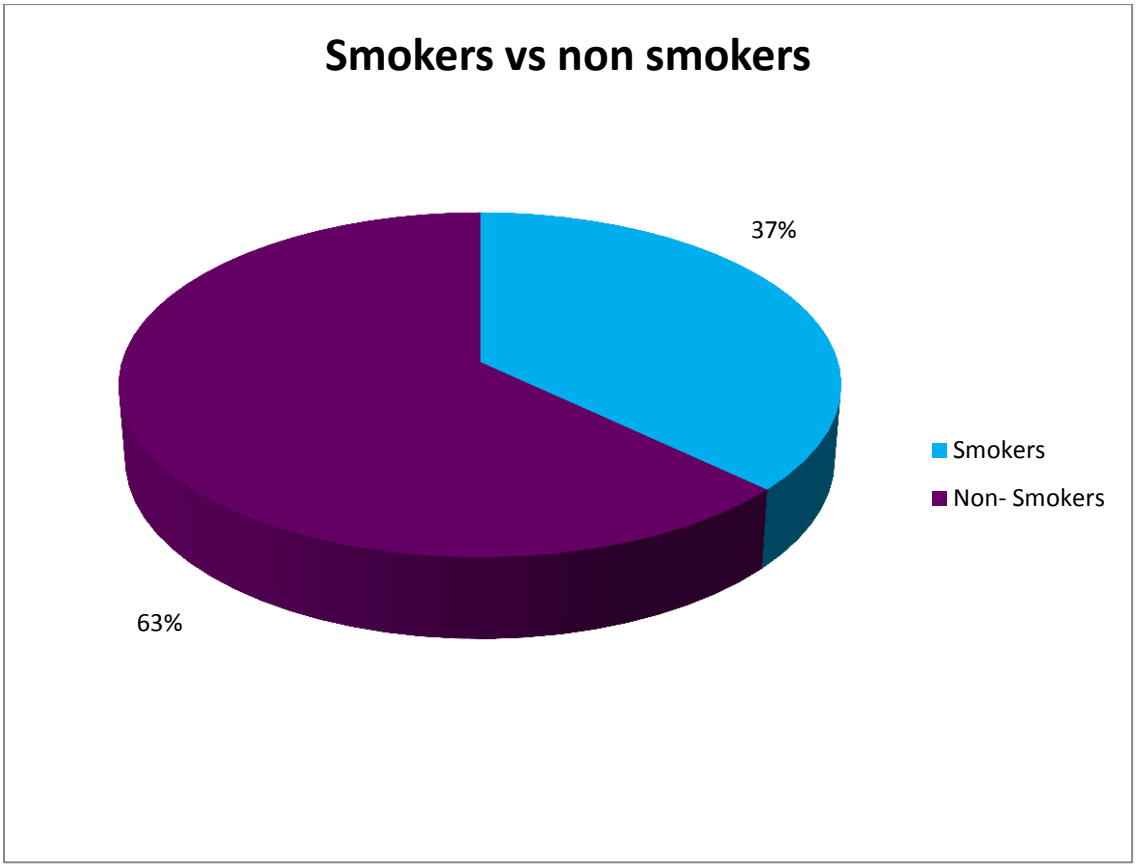



**FIGURE-12 SMOKERS VS NON SMOKERS**

This picture depicts the burden of smoking in stroke. About 37 % of total patients in our study group are smokers. This includes present smoking and persons who have already quit smoking.

And the smoking is almost exclusively present only in males.

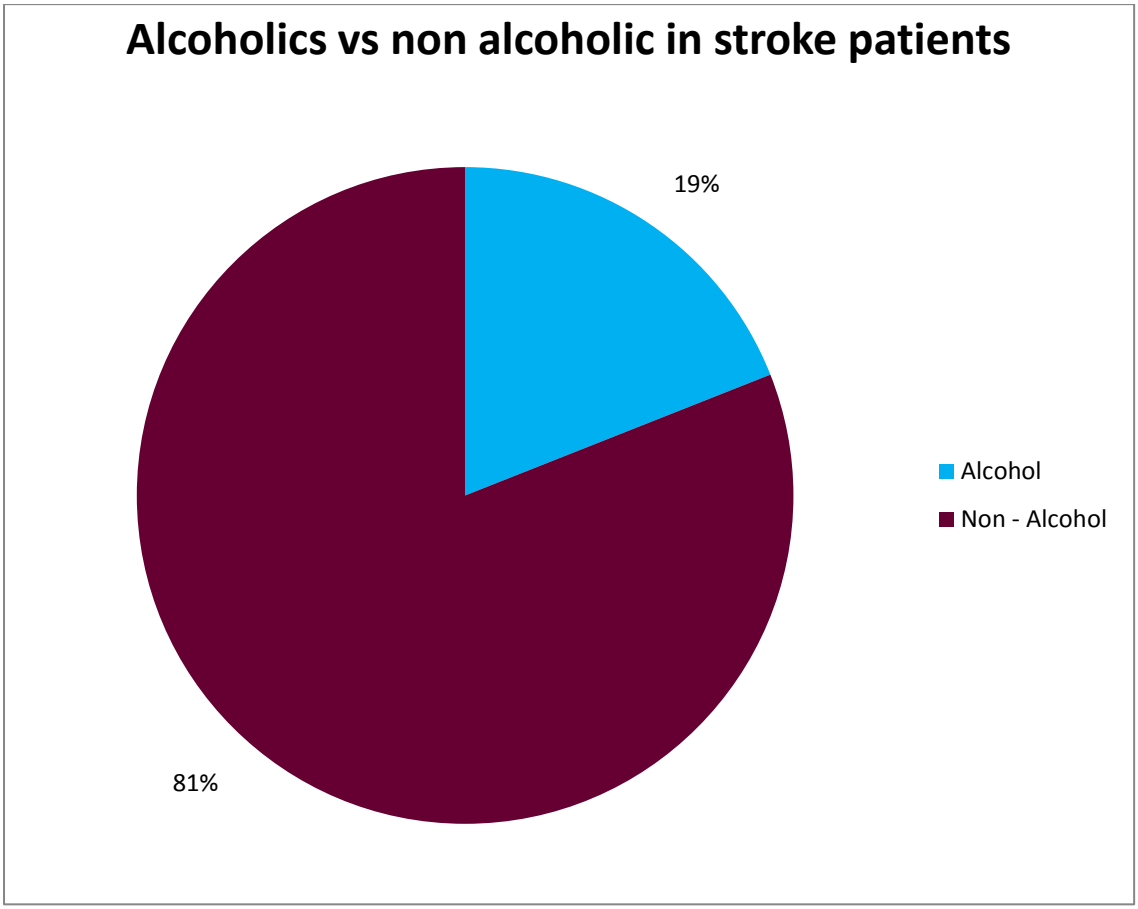



**FIGURE-13 ALCOHOLICS VS NON ALCOHOLIC IN STROKE PATIENTS**

In our study the alcoholic constitutes about 19% and remaining 81% are non-alcoholics and alcoholism was almost exclusively seen in males.

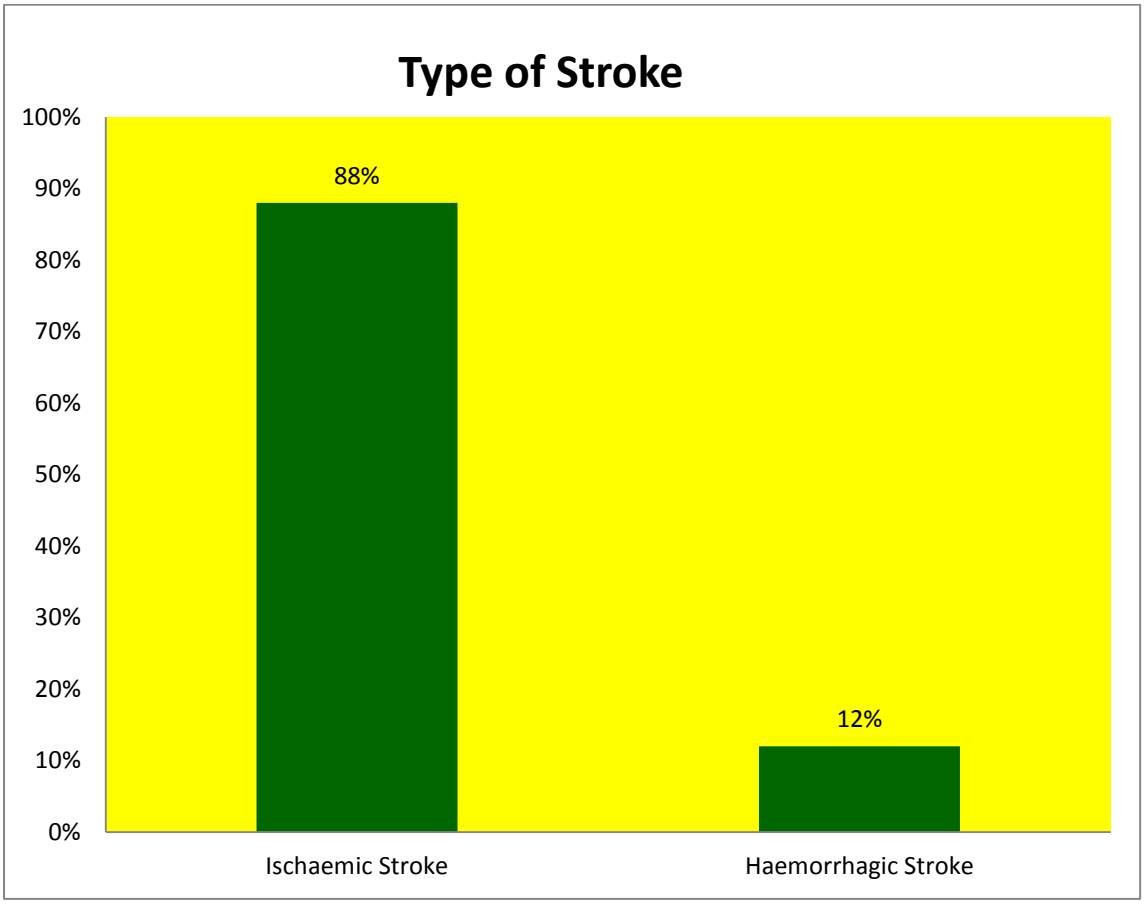



**FIGURE-14 TYPE OF STROKE**

In our study the most common type of stroke is ischemic stroke with a total of 88% and haemorrhagic stroke constitutes about 12%

Hence here also it is proved that ischemic is the most common type of stroke.

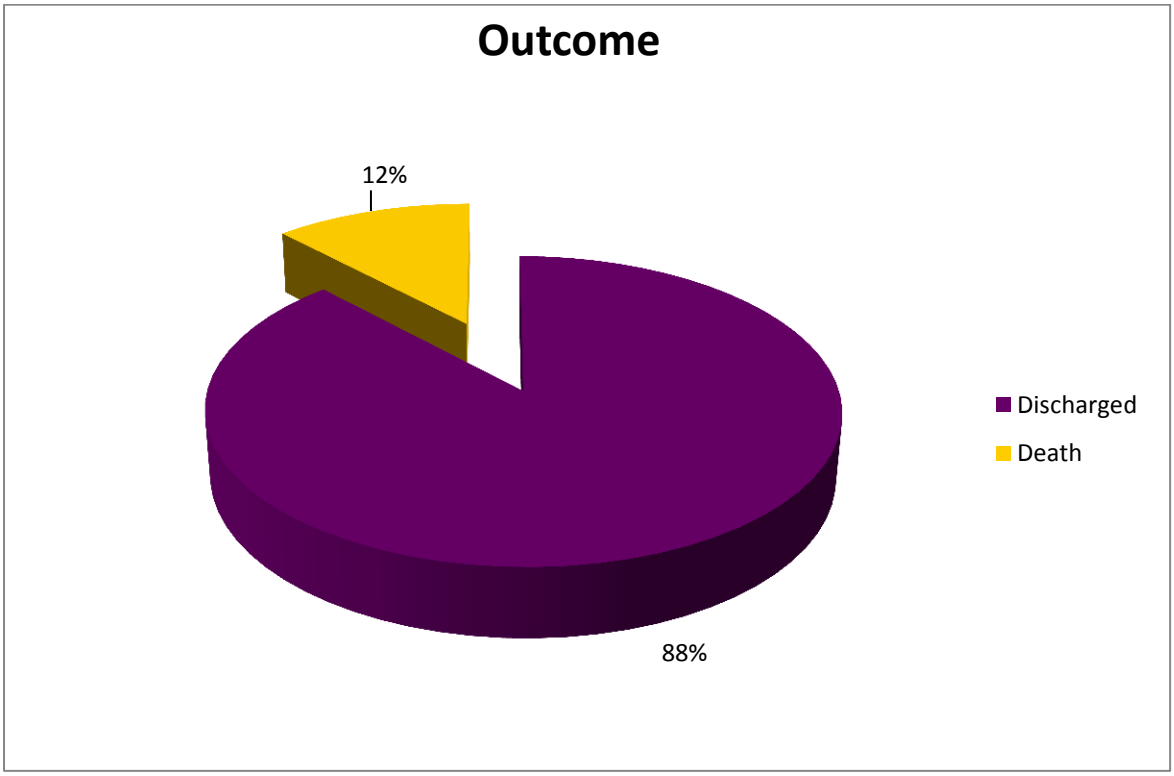



**FIGURE-15 OUTCOME OF STROKE**

Out of 100 patients 12 patients were expired and 88% discharged.

Ischaemic stroke is associated with more mortality in our study group.

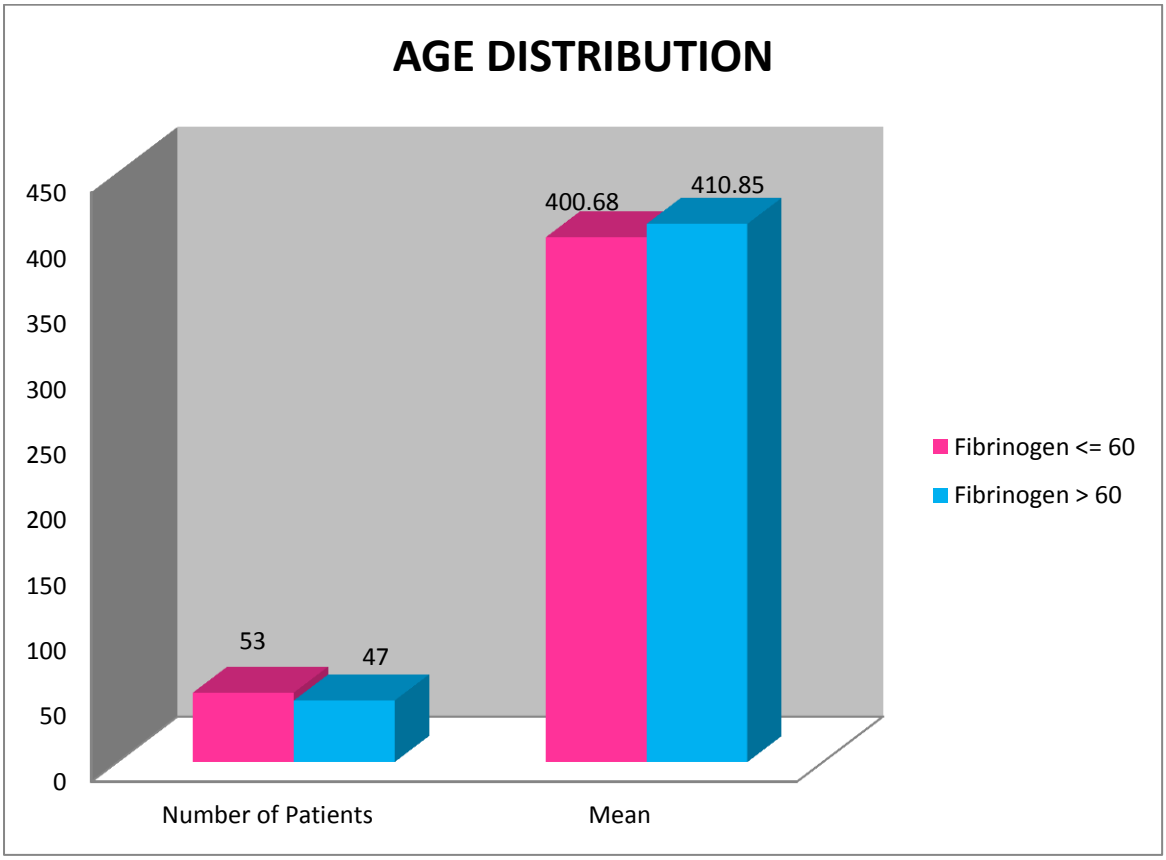



**FIGURE-16 AGE DISTRIBUTION**

This diagram depicts the difference in mean fibrinogen value among the patients aged less than 60 and more than 60. This picture shows that the mean fibrinogen is slightly increased in older individuals with stroke.

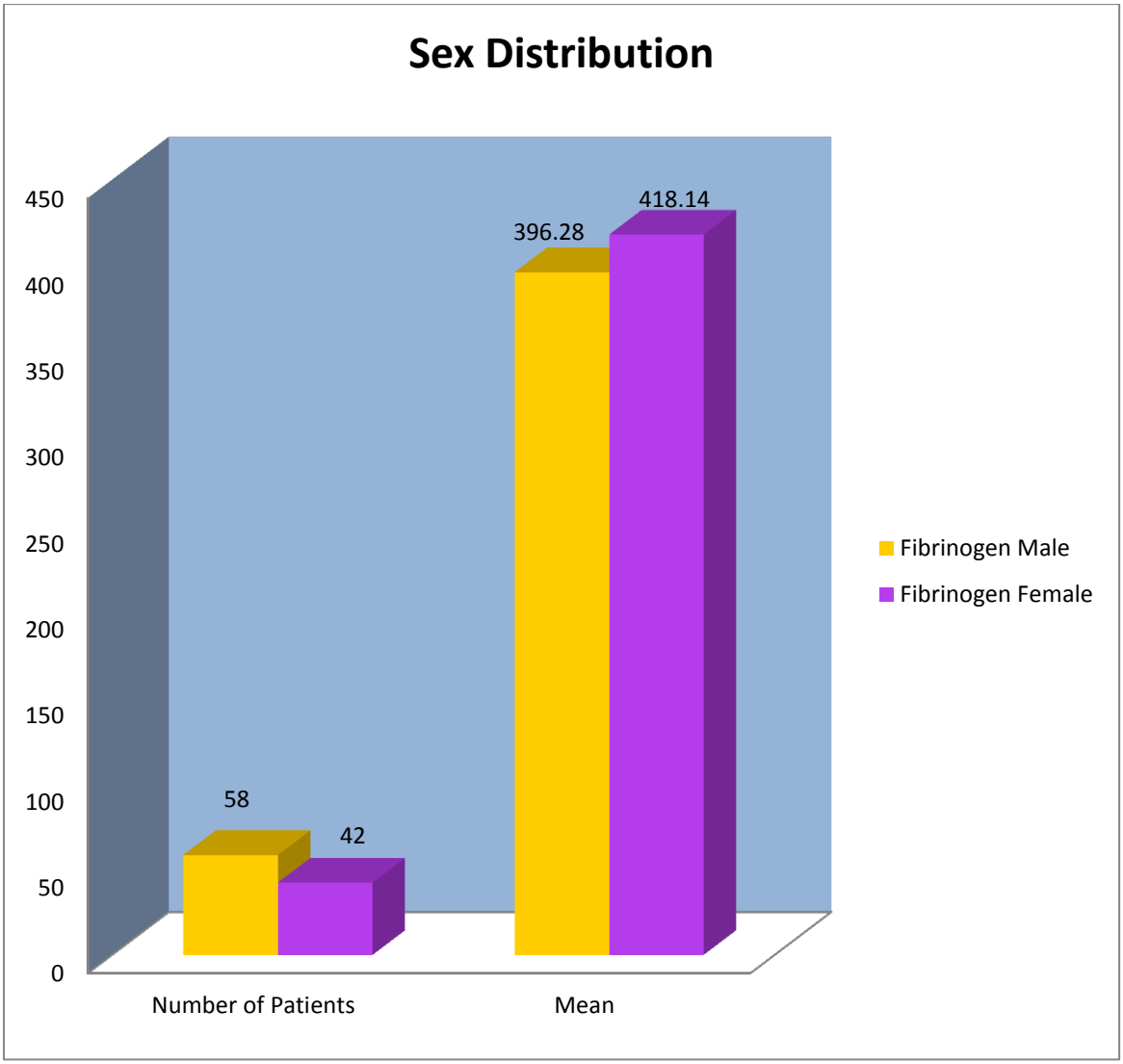



**FIGURE-17 SEX DISTRIBUTION**

This picture depicts the difference in mean fibrinogen value which is slightly higher in female and this increase is not statistically significant.

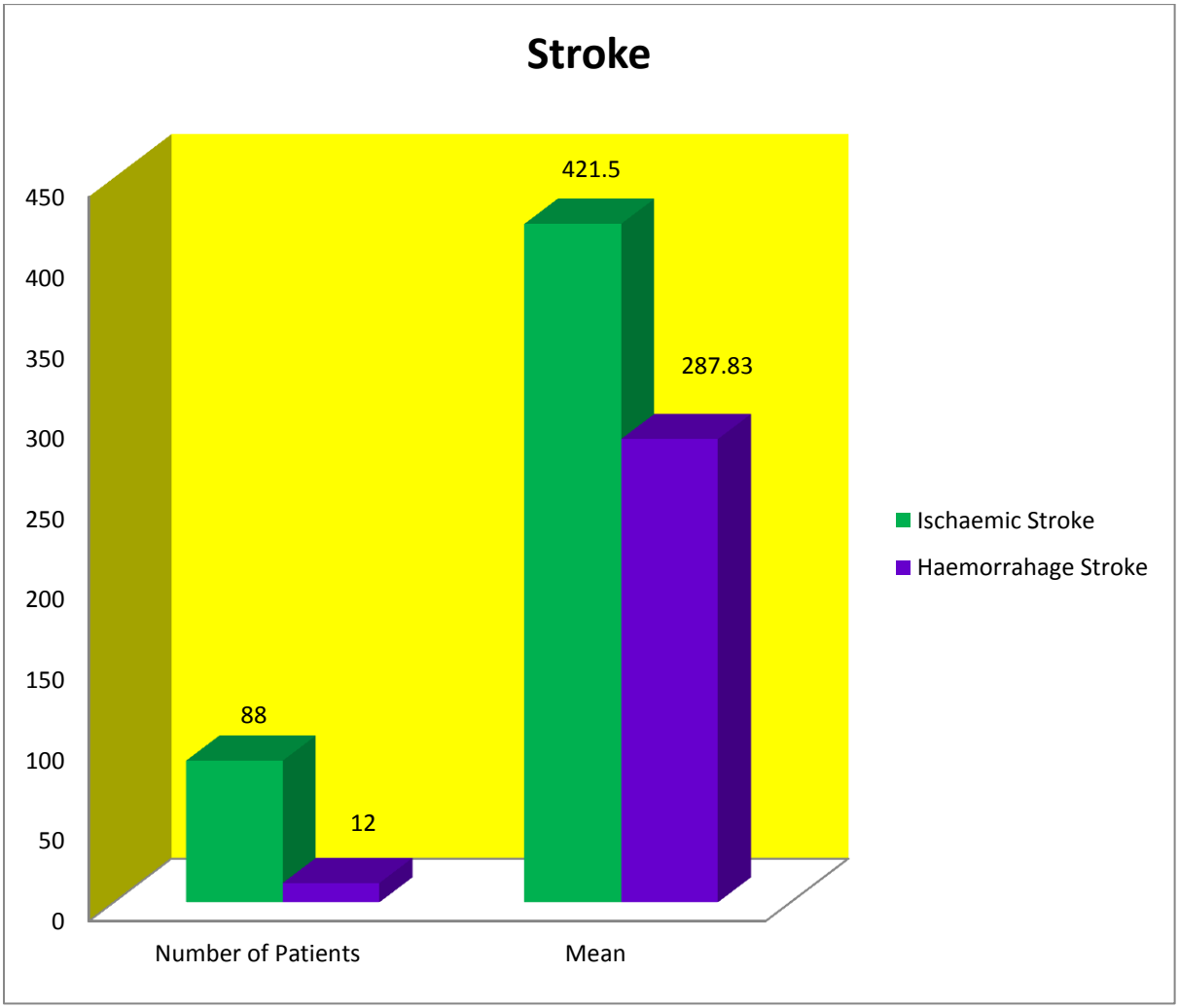



**FIGURE-18 STROKE**

This bar diagram depicts the mean fibrinogen value with ischemic stroke. The mean value is higher in ischemic stroke as compared to haemorrhagic stroke.

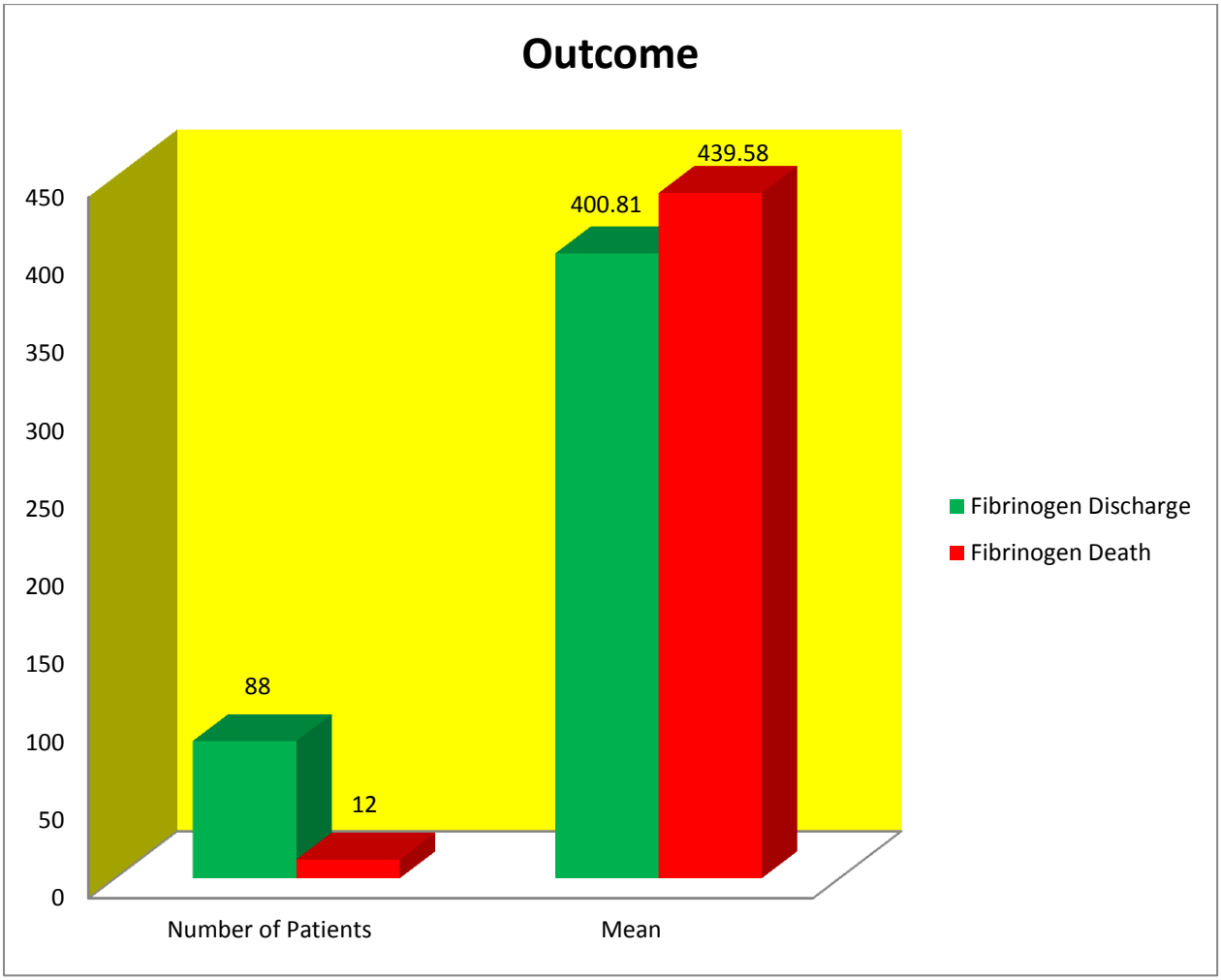



**FIGURE-19 OUTCOME**

This bar diagram represents that mean fibrinogen value was moderately high in patients who expired during the hospital stay.

The mean fibrinogen in death patients was 439.58.

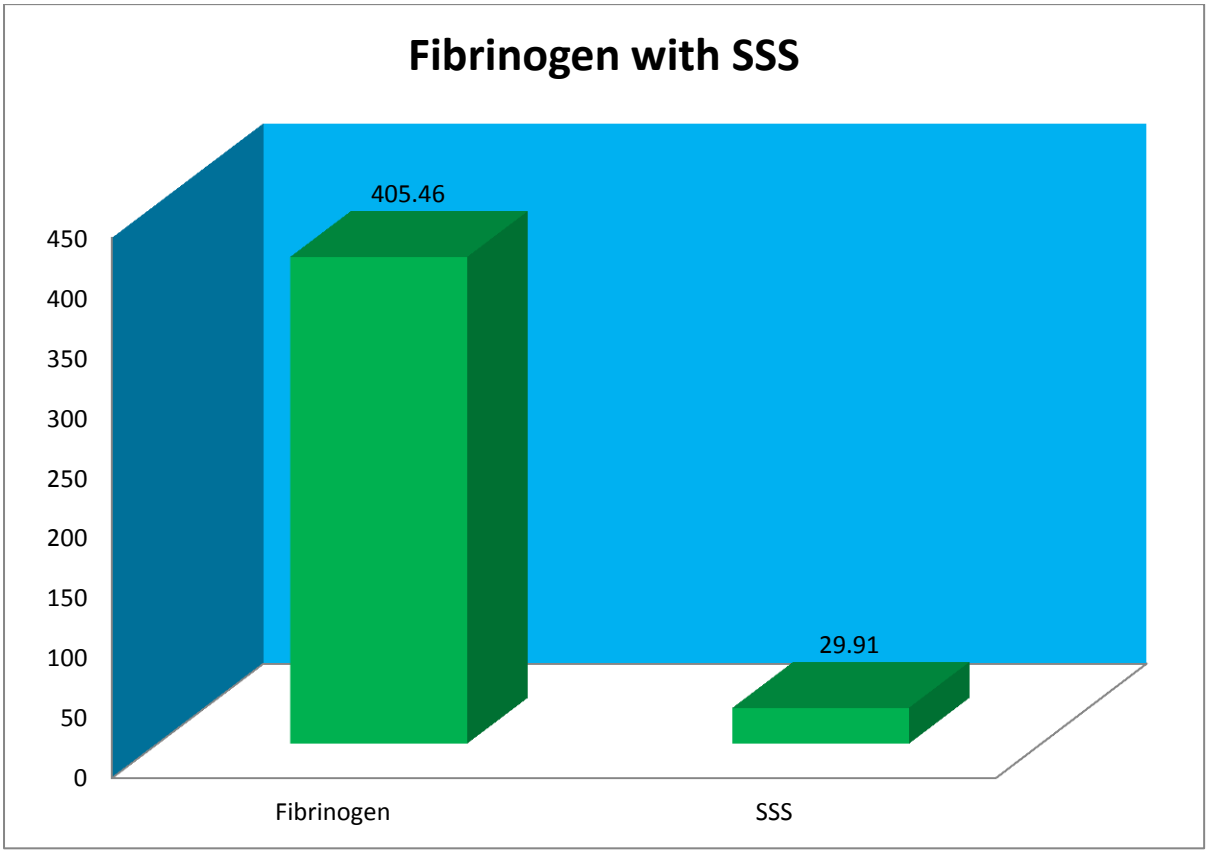



**FIGURE-20 FIBRINOGEN WITH SSS**

Scandinavian stroke scale which measured the severity of stroke patients admitted in our wards. The mean value was 29.91. The correlation between fibrinogen and SSS was statistically significant.

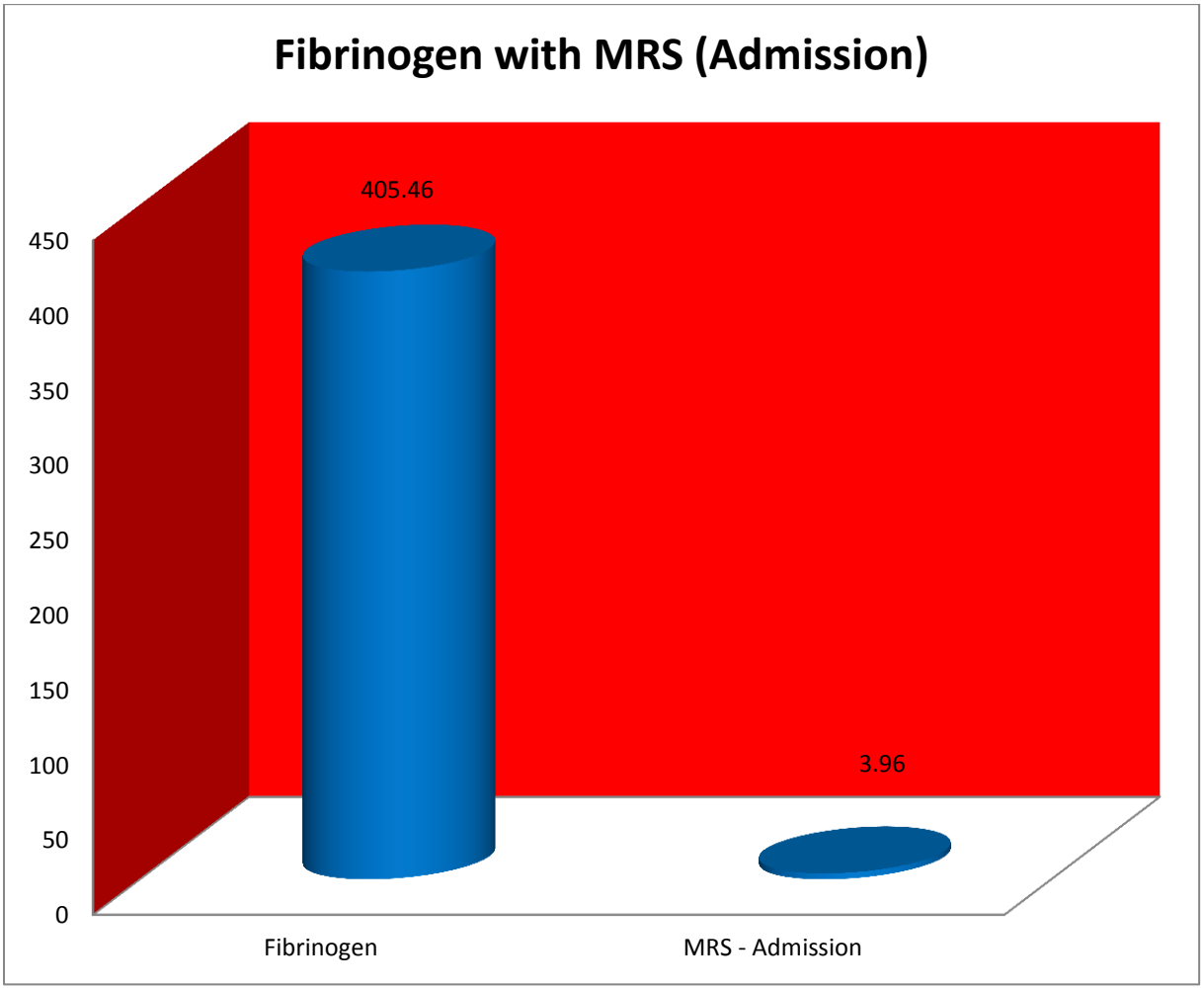



**FIGURE-21 FIBRINOGEN WITH MRS (ADMISSION)**

This picture compares the mean fibrinogen with Modified Rankin scale at the time of admission. The correlation between fibrinogen and MRS at the time of admission was statistically significant.

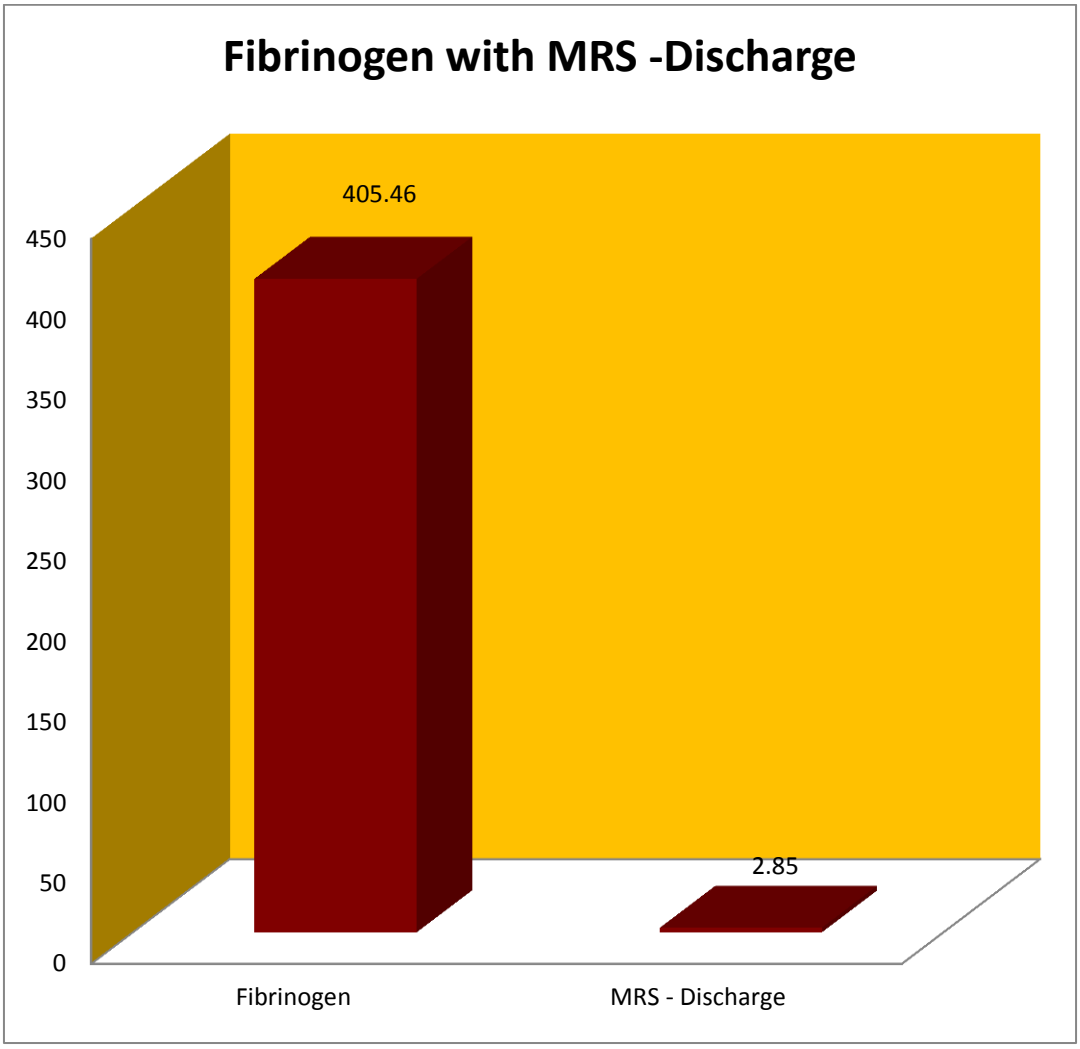



**FIGURE-22 FIBRINOGEN WITH MRS -DISCHARGE**

This diagram shows the mean value of fibrinogen and mean value of modified Rankin scale at the discharge. The mean value of MRS at the time of discharge was 2.85

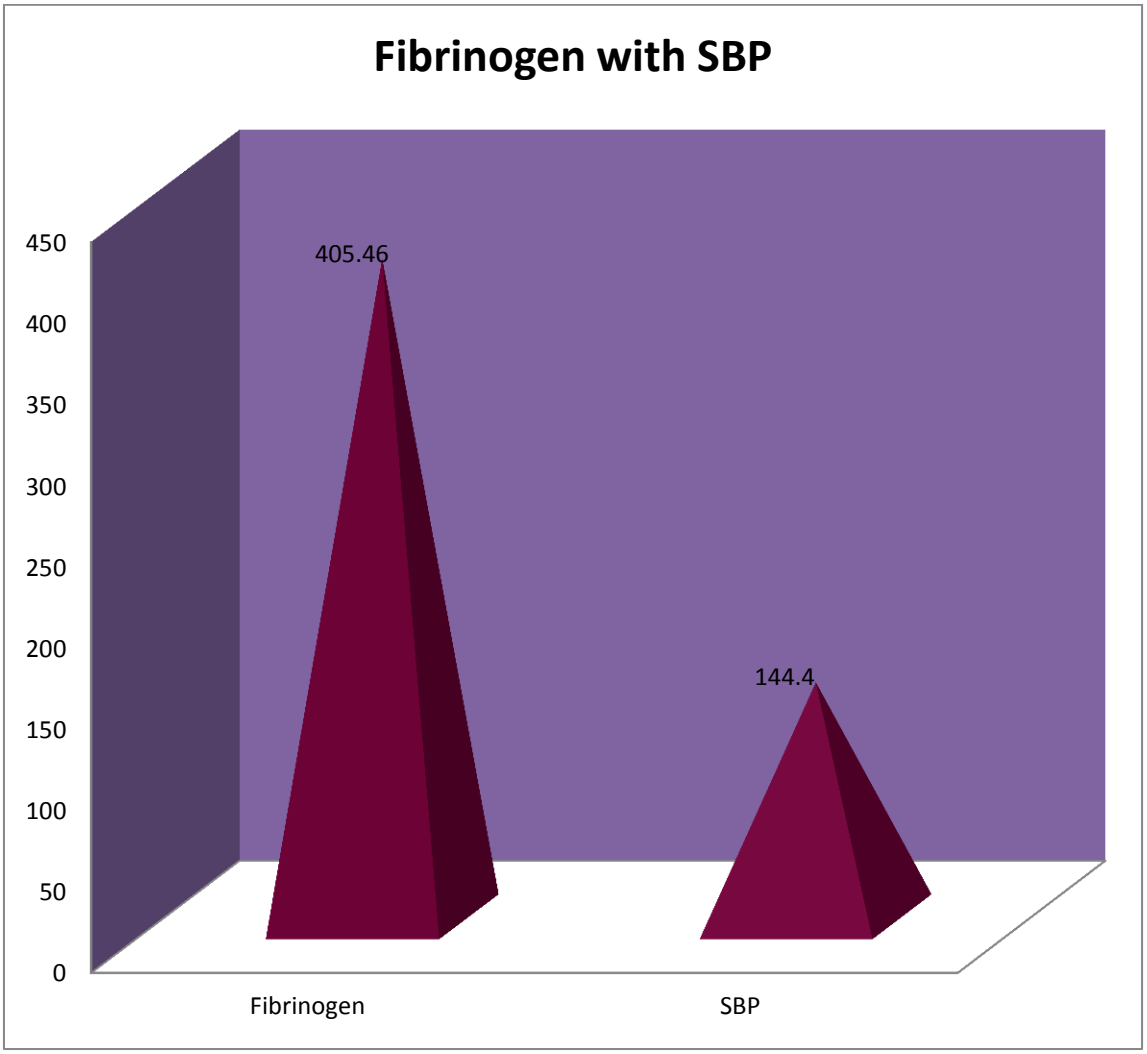



**FIGURE-23 FIBRINOGEN WITH SBP**

The mean systolic blood pressure was 144.4 among the stroke patients in our study. We could not establish a statistically significant relation between fibrinogen and systolic blood pressure.

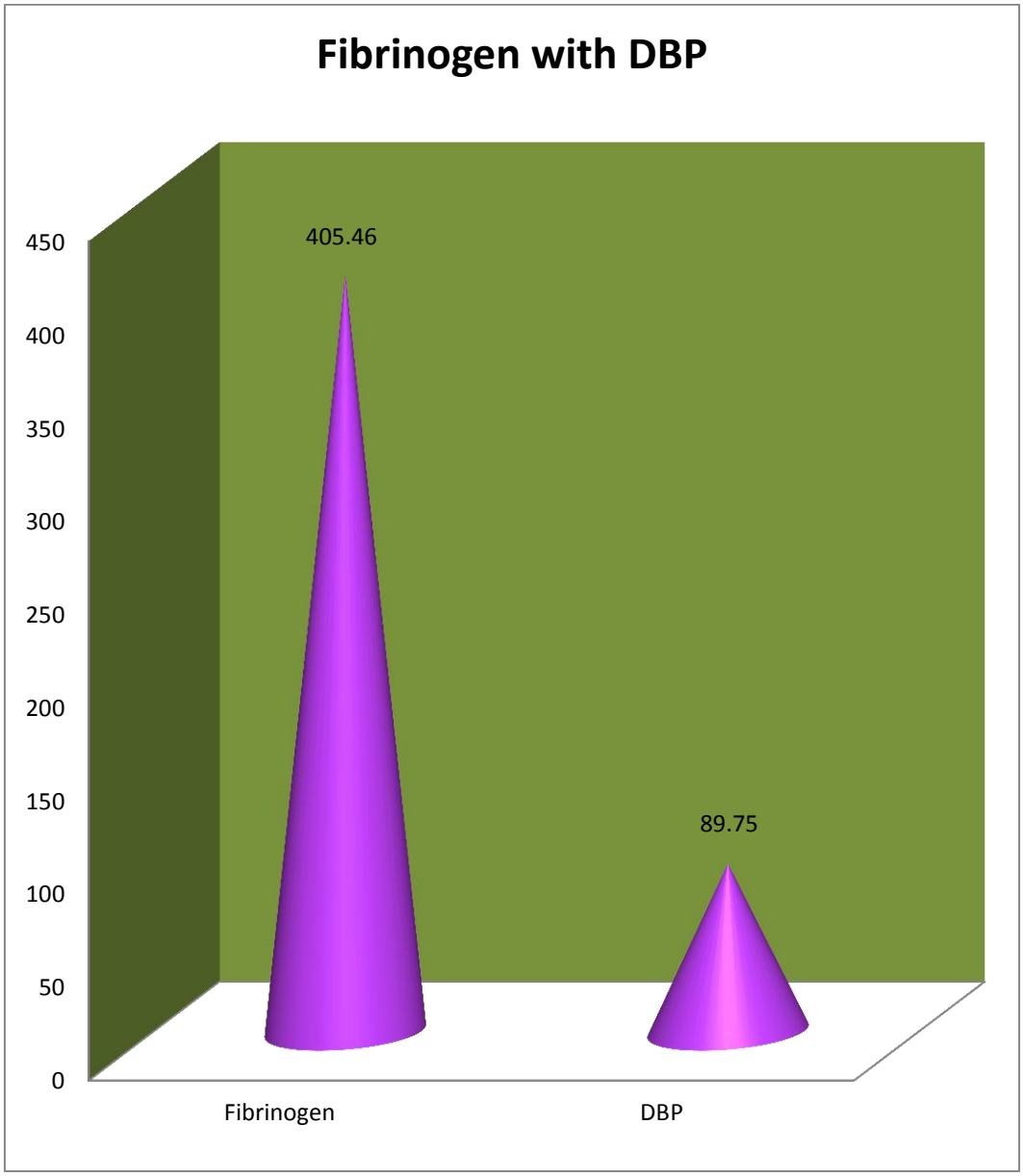



**FIGURE-24 FIBRINOGEN WITH DBP**

The mean diastolic blood pressure was 89.75 for our patients in the study.

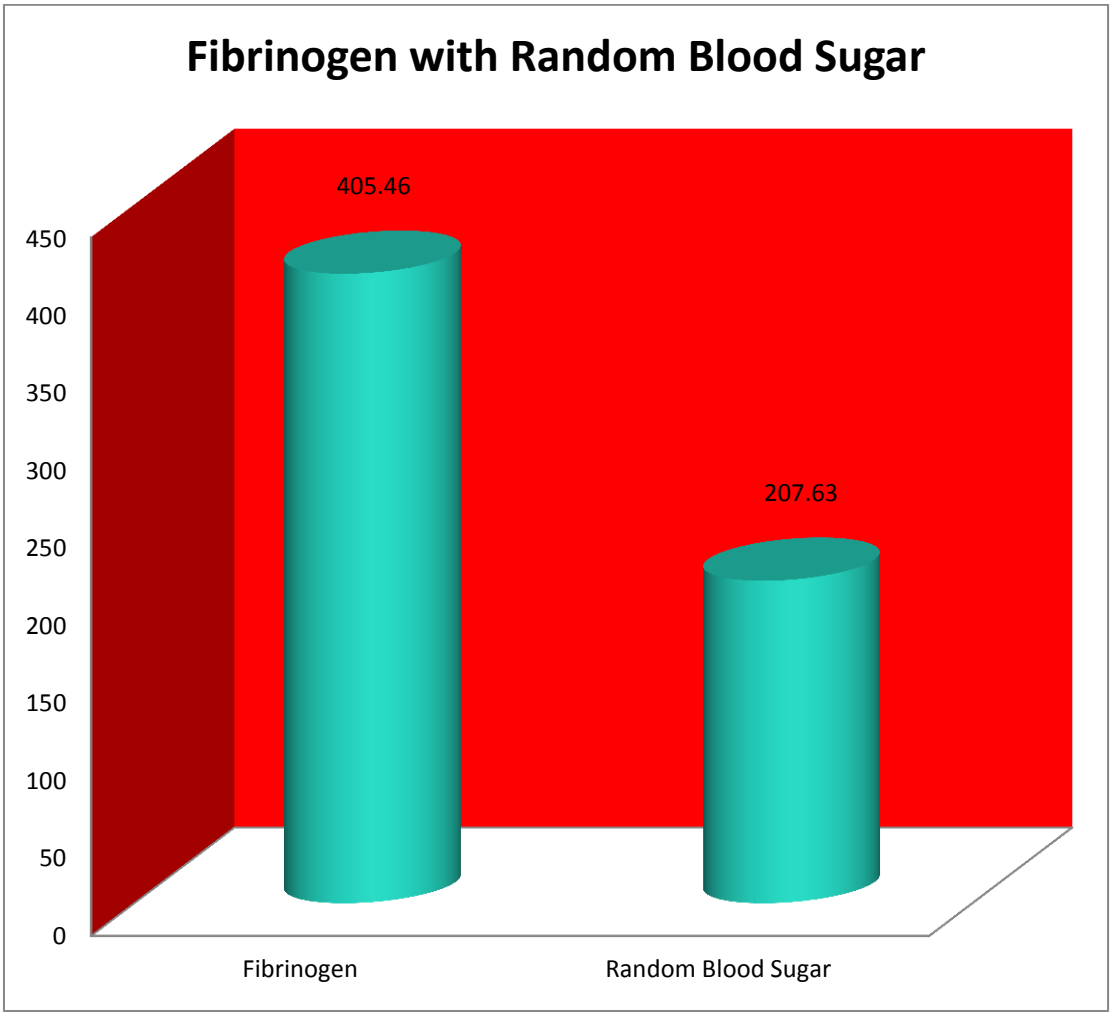



**FIGURE-25 FIBRINOGEN WITH RANDOM BLOOD SUGAR**

This diagram represents the mean value of blood sugar was 207.63.

## COMPARISON OF FIBRINOGEN WITH SMOKERS AND NON SMOKERS

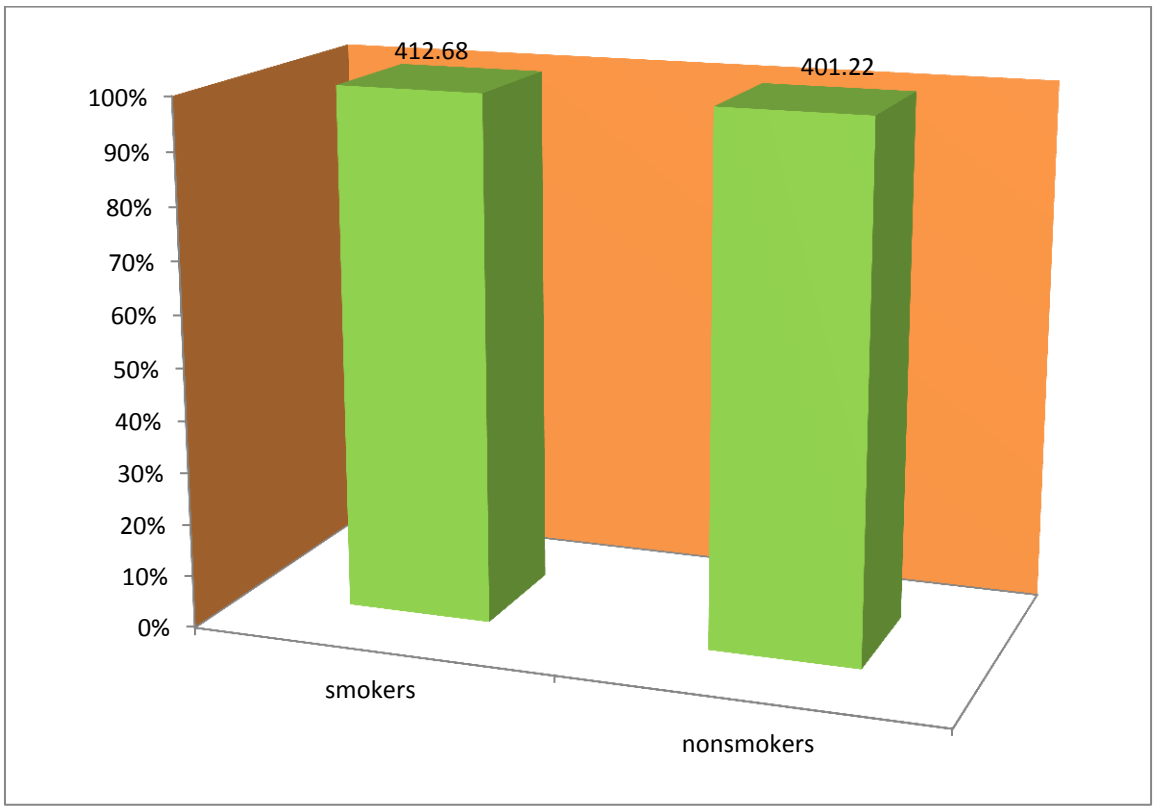



**FIGURE-26 COMPARISON OF FIBRINOGEN WITH SMOKERS AND NON SMOKERS**

This bar diagram compares the mean fibrinogen value with smokers and non-smokers. Although the mean value is increased among smokers we could not establish a statistically significant relation between smokers fibrinogen.

## COMPARISON OF FIBRINOGEN WITH ALCOHOLICS

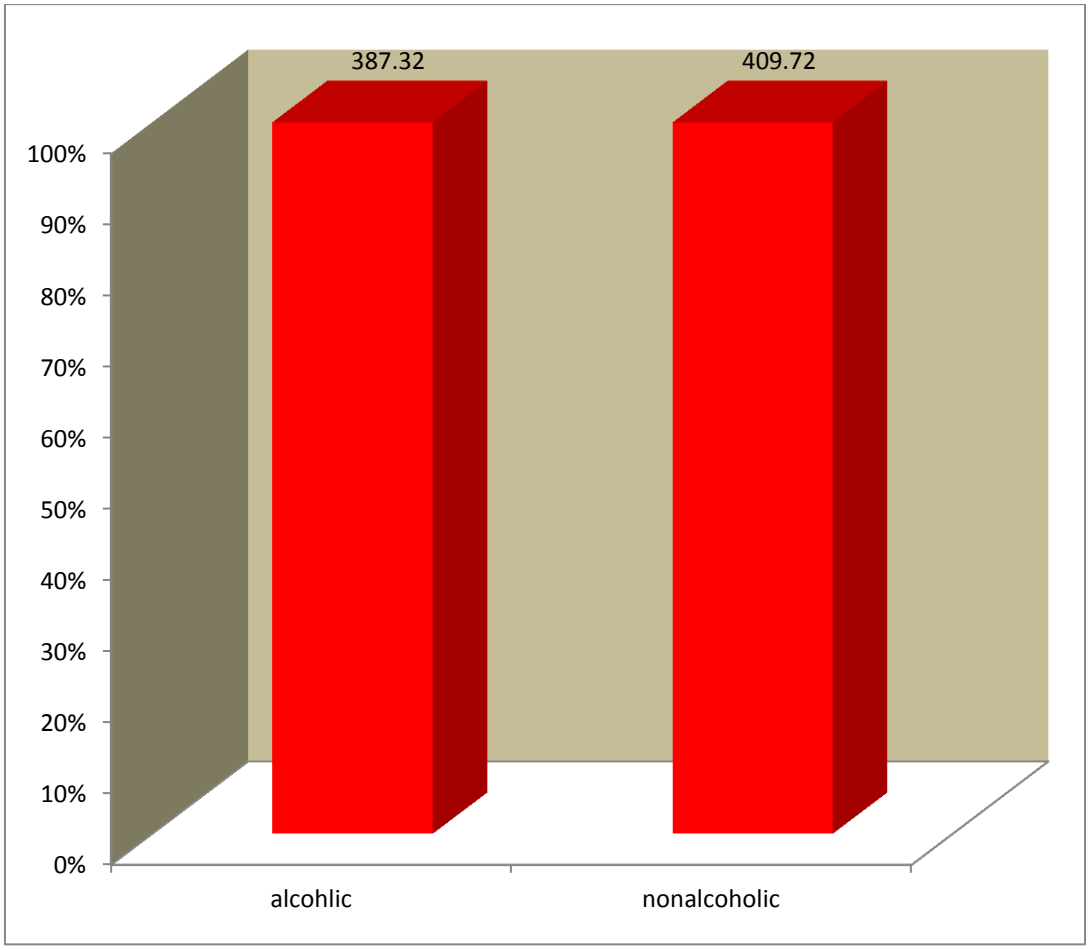



**FIGURE-27 COMPARISON OF FIBRINOGEN WITH ALCOHOLICS**

This picture depicts the mean fibrinogen value in both alcoholics and non-alcoholics. The relation obtained was not statistically significant.

## CORRELATION OF MEAN FIBRINOGEN VALUE WITH HYPERTENSIVES AND NON HYPERTENSIVES

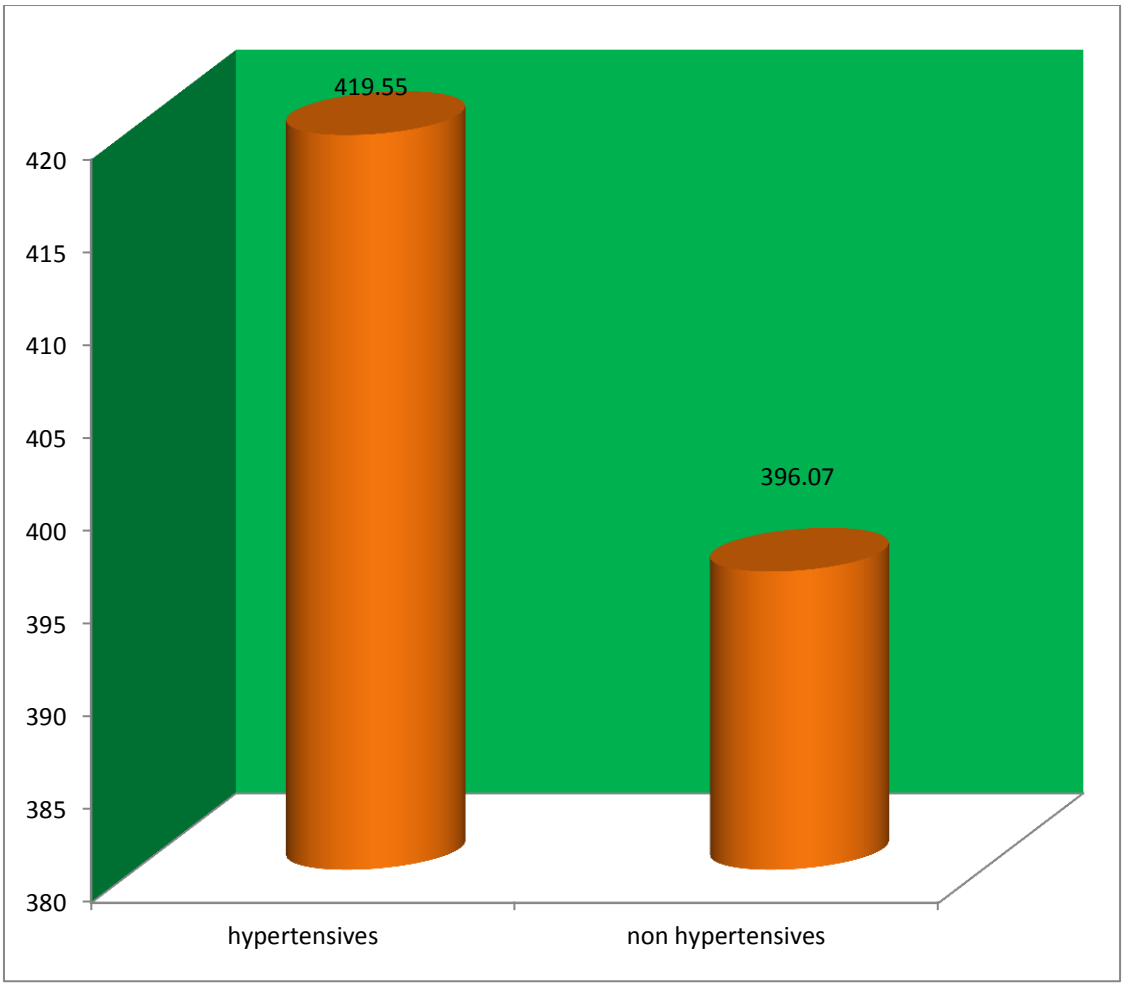



**FIGURE-28 CORRELATION OF MEAN FIBRINOGEN VALUE WITH HYPERTENSIVES AND NON HYPERTENSIVES**

The mean fibrinogen was slightly higher among known hypertensives. But we could not establish a statistically significant relation between these two.

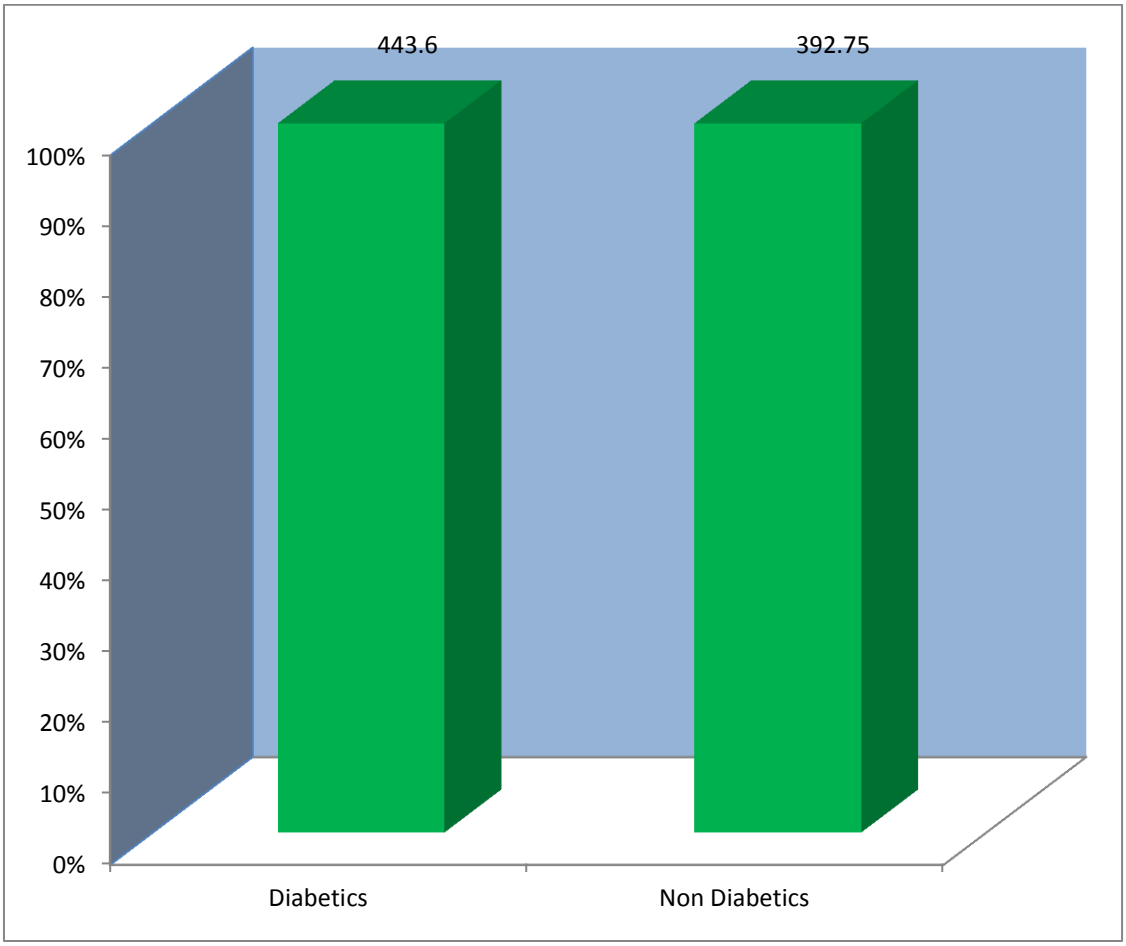
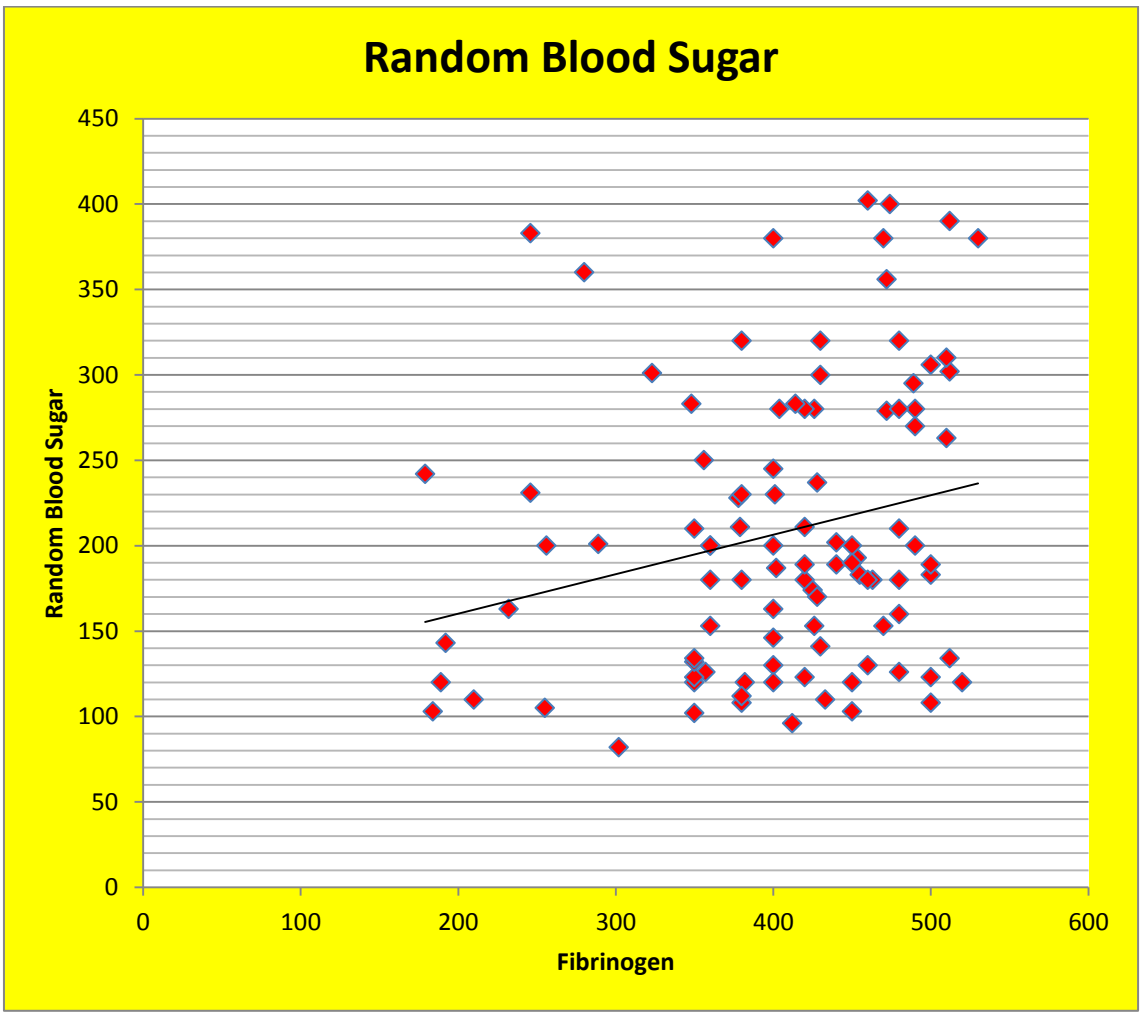



**FIGURE-29 COMPARISON OF MEAN FIBRINOGEN VALUE WITH DIABETES AND NON DIABETES PATIENTS.**

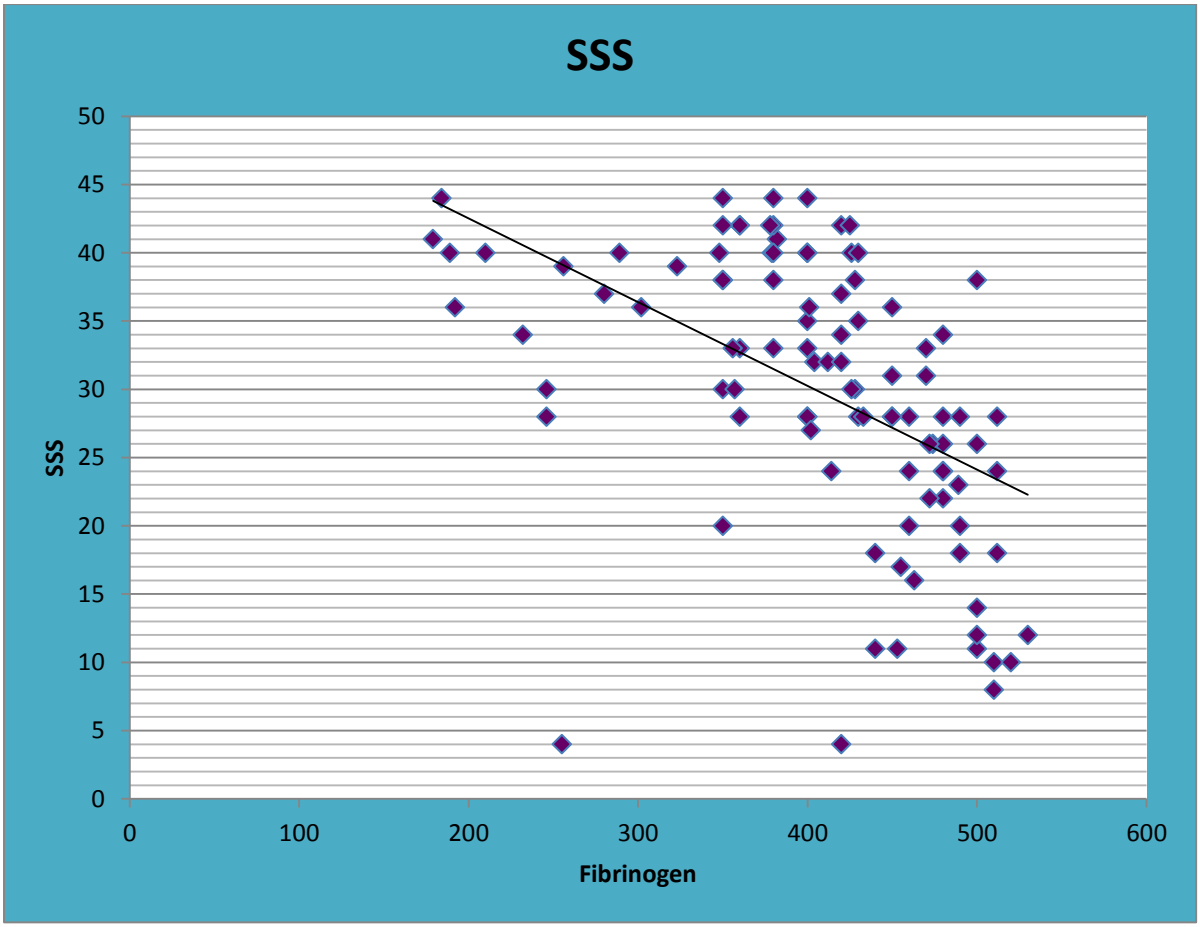
The mean fibrinogen was significantly higher in diabetic patients when compared to non-diabetic patients and the increase in value was statistically significant.

**FIGURE-30 CORRELATION BETWEEN MEAN FIBRINOGEN WITH RANDOM BLOOD SUGAR**



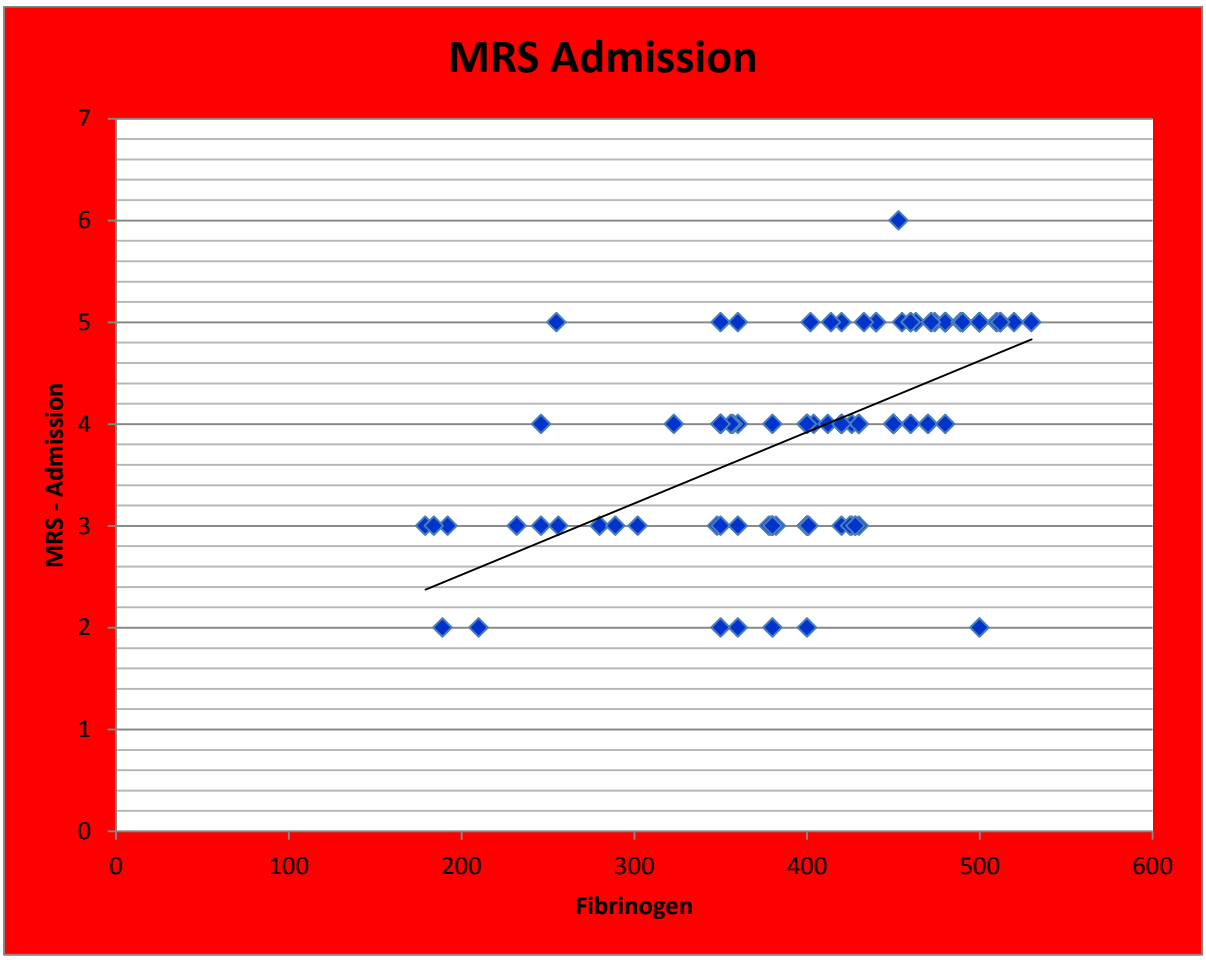

The fibrinogen value at the time of admission was correlated with random blood sugar at the time of admission and there was a significant correlation between these two variables.

**FIGURE-31 CORRELATION BETWEEN FIBRINOGEN AND SSS**



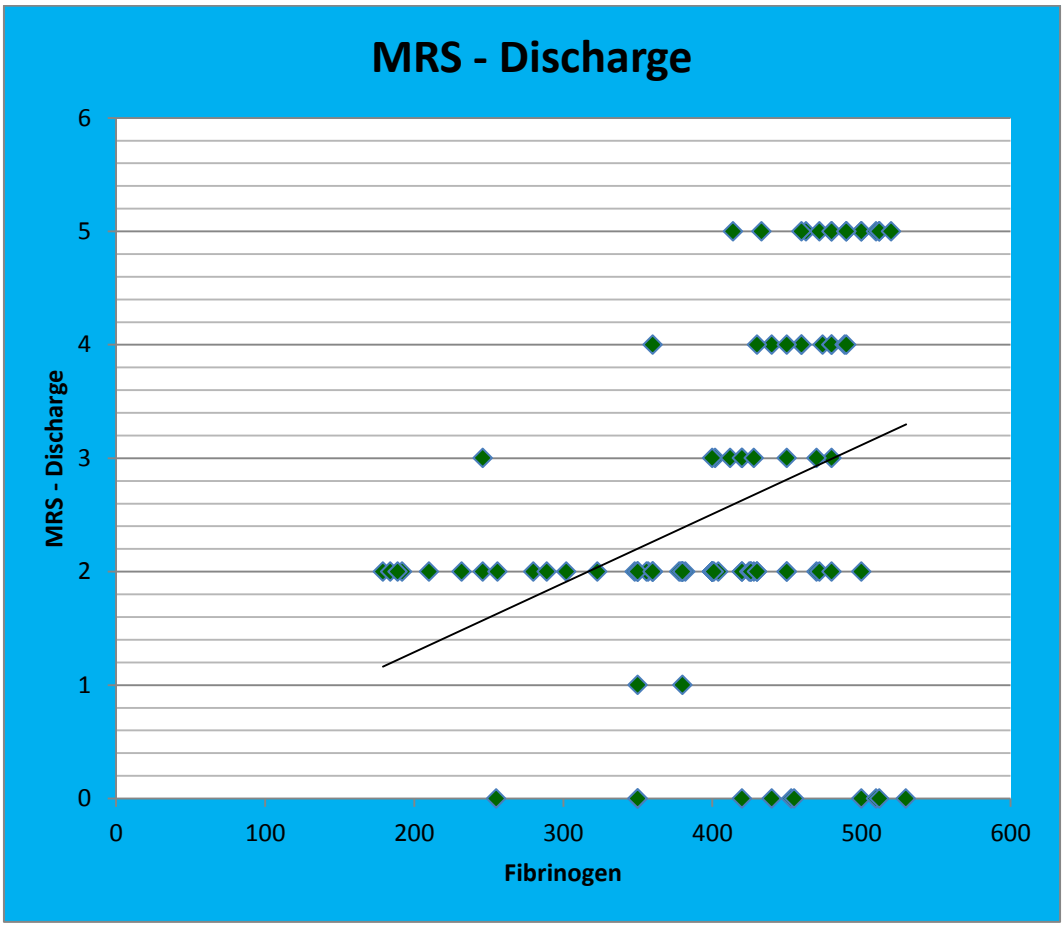

This line chart represents that as the fibrinogen value increases the SSS score decreases. This scoring assesses the severity of stroke and it was found to be statistically significant.

**FIGURE-32 CORRELATION BETWEEN FIBRINOGEN WITH MODIFIED RANKIN SCALE AT THE TIME OF ADMISSION**




This diagram represents the linear relationship between fibrinogen value and Rankin score at the time of admission. This scale represents the functional outcome of patients. In our study higher the fibrinogen value carries poor functional outcome.

**Figure-33 CORRELATION BETWEEN FIBRINOGEN WITH MODIFIED RANKIN SCALE AT DISCHARGE**




The admission fibrinogen value correlated with the functional outcome of patients with MRS at the time of discharge. Patients having higher fibrinogen value at the time of admission has significant disability at the time of discharge and the correlation was statistically significant.

# DISCUSSION

This study was conducted among the Indian population involving 100 patients who got admitted in our hospital with clinical features and investigations suggestive of cerebrovascular accident. We evaluated history regarding smoking, alcoholism known hypertension and diabetes. And also we measured blood pressure random blood sugar and other parameters.

We calculated the severity of stroke at the time of admission by Scandinavian stroke scale and measured the functional outcome of patients by modified Rankin scale at the time of admission and discharge. We measured plasma fibrinogen in all the patients in our study group. In our study no patients were treated with thrombolysis for stroke.

Many studies demonstrated that increased level of inflammatory markers like IL-6, CRP, fibrinogen following an acute stroke predicts an unfavourable outcome among stroke patients. Fibrinogen is one such acute phase protein. Cerebral ischemia triggers the acute phase reaction and thereby increasing the concentration of fibrinogen value following an acute stroke.

We evaluated the fibrinogen value with Scandinavian stroke scale(ranges from 0-58) and found that the fibrinogen value was inversely related with stroke severity and it was found to be statistically significant

($p<0.01$). The mean SSS scoring was 29.91.Hence patients having high fibrinogen value associated with increased severity of stroke.

Swarowskaet all [80] conducted a study of about 266 patients admitted with stroke. They measured the fibrinogen value at admission 7$^{th}$ and 14th day and correlated with the severity and outcome of the patients with NIHSS and MRS measured at day 1 and 30$^{th}$ day and found a significant correlation between fibrinogen and stroke severity and outcome.

Modified Rankin scale ranges from 0-6. The value of 6 indicates the patient is dead. Higher value of MRS score indicate poor functional outcome. In our study the modified Rankin scale measured at the time of admission and discharge correlated well with the fibrinogen value and was statistically significant. The mean MRS at the time of admission was 3.96. Hence higher the fibrinogen value at the time of admission poorer the functional outcome of stroke patients.

We proceeded with computing correlation coefficient for these parameters and found a higher value for MRS-at the time of admission( correlation coefficient-0.594) and least value with diastolic blood pressure(correlation coefficient 0.054)

We also tried to correlate between the fibrinogen value with important risk factors like smoking, alcohol, systemic hypertension and diabetes. The

mean fibrinogen value was increased with smoking systemic hypertension and diabetes. The mean fibrinogen was normal in patients who are alcoholic. And we could establish a statistically significant relationship only with patients having diabetes.

In the Scottish heart health study, plasma fibrinogen was measured in 8824 patients and found a significant fibrinogen elevation in patients with premature heart disease, diabetes, hypertension and intermittent claudication.

In Framingham study they found a significant correlation between smokers and fibrinogen value. The fibrinogen value was elevated in smokers as compared to non-smokers and found to be statistically significant.

Also we found there was a significant correlation between the random blood sugar and diabetes with fibrinogen value depicting the importance of underlying atherosclerotic process in diabetes.

In our study 12 patients were expired during the course of stay in hospital and we found that the mean fibrinogen was elevated among the dead patients indicating higher values of fibrinogen with worst outcome.

The limitation of our study is that we did not measure other inflammatory markers associated with acute stroke like IL-6 C-Reactive protein.

# CONCLUSION

Following conclusion was made from our study.

1. Plasma fibrinogen level at the time of admission correlated with the severity of stroke. This is evidenced by as the plasma fibrinogen value increases the Scandinavian stroke scale decreases.
2. Although the mean fibrinogen value was increased among smokers, hypertensive, and diabetes we could not establish a statistically significant correlation between fibrinogen and smokers and hypertension patients, whereas in diabetics a significant correlation was observed.
3. Plasma fibrinogen acts as a prognostic marker to predict functional outcome of stroke. This is evidenced by higher plasma fibrinogen values correlated with modified Rankin scale at the time of admission and discharge.

## FUTURE DIRECTIONS

Although the fibrinogen as an inflammatory marker, predicts the severity and functional outcome in acute stroke, it was still unclear whether the elevation is an epiphenomenon to stroke. Hence it is important to recognise the mechanisms leading to elevation of this inflammatory marker in stroke so that fibrinogen could be a potential therapeutic target.

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# ANNEXURES

## i) PROFORMA

Name:

Age&Sex

IP No DOA: Address; Ph;

Time duration:

Presenting complaints:

LOC: Seizures: Fever: Others:

Past History

HTN DM PT BA IHD CVA Seizures

Personal history

Smoking Alcoholism

General Examination

BP: pulse RR JVP: Temperature:

CVS

RS

GIT

CNS

**INVESTIGATIONS:**

CBC:

Blood
  Sugar:
  Urea:
Creatinine:
  Electrolytes:

Urine
  Sugar
  Albumin
  Deposits

ECG

CXR

Lipid profile

Serum cortisol

CT Brain:

**SSS**

1. Consciousness
2. Orientation
3. Speech

4. Eye movements
5. Facial palsy
6. Gait
7. Arm power
8. Hand power
9. Leg power

| | |
|---|---|
| ADMISSION | |
| DISCHARGE | |

MRS (0-6)

Patient’s outcome : discharged / death

## iii) ABBREVATIONS

| | |
|---|---|
| CRP | C-reactive protein |
| NIHSS | National institute of health stroke scale |
| TIA | Transient ischemic attack |
| RIND | Reversible ischemic neurological deficit |
| TCD | Transcranial Doppler ultrasound |
| NMDA | N-methyl-D-aspartate |
| NOS | Nitric oxide synthase |
| MMP | Matrix metalloprotease |
| APOE | Apolipoprotein E |
| ASA/AHA | American stroke association/American heart association |
| ICA | Internal carotid artery |
| CCA | Common carotid artery |
| ACA | Anterior cerebral artery |
| PCA | Posterior cerebral artery |
| ACoA | Anterior communicating artery |
| PCoA | Posterior communicating artery |
| SSS | Scandinavian stroke scale |
| MRS | Modified rankin scale |
| SBP | Systolic blood pressure |
| DBP | Diastolic blood pressure |

| Sl.No | NAME | AGE < 60 | AGE > 60 | SEX | SMOKER | ALCOHOLIC | SBP | DBP | SHT | DM | SUGAR | SSS | MRS - Admission | MRS - Discharge | FIBRINOGEN | OUTCOME | ISHEMIC | HMRG | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | ABBUBAKER | 38 | | M | S | | 150 | 90 | | | 193 | 11 | 5 | | 453 | DEATH | + | | |
| 2 | SUBBURAJ | 33 | | M | S | S | 120 | 70 | | | 280 | 40 | 3 | 2 | 426 | DIS | + | | |
| 3 | MURUGAN | 40 | | M | S | | 130 | 80 | | | 146 | 28 | 4 | 2 | 400 | DIS | + | | |
| 4 | MUTHU | 34 | | M | S | S | 160 | 100 | S | S | 163 | 28 | 4 | 2 | 400 | DIS | + | | |
| 5 | SUDALAIMUTH | | 65 | M | S | S | 180 | 100 | S | S | 237 | 30 | 3 | 2 | 428 | DIS | + | | |
| 6 | SELVARAJ | | 80 | M | S | | 180 | 110 | S | | 105 | 4 | 5 | | 255 | DEATH | | + | |
| 7 | SANKARAN | | 65 | M | S | S | 130 | 70 | | | 283 | 40 | 3 | 2 | 348 | DIS | + | | |
| 8 | GOMATHY | | 78 | F | | | 110 | 70 | | | 163 | 34 | 3 | 2 | 232 | DIS | + | | |
| 9 | NAMBIRAJAN | 46 | | M | S | S | 170 | 90 | S | | 82 | 36 | 3 | 2 | 302 | DIS | + | | |
| 10 | ARUMUGAM | | 62 | M | | | 140 | 90 | S | | 231 | 28 | 4 | 3 | 246 | DIS | | + | |
| 11 | MUTHANU | 40 | | F | | | 150 | 90 | | | 153 | 28 | 5 | 4 | 360 | DIS | + | | |
| 12 | MEENATCHI | | 65 | F | | | 180 | 100 | | | 189 | 18 | 5 | 4 | 440 | DIS | + | | |
| 13 | SALAPATHY | 43 | | M | | | 130 | 90 | | | 143 | 36 | 3 | 2 | 192 | DIS | + | | |
| 14 | SUDALIAMMAL | | 65 | F | | | 170 | 90 | S | | 183 | 17 | 5 | | 455 | DEATH | + | | |
| 15 | GANAPAMMA | | 70 | F | | | 190 | 100 | S | | 202 | 11 | 5 | | 440 | DEATH | + | | |
| 16 | SANKARAMMAL | | 65 | F | | | 140 | 80 | | S | 306 | 11 | 5 | 5 | 500 | DIS | + | | |
| 17 | AMBIKAVATHY | | 65 | F | | | 130 | 90 | | S | 400 | 26 | 5 | 4 | 474 | DIS | + | | |
| 18 | MOOKANDI | 36 | | M | S | | 180 | 90 | S | | 187 | 27 | 5 | 3 | 402 | DIS | + | | |
| 19 | PERUMAL | 50 | | M | | S | 200 | 100 | S | | 180 | 33 | 4 | 2 | 380 | DIS | + | | |
| 20 | MURUGESAN | 47 | | M | | S | 130 | 90 | | | 183 | 12 | 5 | | 500 | DEATH | + | | |
| 21 | VASANTH | | 68 | F | | | 130 | 90 | | S | 180 | 22 | 5 | 3 | 480 | DIS | + | | |
| 22 | VASANTH | 58 | | M | S | | 160 | 90 | S | | 120 | 36 | 4 | 2 | 450 | DIS | + | | |
| 23 | RATHINAM | | 68 | F | | | 130 | 90 | | S | 320 | 26 | 5 | 5 | 480 | DIS | | + | |
| 24 | GAAPATHY | 55 | | F | | | 130 | 70 | S | | 123 | 14 | 5 | 5 | 500 | DIS | + | | |
| 25 | PETCHIAMMA | 55 | | F | | | 180 | 90 | S | | 263 | 8 | 5 | 5 | 510 | DIS | + | | |
| 26 | RAJAMANI | | 65 | F | | | 130 | 80 | | | 153 | 33 | 4 | 2 | 470 | DIS | + | | |
| 27 | ABDUL AHAB | 58 | | M | | S | 130 | 70 | | | 301 | 39 | 4 | 2 | 323 | DIS | | + | |
| 28 | MADASAMY | | 65 | M | S | | 130 | 80 | | S | 211 | 34 | 4 | 2 | 420 | DIS | + | | |
| 29 | ESAKKI | 51 | | M | | S | 140 | 86 | | | 242 | 41 | 3 | 2 | 179 | DIS | | + | |
| 30 | RAMACHANDRAN | 50 | | M | | | 130 | 70 | | S | 383 | 30 | 3 | 2 | 246 | DIS | + | | |
| 31 | AVUDAIAMMA | | 80 | F | | | 130 | 80 | | | 280 | 32 | 4 | 2 | 404 | DIS | + | | |
| 32 | VADIVU | 54 | | F | | | 160 | 70 | S | | 211 | 40 | 3 | 2 | 379 | DIS | + | | |
| 33 | SUBBAMMAL | | 65 | F | | | 200 | 100 | S | | 280 | 4 | 5 | - | 420 | DEATH | + | | |
| 34 | PADMANABAN | | 65 | M | S | S | 120 | 70 | | S | 390 | 18 | 5 | 5 | 512 | DIS | + | | |
| 35 | RAMASAMY | | 78 | M | S | | 130 | 80 | | S | 283 | 24 | 5 | 5 | 414 | DIS | + | | |
| 36 | RAJENDRAN | 51 | | M | S | | 170 | 90 | S | | 180 | 16 | 5 | 5 | 463 | DIS | + | | |
| 37 | KARPAGAM | 53 | | F | | | 130 | 90 | | | 141 | 35 | 4 | 4 | 430 | DIS | + | | |
| 38 | SUBBURAJ | 48 | | M | | | 130 | 70 | | S | 180 | 24 | 4 | 4 | 460 | DIS | | + | |
| 39 | GUNASEELAN | 55 | | M | | | 130 | 60 | | | 123 | 37 | 4 | 3 | 420 | DIS | + | | |
| 40 | AYYAMMAL | 41 | | F | | | 130 | 70 | | | 200 | 33 | 4 | 2 | 360 | DIS | + | | |
| 41 | CHELLIAH | 55 | | M | S | | 160 | 80 | S | | 103 | 44 | 3 | 2 | 184 | DIS | + | | |
| 42 | THANGARAJ | 64 | | M | S | | 160 | 80 | S | S | 180 | 42 | 3 | 2 | 420 | DIS | + | | |
| 43 | KALIAMMAL | 55 | | F | | | 160 | 80 | S | | 174 | 42 | 3 | 2 | 425 | DIS | + | | |
| 44 | ESAKKI | 58 | | M | | S | 130 | 80 | | S | 302 | 24 | 5 | 5 | 512 | DIS | + | | |
| 45 | MARIYA | 58 | | F | | | 120 | 70 | | S | 356 | 22 | 5 | 5 | 472 | DIS | + | | |
| 46 | RAJA | | 68 | M | S | | 130 | 90 | | | 102 | 30 | 4 | 2 | 350 | DIS | + | | |
| 47 | ARUMUGAM | | 85 | M | | | 160 | 100 | S | | 120 | 41 | 3 | 2 | 382 | DIS | + | | |
| 48 | SIVA | 50 | | M | | | 130 | 70 | | | 126 | 30 | 4 | 2 | 357 | DIS | + | | |
| 49 | MARIAMMAL | 31 | | F | | | 120 | 80 | | | 200 | 39 | 3 | 2 | 256 | DIS | + | | |
| 50 | KUMAR | | 76 | M | S | | 140 | 70 | S | | 210 | 24 | 5 | 4 | 480 | DIS | + | | |
| 51 | MARIAMMAL | 31 | | F | | | 160 | 100 | S | S | 380 | 12 | 5 | - | 530 | DEATH | + | | |
| 52 | RATHINAMMA | | 62 | F | | | 130 | 80 | | S | 200 | 31 | 4 | 3 | 450 | DIS | + | | |
| 53 | SUBBULAKSHMI | 55 | | F | | | 170 | 100 | S | | 160 | 24 | 5 | 4 | 480 | DIS | + | | |
| 54 | THANGAPANDI | 45 | | M | | | 130 | 70 | S | | 130 | 44 | 3 | 2 | 400 | DIS | + | | |
| 55 | THANGAMMAL | 55 | | F | | | 130 | 90 | | S | 380 | 31 | 4 | 3 | 470 | DIS | + | | |
| 56 | PARAMASIVAN | 60 | | M | S | | 120 | 70 | S | | 310 | 10 | 5 | _ | 510 | DEATH | + | | |
| 57 | SYEALIFATHIMA | 30 | | F | | | 120 | 80 | | | 120 | 44 | 4 | 2 | 350 | DIS | + | | |
| 58 | THANGAMUTHU | 55 | | M | | | 150 | 80 | S | | 200 | 33 | 4 | 3 | 400 | DIS | + | | |
| 59 | PARVATHI | 60 | | F | | | 170 | 100 | S | | 120 | 10 | 5 | 5 | 520 | DIS | + | | |
| 60 | GANESAN | 61 | | M | S | S | 130 | 80 | S | | 200 | 18 | 5 | 5 | 490 | DIS | + | | |
| 61 | PITCHAMMAL | 60 | | F | | | 130 | 70 | | s | 250 | 33 | 4 | 2 | 356 | dis | + | | |
| 62 | RANGASAMY | 50 | | M | s | | 150 | 80 | | s | 300 | 40 | 3 | 2 | 430 | dis | + | | |
| 63 | POOMARI | 75 | | M | | | 160 | 80 | s | s | 360 | 37 | 3 | 2 | 280 | dis | | + | |
| 64 | JEYAM | 60 | | F | | | 160 | 100 | | | 380 | 35 | 3 | 2 | 400 | dis | + | | |
| 65 | MUTHAMMAL | | 80 | F | | | 140 | 80 | | s | 320 | 40 | 3 | 1 | 380 | dis | + | | |
| 66 | SUBBULAKSHMI | 53 | | F | | | 160 | 90 | s | | 153 | 30 | 4 | 2 | 426 | dis | + | | |
| 67 | THANGARASI | 62 | | M | | | 130 | 90 | | S | 320 | 28 | 4 | 2 | 430 | DIS | + | | |
| 68 | DURAI | 65 | | M | S | S | 130 | 70 | | S | 402 | 28 | 5 | 4 | 460 | DIS | + | | |
| 69 | SRIVALLI | 56 | | M | S | | 120 | 70 | | | 126 | 28 | 5 | 5 | 480 | DIS | + | | |
| 70 | MAHARAJN | | 70 | M | S | S | 150 | 90 | S | | 108 | 42 | 3 | 2 | 380 | DIS | + | | |
| 71 | MUTHUKRISNAN | 50 | | M | S | | 120 | 80 | | | 228 | 42 | 3 | 2 | 378 | DIS | + | | |
| 72 | SUDALIAMMAL | | 68 | F | | | 170 | 100 | S | | 295 | 23 | 5 | 4 | 489 | DIS | + | | |
| 73 | CHELLATHAI | | 65 | F | | | 160 | 100 | S | | 103 | 28 | 4 | 2 | 450 | DIS | + | | |
| 74 | PETCHIAMMAL | 48 | | F | | | 120 | 80 | | S | 279 | 26 | 5 | 2 | 472 | DIS | + | | |
| 75 | PTRATCHI | 54 | | F | | | 180 | 100 | | | 123 | 38 | 4 | | 350 | DEATH | | + | |
| 76 | PITCHAMANI | 64 | | M | S | | 130 | 80 | S | | 200 | 42 | 2 | 2 | 360 | DIS | + | | |
| 77 | KRISHNA | 49 | | M | S | | 160 | 90 | S | | 110 | 28 | 5 | 5 | 433 | DIS | + | | |
| 78 | KANIAMMAL | 62 | | F | S | | 110 | 70 | | | 96 | 32 | 4 | 3 | 412 | DIS | + | | |
| 79 | ESAKKIAMMAL | 60 | | F | | | 180 | 90 | s | | 112 | 44 | 2 | 2 | 380 | DIS | + | | |
| 80 | SUBBAMMAL | | 72 | F | | | 120 | 80 | | | 120 | 40 | 2 | 2 | 400 | DIS | + | | |
| 81 | MAHARAJAN | 55 | | M | S | | 150 | 90 | | | 132 | 38 | 3 | 2 | 350 | DIS | + | | |
| 82 | SAHUL HAMEED | 63 | | M | | | 120 | 70 | | | 130 | 20 | 5 | 5 | 460 | DIS | + | | |
| 83 | VINCENT | 48 | | M | S | | 160 | 100 | S | | 280 | 28 | 5 | 4 | 490 | DIS | + | | |
| 84 | GOVIND | 53 | | M | S | | 180 | 100 | S | | 108 | 38 | 2 | 2 | 500 | DIS | + | | |
| 85 | DURAIPANDI | 60 | | M | | S | 130 | 80 | | | 110 | 40 | 2 | 2 | 210 | DIS | | + | |
| 86 | KANI | | 78 | F | | | 190 | 100 | S | | 210 | 20 | 5 | | 350 | DEATH | | + | |
| 87 | RAJAMMA | | 80 | F | | | 180 | 100 | S | | 134 | 28 | 5 | | 512 | DEATH | | + | |
| 88 | RAGURAM | | 78 | M | S | | 120 | 70 | | S | 280 | 34 | 4 | 2 | 480 | DIS | + | | |
| 89 | KUMARAVEL | | 66 | M | S | S | 140 | 89 | | S | 245 | 40 | 3 | 2 | 400 | DIS | + | | |
| 90 | RAMESH | 43 | | M | S | | 130 | 70 | | | 230 | 38 | 3 | 2 | 380 | DIS | + | | |
| 91 | ARAVAN | | 70 | M | S | S | 150 | 90 | | | 189 | 32 | 4 | 3 | 420 | DIS | + | | |
| 92 | RAMAN | | 66 | M | | | 130 | 60 | | S | 270 | 20 | 5 | 5 | 490 | DIS | + | | |
| 93 | RAGUPATHY | | 70 | M | S | | 140 | 70 | | S | 201 | 40 | 3 | 2 | 289 | DIS | | + | |
| 94 | PONNAMAL | | 66 | F | | | 130 | 80 | | | 180 | 42 | 3 | 2 | 360 | DIS | + | | |
| 95 | SANKARAMMAL | | 70 | F | | S | 120 | 70 | S | | 120 | 40 | 2 | 2 | 189 | DIS | + | | |
| 96 | KUMARAN | 50 | | M | | | 130 | 70 | | | 134 | 42 | 2 | 1 | 350 | DIS | + | | |
| 97 | PALANIAMMAL | | 69 | F | | | 120 | 80 | | S | 230 | 36 | 3 | 2 | 401 | DIS | + | | |
| 98 | RASIGAN | 59 | | M | S | | 150 | 80 | S | | 190 | 28 | 4 | 4 | 450 | DIS | + | | |
| 99 | KUMUTHA | | 66 | F | | | 130 | 80 | S | | 170 | 38 | 3 | 3 | 428 | DIS | + | | |
| 100 | SORIMUTHU | | 70 | M | S | S | 150 | 70 | S | | 189 | 26 | 5 | | 500 | DEATH | + | | |