# LDL-Cholesterol in relation to mortality of Intracerebral Haemorrhage and Hemorrhagic transformation of Large Artery Thrombotic Stroke

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*for the award of the degree of*

**M.D. BRANCH - I**
**GENERAL MEDICINE**

**MADRAS MEDICAL COLLEGE**
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# CERTIFICATE

This is to certify that the dissertation titled **"LDL-Cholesterol in relation to mortality of Intracerebral Haemorrhage and Hemorrhagic transformation of Large Artery Thrombotic Stroke"** is the bonafide original work of **Dr. VIJAYASARATHY.N.,** in partial fulfillment of the requirements for M.D. Branch– I (General Medicine) Examination of the Tamilnadu Dr. M.G.R Medical University to be held in APRIL 2012. The Period of study was from April 2011 to November 2011.

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# DECLARATION

I hereby solemnly declare that the dissertation titled "**LDL-Cholesterol in relation to mortality of Intracerebral Haemorrhage and Hemorrhagic transformation of Large Artery Thrombotic Stroke"** was done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during April 2011 to November 2011 under the guidance and supervision of my unit Chief Prof. P.Chitrambalam, M.D.

The dissertation is submitted to the Tamilnadu Dr. M.G.R. Medical University towards the partial fulfillment of requirement for the award of M.D degree (Branch-1) in General Medicine.

Place: **SIGNATURE OF THE CANDIDATE**

Date :

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# CONTENTS

# INTRODUCTION

Stroke is characterized by the sudden loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurologic function. Also previously called cerebrovascular accident (CVA) or stroke syndrome, stroke is a nonspecific term encompassing a heterogeneous group of pathophysiologic causes.[54]

Broadly, however, strokes are classified as either hemorrhagic or ischemic. Acute ischemic stroke refers to stroke caused by thrombosis or embolism and is more common than hemorrhagic stroke. (Prior literature indicated that only 8-18% of strokes are hemorrhagic, but a retrospective review from a stroke center found that 40.9% of 757 strokes included in the study were hemorrhagic. [54]

The terms intracerebral hemorrhage (ICH) and hemorrhagic stroke are used interchangeably in this discussion and are regarded as separate entities from hemorrhagic transformation of ischemic stroke. Intracerebral

hemorrhage accounts for 10-15% of all strokes and is associated with higher mortality rates than cerebral infarctions. [54]

Patients with hemorrhagic stroke present with similar focal neurologic deficits but tend to be more ill than patients with ischemic stroke. Patients with intracerebral bleeds are more likely to have headache, altered mental status, seizures, nausea and vomiting, and/or marked hypertension; however, none of these findings reliably distinguishes between hemorrhagic stroke and ischemic stroke. Though stroke is less common in children, the clinical presentation is similar. [54]

Stroke is one of the leading causes of mortality and morbidity in India. Community surveys have shown a crude prevalence rate for hemiplegia in the range of 200 per 1,00,000 persons, nearly 1.5% of all urban hospital admissions, 4.5% of all medical and around 20% neurological cases.

The association between cholesterol and stroke remain uncertain. Epidemiological studies have failed to associate cerebral infarction and cholesterol, but they have found an inverse relation with the incidence of intracerebral hemorrhage (ICH).[1,6]

SPARCL study suggests that statins increase the occurrence of ICH, which enhances the controversy.[2] Moreover, an association between low cholesterol and mortality attribuable to ICH has been documented in several large population-based studies.[3,4] Additionally, higher cholesterol levels have been associated with better short-term health outcome after stroke, including ICH.[5,7]

Hemorrhagic transformation (HTf) frequently complicates ischemic stroke with or without thrombolytic treatment. HTf after acute ischemic stroke is known to associate with poor outcome and delays the initiation of proper anticoagulation treatment for stroke with cardioembolism (CE). HTf occurs after extravasation of blood over damaged cerebral vascular endothelium in acute ischemic stroke.

Similar to the association of low LDL-C with incidence of hemorrhagic stroke, there should be an association of low LDL-C cholesterol with incidence of hemorrhagic transformation in ischemic stroke.

This study is intended to substantiate or disprove the associations

# AIMS AND OBJECTIVES

1. To classify stroke patients in to acute hemorrhagic stroke and acute large artery thrombotic stroke.

2. To exclude the patients with recurrent stroke or patients taking antilipidemic drugs.

3. To measure Lipid Profile including LDL-cholesterol for the above patients.

4. To find the association of LDL-cholesterol levels and some other parameters with the 30 day mortality in hemorrhagic stroke patients.

5. To find the association of LDL-cholesterol levels and few other parameters with the incidence of hemorrhagic transformation in large artery thrombotic stroke patients.

# REVIEW OF LITERATURE

## HEMORRHAGIC STROKE

The etiologies of stroke are varied, but they can be broadly categorized into ischemic or hemorrhagic infarctions. Approximately 80-87% of strokes are from ischemic infarction due to thrombotic or embolic cerebrovascular occlusion. Hemorrhagic infarctions comprise most of the remainder of strokes, with a smaller number due to aneurysmal subarachnoid hemorrhage. Furthermore, 20-40% of patients with ischemic infarction may develop hemorrhagic transformation within 1 week after ictus. Intracerebral hemorrhage accounts for 10-15% of all strokes and is associated with higher mortality rates than cerebral infarctions.[54]

**CAUSES:**[54]

- Cerebral amyloidosis (affects people who are elderly and may cause up to 10% of intracerebral hemorrhages)

- Coagulopathies (eg, due to underlying systemic disorders such as bleeding diathesis or liver disease)
- Anticoagulant therapy
- Thrombolytic therapy for acute myocardial infarction (MI) and acute ischemic stroke (can cause iatrogenic hemorrhagic transformation)
- Arteriovenous malformation
- Intracranial aneurysm
- Vasculitis
- Intracranial neoplasm

The risk of stroke is increased with the following factors:

- Advanced age
- Hypertension (up to 60% of cases)
- Previous history of stroke
- Alcohol and illicit drug use, such as cocaine and other sympathomimetic drugs

## CLINICAL FEATURES:

Generalized symptoms, including nausea, vomiting, and headache as well as an altered level of consciousness may indicate increased intracranial pressure and are more common with hemorrhagic strokes or large ischemic strokes. Seizures are more common in hemorrhagic stroke than in ischemic stroke and occur in up to 28% of hemorrhagic strokes, generally at the onset of the intracerebral hemorrhage or within the first 24 hours. [55]

Other, more focal, symptoms of stroke include weakness or paresis that may affect a single extremity, one half of the body, or all 4 extremities; facial droop; monocular or binocular blindness; blurred vision or visual field deficits; dysarthria and trouble understanding speech; vertigo or ataxia; and aphasia. The neurologic deficits reflect the area of the brain typically involved, and stroke syndromes for specific vascular lesions have been described. [55]

Intracerebral hemorrhage may be clinically indistinguishable from ischemic stroke. Hypertension is commonly a prominent finding. An acute onset of neurologic deficit, altered level of consciousness/mental status, or coma is more common with hemorrhagic stroke than with ischemic stroke. Often, this is due to an increase in intracranial pressure. Meningismus may result from blood in the ventricles. [55]

Specific brain sites and deficits involved in hemorrhagic stroke include the following: [55]

- Putamen - Contralateral hemiparesis, contralateral sensory loss, contralateral conjugate gaze paresis, homonymous hemianopia, aphasia, neglect, or apraxia

- Thalamus - Contralateral sensory loss, contralateral hemiparesis, gaze paresis, homonymous hemianopia, miosis, aphasia, or confusion

- Lobar - Contralateral hemiparesis or sensory loss, contralateral conjugate gaze paresis, homonymous hemianopia, abulia, aphasia, neglect, or apraxia

- Caudate nucleus - Contralateral hemiparesis, contralateral conjugate gaze paresis, or confusion

- Brainstem - Quadriparesis, facial weakness, decreased level of consciousness, gaze paresis, ocular bobbing, miosis, or autonomic instability

- Cerebellum - Ataxia (usually beginning in the trunk), ipsilateral facial weakness, ipsilateral sensory loss, gaze paresis, skew deviation, miosis, or decreased level of consciousness

Other signs of cerebellar or brainstem involvement include the following:[55]

- Gait or limb ataxia
- Vertigo or tinnitus

- Nausea and vomiting
- Hemiparesis or quadriparesis
- Hemisensory loss or sensory loss of all 4 limbs
- Eye movement abnormalities resulting in diplopia or nystagmus
- Oropharyngeal weakness or dysphagia
- Crossed signs (ipsilateral face and contralateral body)

Many other stroke syndromes are associated with intracerebral hemorrhage and range from mild headache to neurologic devastation. At times, a cerebral hemorrhage may present as a new-onset seizure.

**WORKUP:**

Brain imaging is a crucial step in a patient's evaluation and must be obtained on an emergent basis. Brain imaging aids in making the diagnosis of hemorrhage, and it may identify complications such as intraventricular hemorrhage, brain edema, or hydrocephalus. Either NCCT scanning or magnetic resonance imaging (MRI) of the brain is the modality of choice. [56]

Imaging has greatly evolved in the past 2 decades, and advanced CT and magnetic resonance neuroimaging techniques have been developed

for improved physiologic imaging of acute stroke. These techniques allow clinicians to assess for the core infarct size and to characterize cerebral blood volume and cerebral blood flow to identify potentially salvageable tissue at risk for infarction (ie, ischemic penumbra). Some examples of these techniques include diffusion-weighted MRI (DWI) and perfusion imaging of acute stroke with magnetic resonance and CT scanning. [56]

CT scanning and magnetic resonance angiography (MRA) can give useful information regarding large-vessel occlusion, which is an important consideration, as intraarterial interventions for acute ischemic stroke are available. Although the sensitivity of CT scanning and MRI for large-vessel occlusion is conceivably similar, CT angiography (CTA) may be more practical for several reasons. For example, its more rapid image acquisition makes CTA less susceptible to motion artifacts, more accurate at depicting vascular anatomy, and more sensitive for stenosis, occlusion, vascular malformations, and aneurysms. [56]

Imaging with CT studies has multiple logistic advantages for patients with acute stroke; it is able to more rapidly acquire images than magnetic resonance studies, allowing for assessment with an examination that

includes NCCT, CTA, and CT perfusion in less than 10 minutes. Expedient acquisition is of the utmost importance in acute stroke imaging because of the narrow window of time available for definitive ischemic stroke treatment with pharmacologic agents and mechanical devices. CT studies can also be performed in patients who are unable to tolerate a magnetic resonance examination or who have contraindications to MRI, including pacemakers, aneurysm clips, or other ferromagnetic materials in their bodies. Additionally, CT examination is more easily accessible for patients who require special equipment for maintaining and monitoring life support. [56]

Ultrasonography has multiple uses in the workup of stroke patients. This examination is usually performed on a nonemergent basis to evaluate cerebrovascular ischemic disease preoperatively or in the acute setting after evaluation with CT scanning or MRI. [56]

Transthoracic and transesophageal echocardiography (TTE and TEE, respectively) may also be used in assessing for cardioembolic disease and patent foramen ovale or, more acutely, to exclude thoracic aortic dissection. [56]

Conventional angiography is the gold standard in evaluating for cerebrovascular disease, as well as for disease involving the aortic arch and great vessels in the neck, and for providing less invasive endovascular interventions. This modality can be performed to clarify equivocal findings or to confirm and treat disease seen on MRA, CTA, transcranial Doppler, or neck ultrasonograms. [56]

Angiography is also useful in preoperative evaluation for hemodynamically significant or flow limiting lesions and to confirm the presence of trickle flow versus occlusion seen on ultrasonography when considering carotid endarterectomy. Angiography is also more sensitive than MRA for detecting ulceration and is superior to both MRA and CTA for detecting vasculitis. Angiography allows for endovascular treatment with intraarterial thrombolytic therapy or mechanical thrombectomy in acute stroke and for stenting of patients with arterial stenosis intracranially or in the neck. It can also be used to characterize and treat aneurysms and vascular malformations using stents and embolic agents, such as coils or other embolic material. [56]

**MANAGEMENT:**

Medications used in the treatment of acute stroke include anticonvulsants to prevent seizure recurrence, antihypertensive agents to reduce BP and other risk factors of heart disease, and osmotic diuretics to decrease intracranial pressure in the subarachnoid space. [57]

Perform endotracheal intubation for patients with a decreased level of consciousness and poor airway protection. Intubate and hyperventilate if intracranial pressure is increased, and initiate administration of mannitol for further control. Rapidly stabilize vital signs, and simultaneously acquire emergent CT scan. [57]

*Management of seizures:*

Early seizure activity occurs in 4-28% of patients with intracerebral hemorrhage, and these seizures are often nonconvulsive seizures.[23, 21]Seizure activity should be rapidly controlled with a benzodiazepine, such as lorazepam or diazepam, accompanied by either phenytoin or fosphenytoin loading. Prophylactic anticonvulsant therapy is recommended

in patients with lobar hemorrhages to reduce the risk of early seizures.[1, 23] However, the use of prophylactic anticonvulsant therapy in all cases of intracerebral hemorrhage is controversial, as no prospective controlled trials have demonstrated a clear benefit. [57]

According to the AHA/ASA 2010 guidelines for management of spontaneous ICH, patients with a change in mental status and whose EEG shows electrographic seizures should receive antiepileptic drugs.[57]

*Blood pressure control:*

No controlled studies define optimum BP levels, but greatly elevated BP is thought to lead to rebleeding and hematoma expansion. Patients who have had a stroke may lose their cerebral autoregulation of cerebral perfusion pressure. Rapid or aggressive BP lowering may compromise cerebral perfusion. Nicardipine, labetalol, esmolol, and hydralazine are agents that may be used when necessary for BP control. Avoid nitroprusside because it may raise intracranial pressure. [57]

The American Heart Association guidelines for treating elevated BP are as follows :

- If systolic BP is >200 mm Hg or mean arterial pressure (MAP) is >150 mm Hg, then consider aggressive reduction of BP with continuous IV infusion with frequent BP (every 5 min) checks.
- If systolic BP is >180 mm Hg or MAP is >130 mm Hg and there is evidence or suspicion of elevated intracranial pressure, then consider monitoring of intracranial pressure and reducing BP using intermittent or continuous IV medications to maintain cerebral perfusion pressure >60-80 mm Hg.

- If systolic BP is >180 or MAP is >130 mm Hg and there is NOT evidence or suspicion of elevated intracranial pressure, then consider modest reduction of BP (target MAP of 110 mm Hg or target BP of 160/90 mm Hg) with BP checks every 15 minutes.

One prospective study found a hazard ratio of 1.89 for the risk of poor outcome for each 10% decrease in systolic BP in the first 24 hours of an

acute stroke. Another study found that the use of calcium channel blockers acutely lowered diastolic BP and was associated with worse outcomes[57]

Current recommendations include avoiding more than 10% reduction of BP within the first 24 hours, unless values exceed certain thresholds. These values, which are not based on any specific randomized studies, are 220 mm Hg systolic (some recommend 200 mm Hg systolic) and 115 mm Hg diastolic. Suggested agents for use in the acute setting are beta-blockers (eg, labetalol) and angiotensin-converting enzyme inhibitors (ACEIs) (eg, enalapril). For more refractory hypertension, agents such as nicardipine, nitroprusside, and hydralazine are used. [57]

*Medical treatment of increased intracranial pressure:*

Elevated intracranial pressure may result from the hematoma itself, surrounding edema, or both. The frequency of increased intracranial pressure in patients with intracerebral hemorrhage is not known. [57]

Elevate the head of the bed to 30 degrees. This improves jugular venous outflow and lowers intracranial pressure. The head should be midline and not turned to the side. Provide analgesia and sedation as needed. [57]

More aggressive therapies such as osmotic therapy (mannitol, hypertonic saline), barbiturate anesthesia, and neuromuscular blockage generally require concomitant monitoring of intracranial pressure and BP with an intracranial pressure monitor to maintain adequate cerebral perfusion pressure (CPP) greater than 70 mm Hg. A randomized controlled study of mannitol in intracerebral hemorrhage failed to demonstrate any difference in disability or death at 3 months. [57]

Hyperventilation (partial pressure of carbon dioxide [$PaCO_2$] of 25 to 30-35 mm Hg) is not recommended, because its effect is transient, it decreases CBF, and it may result in rebound elevated intracranial pressure.[1]Glucocorticoids are not effective and result in higher rates of complications with poorer outcomes. [57]

### *Surgical Intervention*

Craniotomy and evacuation:

One of the modalities of treatment is craniotomy and surgical evacuation of hematoma. The role of surgical treatment for supratentorial intracranial hemorrhage remains controversial. Outcomes in published studies are conflicting. A published meta-analysis of studies suggested some promise for early surgical intervention. However, one study comparing early surgery versus initial conservative treatment failed to demonstrate a benefit with surgery. [57]

Surgical intervention for cerebellar hematoma has been shown to improve outcome. It can be lifesaving in the prevention of brainstem compression.

Endovascular treatment of aneurysms:

Endovascular treatment of aneurysms using coils has been increasingly used in recent years with great success as an alternative to

surgical clipping (see the following images), although controversy still exists over which treatment is ultimately superior. [57]

**ACUTE ISCHEMIC STROKES:**

Acute ischemic strokes are the result of vascular occlusion secondary to thromboembolic disease. Ischemia results in cell hypoxia and depletion of cellular adenosine triphosphate (ATP). Without ATP, energy failure results in an inability to maintain ionic gradients across the cell membrane and cell depolarization. With an influx of sodium and calcium ions and passive inflow of water into the cell, cytotoxic edema results.[49]

*Etiology:*

Ischemic strokes result from events that limit or stop blood flow, such as extracranial or intracranial thrombosis embolism, thrombosis in situ, or relative hypoperfusion. As blood flow decreases, neurons cease

functioning, and irreversible neuronal ischemia and injury begin at blood flow rates of less than 18 mL/100 g of tissue/min.[49]

**Risk factors**:

Risk factors for ischemic stroke include modifiable and nonmodifiable etiologies. Identification of risk factors in each patient can uncover clues to the cause of the stroke and the most appropriate treatment and secondary prevention plan.[49]

Nonmodifiable risk factors include the following:

- Age
- Race
- Sex
- Ethnicity
- History of migraine headaches
- Sickle cell disease

- Fibromuscular dysplasia
- Heredity

Modifiable risk factors include the following:

- Hypertension (the most important)
- Diabetes mellitus
- Cardiac disease - Atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies allowing right to left shunting, such as a patent foramen ovale and atrial and ventricular enlargement
- Hypercholesterolemia
- Transient ischemic attacks (TIAs)
- Carotid stenosis
- Hyperhomocystinemia
- Lifestyle issues - Excessive alcohol intake, tobacco use, illicit drug use, obesity, physical inactivity
- Oral contraceptive use

Among the types of cardiac disease that increase stroke risk are atrial fibrillation, valvular disease, mitral stenosis, and structural anomalies

allowing right-to-left shunting, such as a patent foramen ovale and atrial and ventricular enlargement.

**Large-artery occlusion**:

Large artery occlusion typically results from embolisation of atherosclerotic debris originating from the common or internal carotid arteries or from a cardiac source. A smaller number of large-artery occlusions may arise from plaque ulceration and in situ thrombosis. Large-vessel ischemic strokes more commonly affect the MCA territory with the ACA territory affected to a lesser degree.[49]

*Investigations***:**

Laboratory evaluation of the patient with ischemic stroke should be driven by comorbid illnesses as well as the potential acute stroke. Additional laboratory tests are tailored to the individual patient. They may include rapid plasma reagent (RPR), toxicology screen, fasting lipid profile,

sedimentation rate, pregnancy test, antinuclear antibody (ANA), rheumatoid factor, and homocysteine.[51]

CT is the most commonly used form of neuroimaging in the acute evaluation of patients with apparent acute stroke. MRI with magnetic resonance angiography (MRA) has been a major advance in the neuroimaging of stroke; MRI not only provides great structural detail but also can demonstrate impaired metabolism. [51]

Carotid duplex scanning is one of the most useful tests in evaluating patients with stroke. Increasingly, it is being performed earlier in the evaluation, not only to define the cause of the stroke but also to stratify patients for either medical management or carotid intervention if they have carotid stenoses. [51]

Digital subtraction angiography is considered the definitive method for demonstrating vascular lesions, including occlusions, stenoses, dissections, and aneurysms[51]

CBC count serves as a baseline study and may reveal a cause for the stroke (eg, polycythemia, thrombocytosis, thrombocytopenia, leukemia) or provide evidence of concurrent illness (eg, anemia). [51]

Chemistry panel serves as a baseline study and may reveal a stroke mimic (eg, hypoglycemia, hyponatremia) or provide evidence of concurrent illness (eg, diabetes, renal insufficiency). [51]

Coagulation studies may reveal a coagulopathy and are useful when thrombolytics or anticoagulants are to be used. In patients who are not anticoagulated and in whom there is no suspicion for coagulation abnormality, administration of recombinant tissue-type plasminogen activator (rt-PA) should not be delayed awaiting laboratory studies. [51]

Cardiac biomarkers are important because of the association of cerebral vascular disease and coronary artery disease. Additionally, several studies have indicated a link between elevations of cardiac enzyme levels and poor outcome in ischemic stroke[51]

**Hemorrhagic Transformation of ischemic stroke:**

Hemorrhagic transformation represents the conversion of a bland infarction into an area of hemorrhage. Proposed mechanisms for hemorrhagic transformation include reperfusion of ischemically injured tissue, either from recanalization of an occluded vessel or from collateral blood supply to the ischemic territory or disruption of the blood-brain barrier. With disruption of the blood-brain barrier, red blood cells extravasate from the weakened capillary bed, producing petechial hemorrhage or more frank intraparenchymal hematoma.[53]

Hemorrhagic transformation of an ischemic infarct occurs within 2-14 days post ictus, usually within the first week. It is more commonly seen following cardioembolic strokes and is more likely with larger infarct size.Hemorrhagic transformation is also more likely following administration of tissue plasminogen activator (tPA) and with noncontrast CT scans demonstrating areas of hypodensity.[53]

There has been a long-standing dispute over the increased risk of cerebral hemorrhage at lower levels of cholesterol. Various reports[21,30,31]

stated that low cholesterol level was associated with cerebral hemorrhage, but others[32,33] reported against the positive association of low cholesterol level and hemorrhagic stroke. Whereas the initial lipid-lowering therapy trial[34] reported the absence of significant association, recent intensive lipid-lowering treatment trial[23] showed a 68% increase of hemorrhagic stroke by treating with 80-mg atorvastatin.

The underlying biological explanation over the mechanism of increased cerebral hemorrhages at low levels of TC or LDLC is not yet established. There has been reports that adequate cholesterol may be important for maintaining the integrity of cerebral small vessels,[22,35] and that experimental injection of immunoliposome may ameliorate the endothelial damage after thrombolysis.[36] Additionally, cerebral microbleeds, which may reflect the blood extravasation around cerebral small vessels,[37] were known to be prevalent in ischemic stroke patients with low TC levels.[38]

Finally, the low TC or LDLC levels without lipid-lowering therapy may reflect poor general medical condition, which is indicative of increased HTf

after ischemic stroke. [39] From these considerations, low levels of TC and LDLC may increase the incidence of cerebral hemorrhage by way of disturbed cerebral small vessel integrity.

These findings lead to the question of under what circumstances does HTf occur. Blood–brain barrier consists of endothelial cells of cerebral microvessels and the basement membrane and protects the brain against noxious chemicals, variations in blood composition, and breakdown of the concentration gradient.[40] HTf is linked to the processes that alter the integrity of the neurovascular unit, which consists of BBB, astrocytes, and adjacent neurons,[15] and that causes the extravasation of blood over ischemic vascular endothelial cells. After ischemic insult, the permeability of BBB increases significantly,[41] resulting in the extravasation of plasma components and edema formation.[42]

Moreover, not only the vascular endothelial cells but also the astroglial cells are known to protect against the increasing permeability after hypoxic insult.[43] Therefore, after long-standing subclinical hypoxic injury to the brain, it is possible that the cumulative damage on endothelial

cells, astroglia, and neurons, ie, the neurovascular unit, may evoke HTf after acute ischemic stroke.

One of the most important points distinguishing LAA from CE is the stenosis of proximal cerebral large arteries. The stenosed proximal arteries may damage cerebral neurovascular units of relevant territory in various ways. The narrow proximal larger arteries are known to associate with low perfusion state in the brain,[44] and microemboli are reported to increase in stenosis of proximal arteries.[45]

In contrast, CE, by definition, implies heart-originating embolism without meaningful cerebral arterial stenosis,[25] and may have relatively intact neurovascular unit without long-standing subclinical injuries. In other words, HTf may tend to occur in the cerebral vessels of LAA patients who have been exposed to various injuries associated with proximal arterial stenosis in the hemorrhage-prone condition of low TC or low LDLC. However, in the cerebral vessels of CE, which contain relatively intact neurovascular unit than those of LAA, low levels of TC or LDLC may have limited influence on the occurrence of HTf.

# MATERIALS AND METHODS

Setting : In-patients department,

Institute of Internal Medicine,

Rajiv Gandhi Government General Hospital,

Madras Medical College, Chennai.

Ethical committee Approval : Obtained

Design of study : Cross sectional study

Period of study : April2011 to November2011.

Sample size : 100 patients.

## Materials & Methods :

### Inclusion Criteria:

All new onset Acute ischemic stroke of atherothrombotic etiology, and Acute intracerebral hemorrhage

### Exclusion criteria:

The following patients were excluded from the study group:

1. Patients having Embolic stroke
2. Patients having Recurrent stroke
3. Patients with Small vessel disease
4. Stroke of other known etiologies
5. Stroke of unknown etiologies
6. Transient ischemic attacks
7. Patients requiring neurosurgical procedures
8. Patients already taking antilipidemic drugs
9. Patients thrombolysed and developing hemorrhagic transformation

10. Patients with bleeding diathesis or drug induced bleeding

**Methodology & Investigation details for ICH patients:**

Intracerebral hemorrhage patients admitted to our hospital, other than those coming under exclusion criteria are taken up. The history of diabetes, systemic hypertension, antilipidemic drug intake and smoking and alcohol history, all are recorded. Their vitals, GCS are recorded. Lipid profile including LDL-C, HDL-C, Total C, Triglycerides all are done and recorded. ICH site, and volume are noted down. Volume <40ml is considered as mild; 40-60ml moderate and >60ml is considered severe.

The patients are followed up over a period of one month and the

mortality related to ICH per se is noted down. Then the patients are segregated into two groups: patients who died and patients who survived. The two study groups are compared according to their mean and standard deviation for lipid profile and BP. Any statistically significant difference is noted down.

**Methodology and investigation details for thrombotic stroke:**

All thrombotic infarct patients with occlusion of large arteries like Proximal MCA, PCA are taken into account. History of smoking, Alcoholism, diabetes, systemic hypertension, drug intake and previous history of stroke are recorded. With the exclusion criteria, some of the patients are excluded. Basic investigations like Blood sugar, Lipid profile are taken. Admission BP and GCS are noted down.

All patients have to undergo a repeat CT preferably at one week

interval to look for hemorrhagic transformation. The data is analysed by grouping the patients into two groups – those with and without hemorrhagic transformation.

**DATA ANALYSIS:**

After collection, the data is segregated in to various groups and analysed using unpaired t test and chi square test. P values are calculated and the statistical significance interpreted.

# RESULTS

## INTRACEREBRAL HEMORRHAGE PATIENTS

Patient characteristics for ICH:

| Patient character | Percentage or median with quartiles |
|---|---|
| AGE: | |
| <40yrs | 2% |
| 40 – 50 yrs | 28% |
| 50 - 60yrs | 34% |
| 60 – 70yrs | 22% |
| >70yrs | 14% |
| Males | 70% |
| Females | 30% |
| H/O diabetes | 36% |
| H/O systemic hypertension | 46% |
| H/O smoking | 46% |
| H/O alcoholism | 36% |

Patient profile after admission:

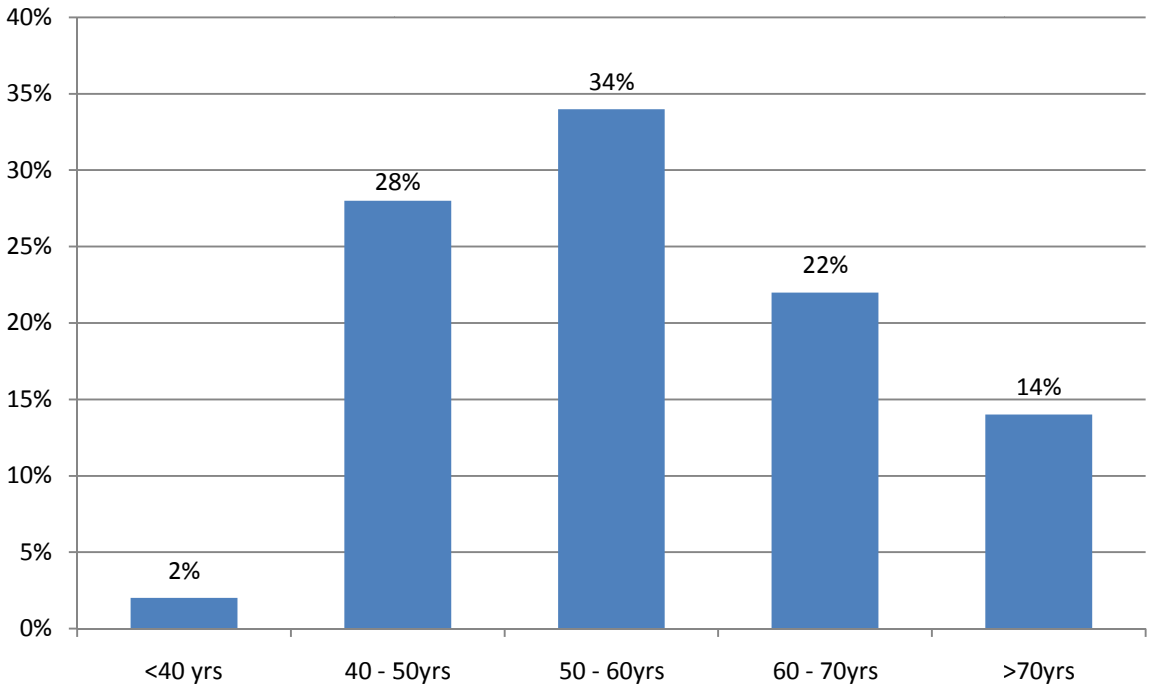
| Parameter | Percentage |
|---|---|
| BP: | |
| Systolic: | |
| ≤140mmHg | 12% |
| 140-160mmHg | 20% |
| >160mmHg | 68% |
| Diastolic: | |
| ≤90mmHg | 12% |
| 90 – 100mmHg | |

| | |
|---|---|
| >100mmHg | 20% |
| | 68% |
| Total cholesterol | |
| 150 – 200 | 78% |
| ≥200 | 22% |
| Triglycerides | |
| ≤150 | 22% |
| 150 – 199 | 54% |
| ≥200 | 24% |
| HDL | |
| <40 | 34% |
| ≥40 | 66% |
| LDL – cholesterol | |
| <100 | 30% |
| 100 – 110 | 20% |
| >110 | 50% |
| ICH site | |
| Gangliocapsular, thalamic | 60% |
| Lobar | 40% |
| ICH volume | |
| Mild | 24% |
| Moderate | 40% |
| Massive | 36% |
| GCS | |
| >10 | 16% |
| 6 – 10 | 42% |
| < 6 | 42% |
| 90 day mortality | 52% |

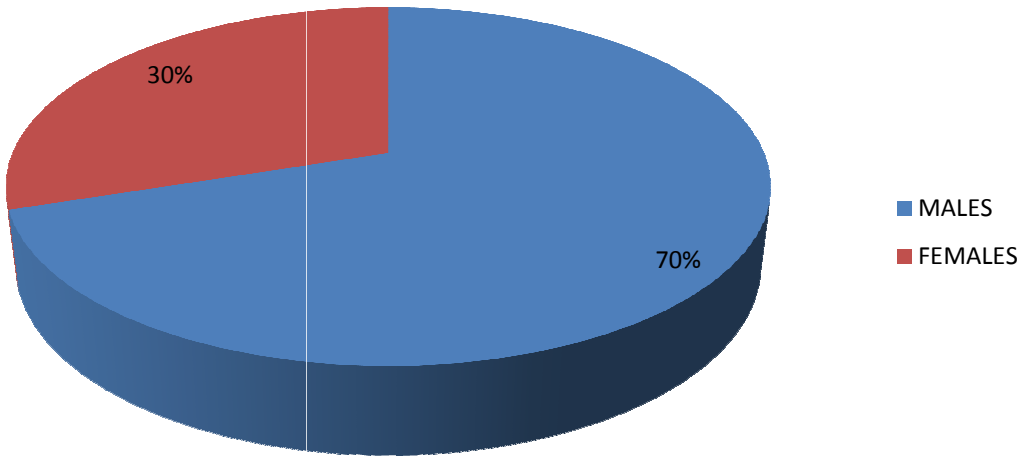
Comparison of died and survived patients in 30 days:

| Parameter | Among died patients 26pts | Among survived patients 24pts |
|---|---|---|
| LDL-C | | |
| <100 | 42% | 17% |
| 100 – 110 | 23% | 17% |
| >110 | 35% | 66% |
| Total cholesterol | | |
| 150 – 199 | 77% | 79% |
| ≥200 | 23% | 21% |
| Triglycerides | | |
| <150 | 23% | 17% |
| 150 – 200 | 62% | 54% |
| >200 | 15% | 29% |
| BP on admission: | | |
| <160/100 | 19% | 29% |
| >160/100 | 81% | 71% |
| Lobar | 46% | 29% |
| Gangliocapsular and thalamic | 54% | 71% |

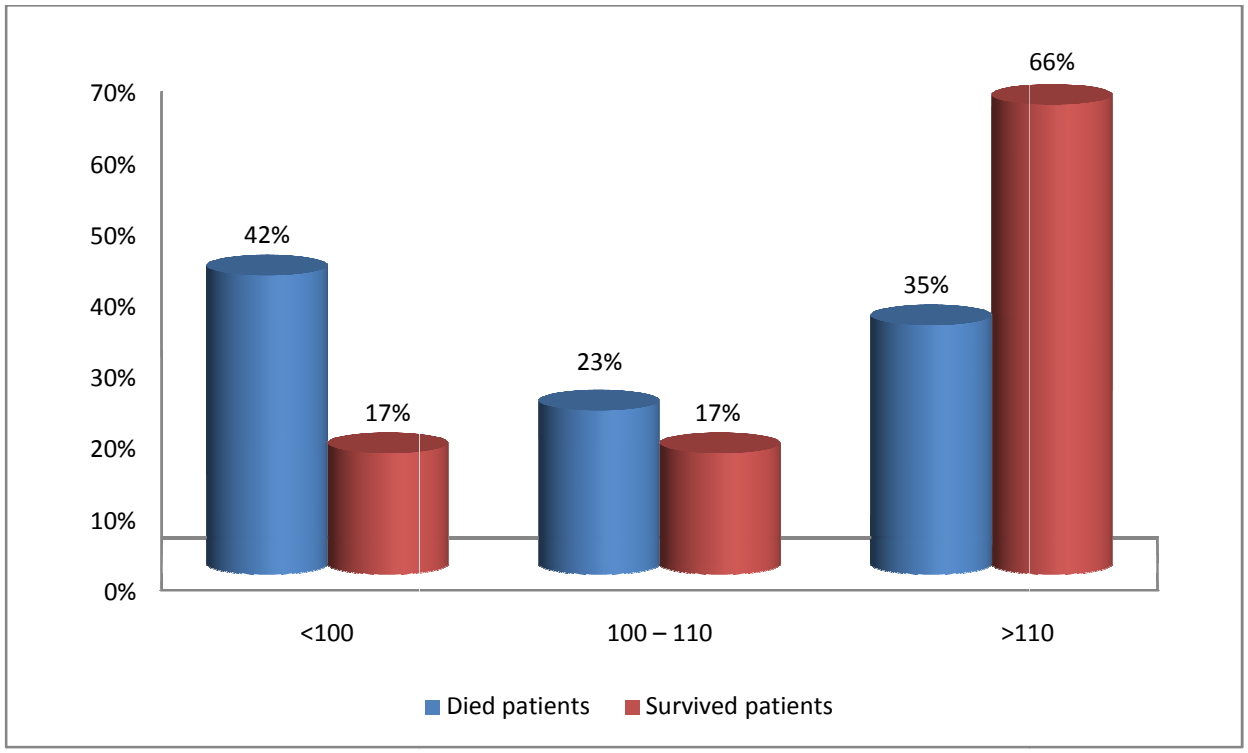
## Age distribution



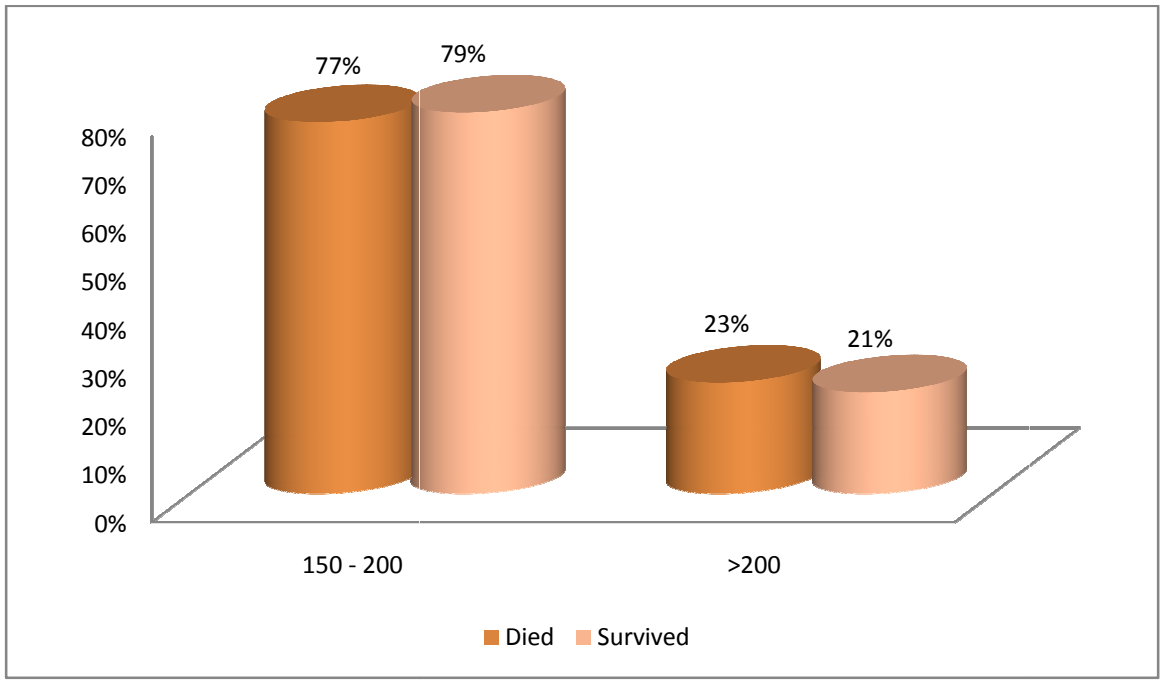

## SEX DISTRIBUTION



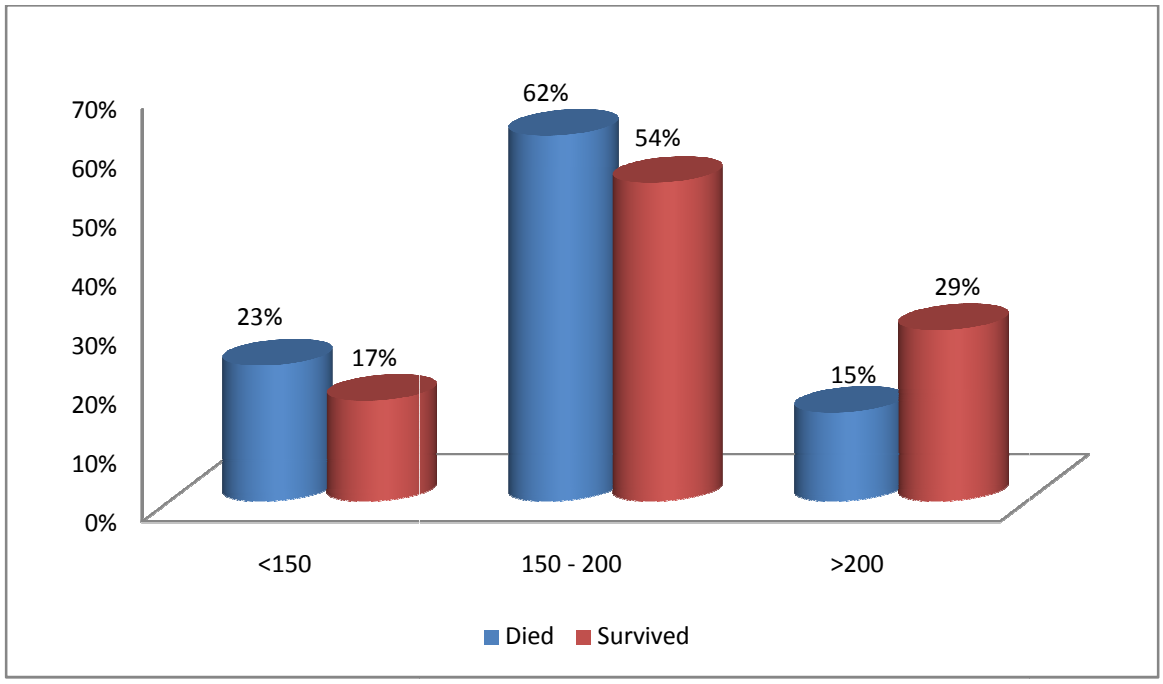
## LDL-Cholesterol among survived and died patients



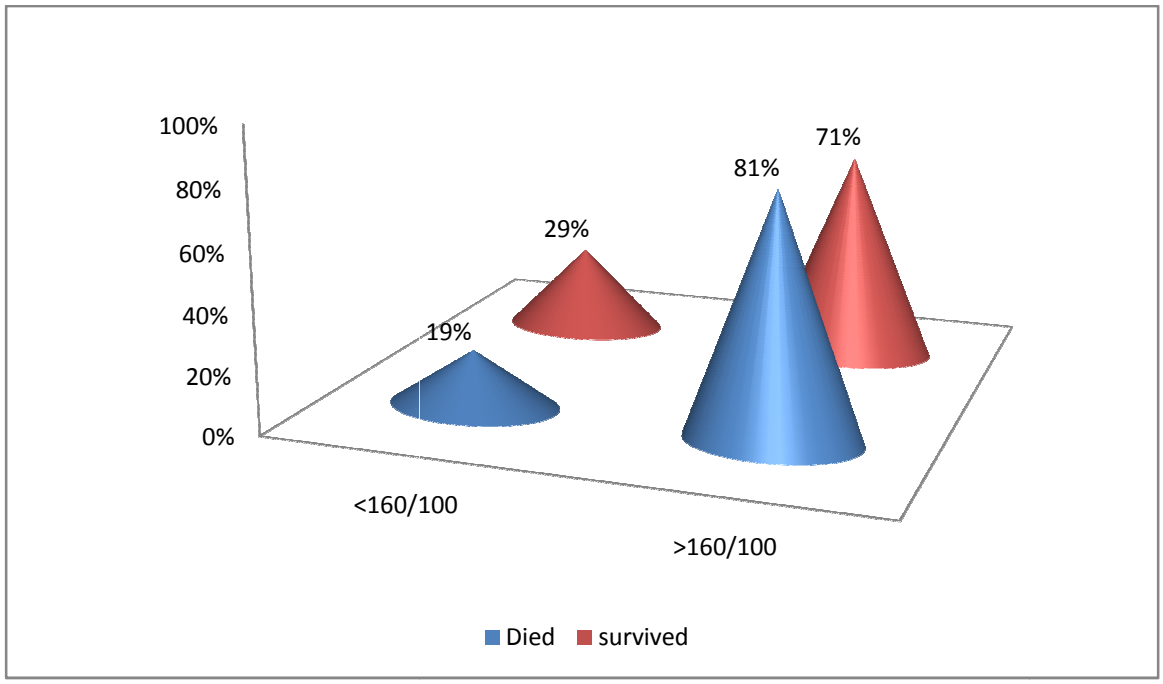

## Total Cholesterol among died and survived patients



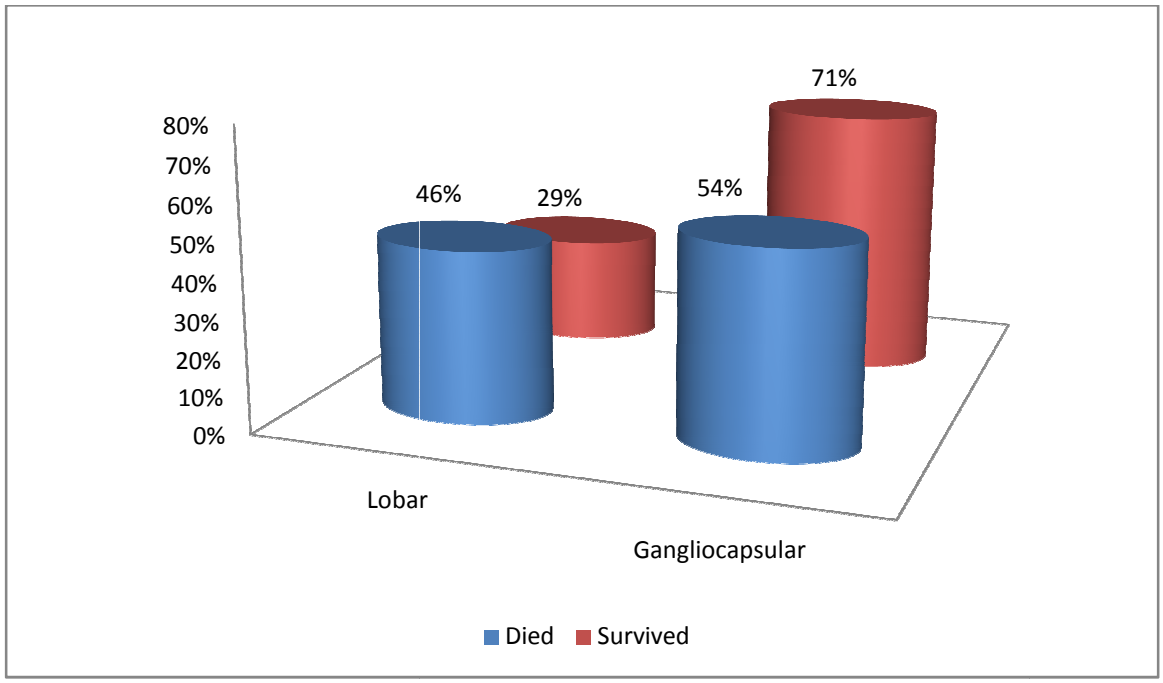
**Triglycerides among died and survived patients:**




**Comparison of Admission BP among died and survived patients:**



**Site of Hemorrhage and survival rate:**



## LARGE ARTERY THROMBOTIC INFFARCT PATIENTS

| Patient character | Percentage or median with quartiles |
|---|---|
| AGE: | |
| <40yrs | 6% |
| 40 – 50 yrs | 16% |
| 50 - 60yrs | 42% |
| 60 – 70yrs | 26% |
| >70yrs | 10% |
| Males | 68% |
| Females | 32% |
| H/O diabetes | 50% |
| H/O systemic hypertension | 48% |
| H/O smoking | 40% |
| H/O alcoholism | 36% |

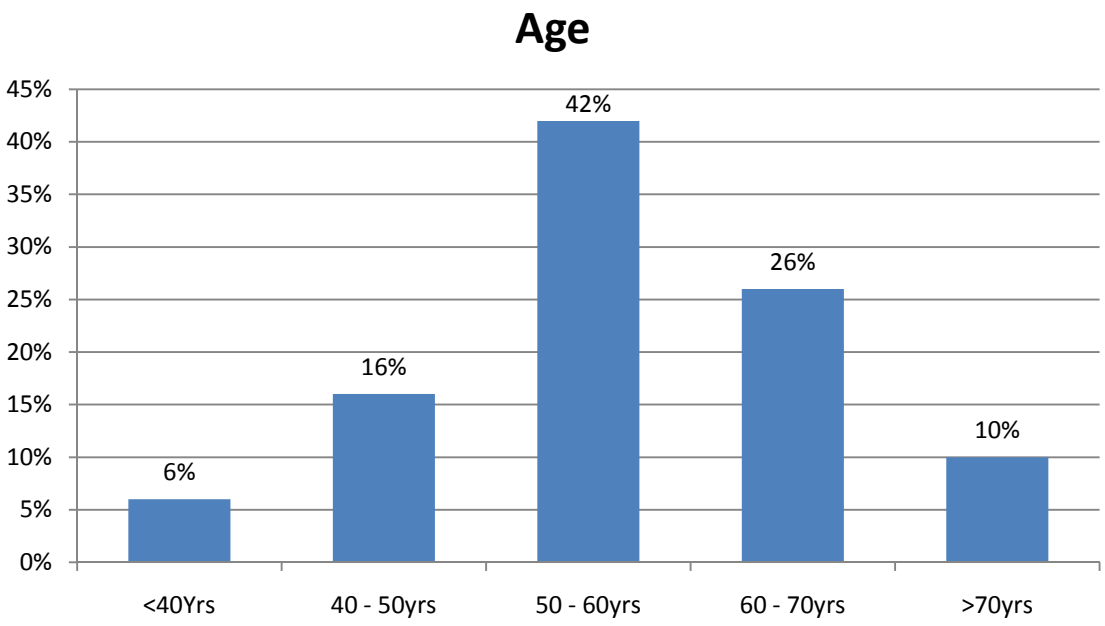
Patient profile after admission:

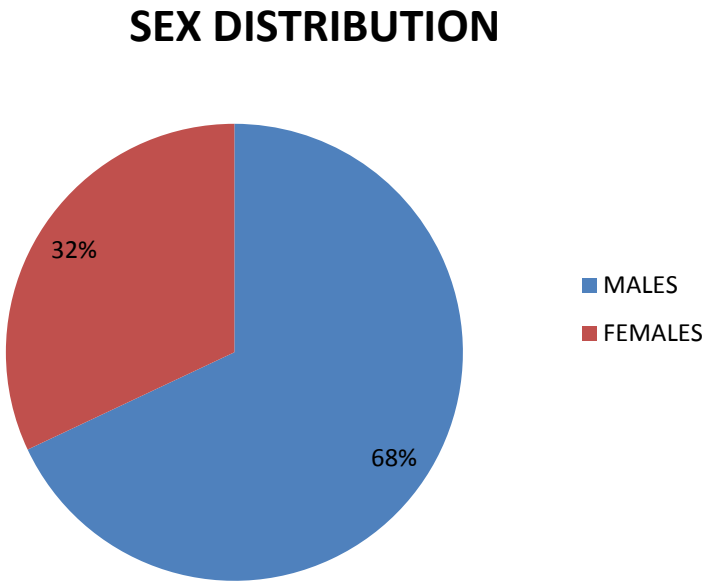
| Parameter | | Percentage |
|---|---|---|
| BP: | | |
| Systolic: | | |
| | ≤140mmHg | 14% |
| | 140-160mmHg | 42% |
| | >160mmHg | 44% |
| Diastolic: | | |
| | ≤90mmHg | 32% |
| | 90 – 100mmHg | 32% |
| | >100mmHg | 36% |
| Total cholesterol | | |
| | 150 – 200 | 82% |
| | ≥200 | 18% |
| Triglycerides | | |
| | ≤150 | 14% |
| | 150 – 199 | 64% |
| | ≥200 | 22% |

| | |
|---|---|
| HDL | |
| <40 | 42% |
| ≥40 | 58% |
| LDL – cholesterol | |
| <100 | 28% |
| 100 – 110 | 32% |
| >110 | 40% |
| Infarct territory | |
| ACA | 2% |
| MCA | 82% |
| PCA | 16% |
| GCS | |
| >10 | 6% |
| 6 – 10 | 76% |
| < 6 | 18% |
| Hemorrhagic transformation | 28% |

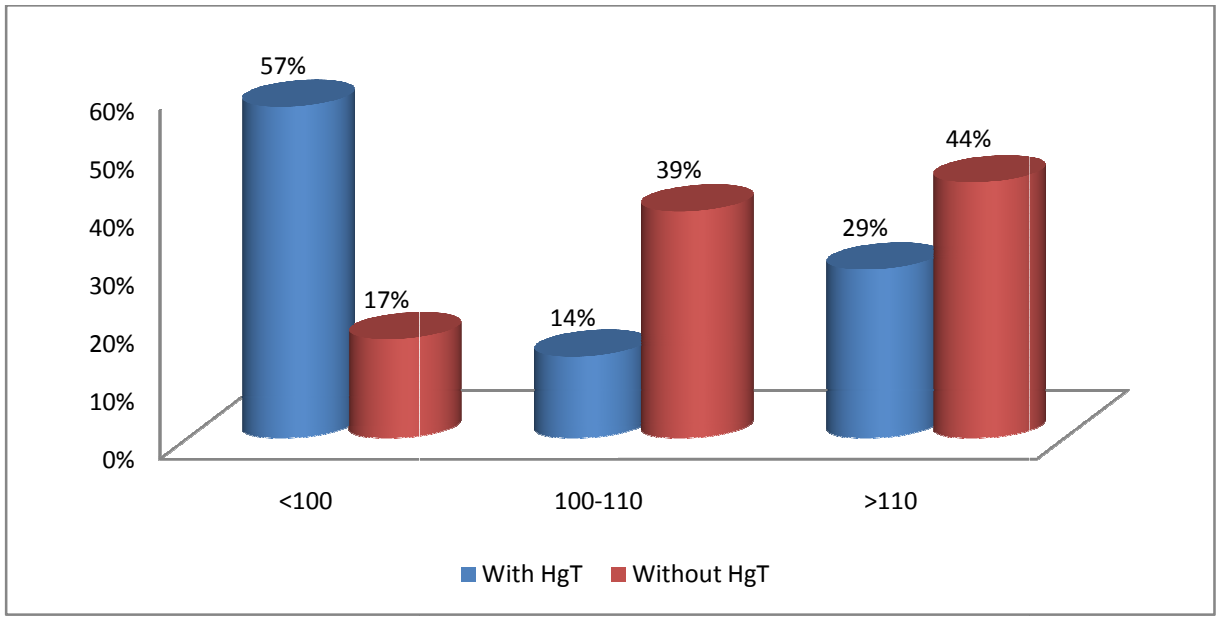
Comparison of patients with and without hemorrhagic transformations:

| Parameter | Among patients with Hgic transformation 14pts | Among patients without Hgic transformation 36pts |
|---|---|---|
| LDL-C | | |
| <100 | 57% | 17% |
| 100 – 110 | 14% | 39% |
| >110 | 29% | 44% |
| Total cholesterol | | |
| 150 – 199 | 86% | 81% |
| ≥200 | 14% | 19% |
| Triglycerides | | |
| <150 | 0% | 8% |
| 150-200 | 71% | 73% |
| >200 | 29% | 19% |
| BP on admission: | | |
| <160/100 | 50% | 36% |
| >160/100 | 50% | 64% |
| MCA teritorry | 86% | 83% |
| PCA teritorry | 14% | 17% |

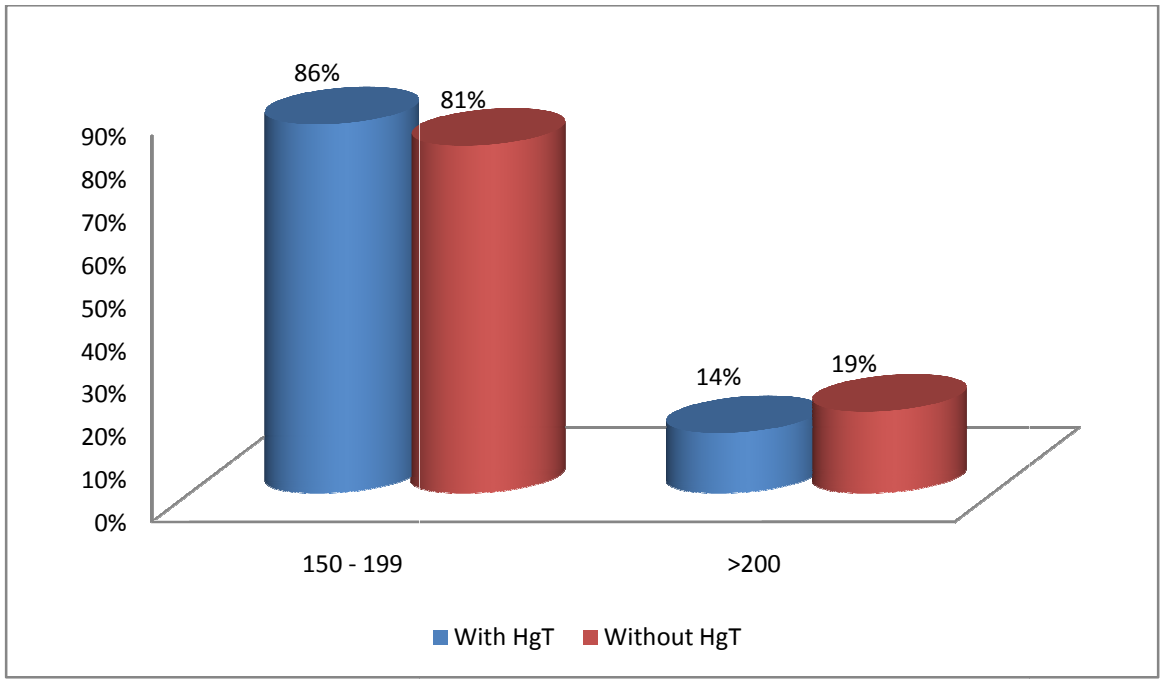

Age
45%
40%
35%
30%
25%
20%
15%
10%
5%
0%
6%
16%
42%
26%
10%
<40Yrs
40 - 50yrs
50 - 60yrs
60 - 70yrs
>70yrs


SEX DISTRIBUTION
32%
68%
MALES
FEMALES

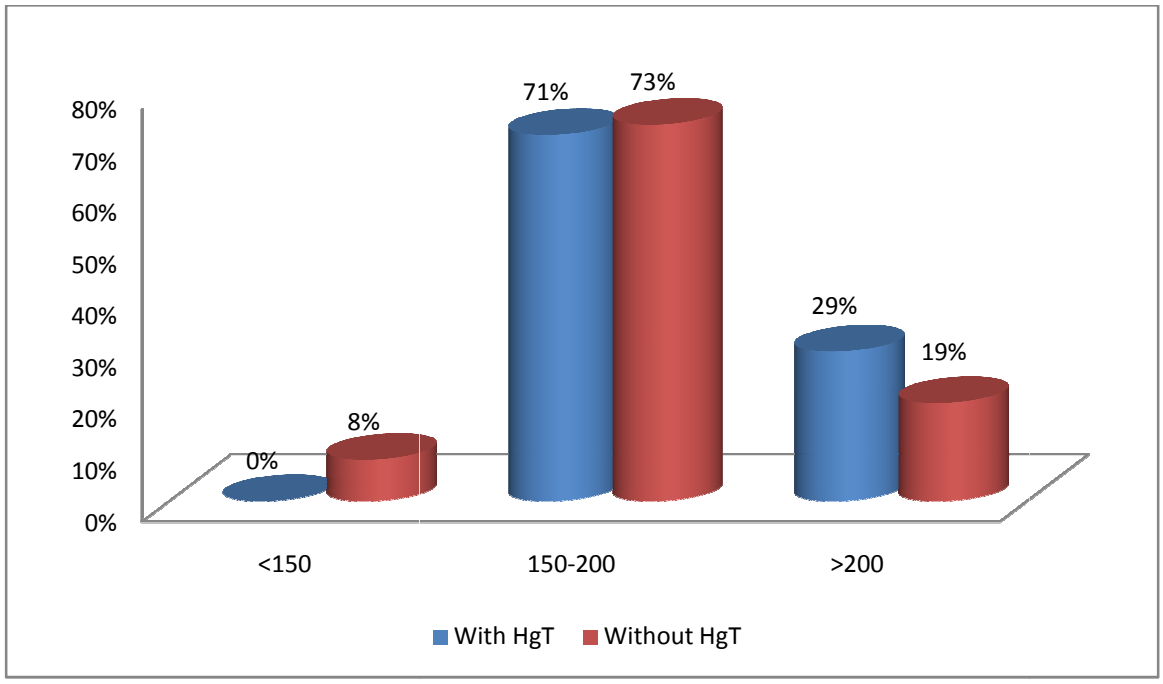
**LDL- cholesterol among patients with and without hemorrhagic transformation**



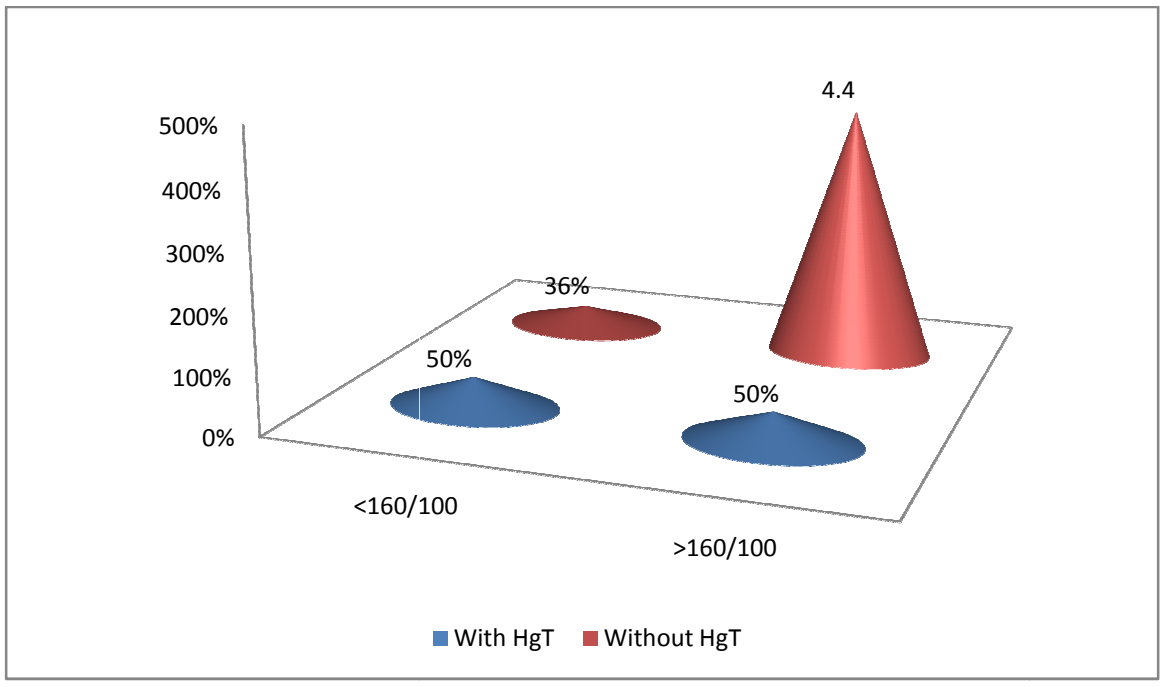

**Total cholesterol among patients with and without Hemorrhagic transformation**



## Triglycerides among both the categories:




## Admission BP among the two categories:



# DISCUSSION

## Mortality in ICH:

| Parameter | **Mean ± SD for Died patients n=26** | **Mean ± SD for Survived pts N=24** | **P value** |
|---|---|---|---|
| LDL - C | 108 ± 24 | 116 ± 17 | 0.1697 (ns) |
| Total C | 180 ± 23 | 191 ± 18 | 0.0538 (ss) |
| TGL | 168 ± 30 | 181 ± 27 | 0.1031 (ns) |
| HDL | 40 ± 5 | 40 ± 5 | 0.7981 (ns) |
| Systolic BP | 171 ± 37 | 169 ± 20 | 0.8556 (ns) |
| Diastolic BP | 110 ± 22 | 114 ± 13 | 0.4256 (ns) |

According to the above statistics, the mean LDL-C of patients with ICH who died was 108 with a standard deviation of 24; Where as it was 116 with a standard deviation of 17. Though the levels of LDL-C is little lower in patients who died, the p value is 0.1697 which implies that this is not statistically significant. This contradicts the study conducted by Jose Maria et al, who proved that lower LDL-C predicts ICH mortality.

The mean total cholesterol of patients who died was 180 with a SD of 23; for patients who survived it was 191 with a SD of 18. This data carries a P value of 0.0538 and is not of much significance statistically. But we can imply that a lower total cholesterol can predict mortality to some extent. Studies have a revealed a U shaped relationship between total cholesterol and all cause mortality.[8]

The mean triglycerides of patients who died was 168 with a SD of 30, and of patients who survived was 181 with a SD of 27; The P value was 0.1031; Again though this is not statistically significant, we can infer that to some extent lower triglyceride levels similar to total cholesterol levels, can predict mortality to some extent.

The HDL levels of both the study groups were almost same and no significant value could be obtained

Similary the systolic and diastolic BP are also of the same among both the study groups and no significant difference obtained.

.

Some authors suggest that higher cholesterol levels are associated with lesser hemorrhage growth.[9] Cholesterol is known to have effects on the vasculature and is essential for normal membrane fluidity, and adequate cholesterol levels may be important for maintaining the integrity of vessels and their resistance to rupture.[10]

Theoretically, statins may increase the risk of cerebral hemorrhage because high cholesterol apparently protects against ICH.[2] Meta-analyses provide evidence that the statins significantly reduce the risk of ischemic stroke, however a recent review suggests that this beneficial effect is partly reduced by increasing ICH.[11]

Other predictors of mortality in ICH:

AGE vs MORTALITY [P = 0.4720] not significant

| PATIENTS | AGE <40 | 40-50 | 50-60 | 60-70 | >70 |
|---|---|---|---|---|---|
| DIED | 1 | 7 | 5 | 8 | 5 |
| SURVIVED | 0 | 7 | 12 | 3 | 2 |

ICH incidence is highest in the age group 50 – 60yrs. But the mortality seems to be highest in older age groups. But the p valus is higher and this is not statistically significant

SEX vs MORTALITY [P = 0.9318] not significant

| PATIENTS | MALES | FEMALES |
|---|---|---|
| DIED | 18 | 8 |
| SURVIVED | 17 | 7 |

Incidence of ICH is more among males. But the mortality seems to be that of same incidence in both sexes. P value is much higher and the test is not statistically significant

ICH VOLUME vs MORTALITY [P = 0.0006] very much significant

| PATIENTS | ICH VOLUME <40ml | ICH VOLUME 40 – 60ml | ICH VOLUME >60ml |
|---|---|---|---|
| DIED | 0 | 8 | 18 |
| SURVIVED | 12 | 12 | 0 |

When the ICH volume goes more than 60ml, all patients in our study invariably died. This test carries a p value of 0.0006 and is very much statistically significant.

ICH SITE vs MORTALITY [P = 0.2319] not significant

| PATIENTS | GANGLIOCAPSULAR | THALAMIC | LOBAR |
|---|---|---|---|
| DIED | 14 | 0 | 12 |
| SURVIVED | 11 | 5 | 8 |

Gangliocapsular hemorrhage is more commoner than lobar. But mortality is almost equal among both groups. None of the thalamic hemorrhage patients died. But that is because the volume of hemorrhage is very less. The test carries a P value of 0.2319 and not of statistically significant.

From the above data, it is clear that mortality is significantly related to the ICH volume and not much significantly related to the other parameters like age, sex, and site of ICH

## Hemorrhagic Transformation in Large Artery Infarct:

| Parameter | Mean ± SD for pts with HgT n = 15 | Mean ± SD for Pts without HgT N = 35 | P value |
|---|---|---|---|
| LDL - C | 100 ± 15 | 113 ± 17 | 0.015 (ss) |
| Total C | 177 ± 17 | 188 ± 17 | 0.0345 (ss) |
| TGL | 181 ± 22 | 179 ± 23 | 0.7654 (ns) |
| HDL | 41 ± 7 | 40 ± 5 | 0.5789 (ns) |
| Systolic BP | 165 ± 16 | 161 ± 24 | 0.5416 (ns) |
| Diastolic BP | 101 ± 10 | 129 ± 17 | 0.5208 (ns) |

The mean LDL-C among patients with Hemorrhagic transformation was 100 with a SD of 15 whereas, it was 113 with a SD of 17 for patients without hemorrhagic transformation. This carries a P value of 0.015 and is statistically significant.

The mean Total cholesterol for patients with Hemorrhagic transformation was 177 with a SD of 17 and it was 188 with a SD of 17 among patients without Hemorrhagic transformation. This carries a P value of 0.0345 and is also statistically significant.

In contrast, the triglycerides, HDL-C and BP were almost same among the two groups with and without Hemorrhagic transformation and they carry no significant correlation.

Other parameters in relation to Hemorrhagic transformation:

AGE vs HEMORRHAGIC TRANSFORMATION [P = 0.1790], not significant

| | Age <40 | 40-50 | 50-60 | 60-70 | >70 |
|---|---|---|---|---|---|
| With HgT | 3 | 2 | 4 | 5 | 1 |
| Without HgT | 0 | 6 | 17 | 8 | 4 |

Again the incidence of large artery thrombotic stroke is more in the age group 50 – 60yrs. But there is no significant difference in the incidence of hemorrhagic transformation among various age

groups. The test carries a higher P value and is not statistically significant.

SEX vs HEMORRHAGIC TRANSFORMATION [P = 0.9119] not significant

| | Males | Females |
|---|---|---|
| Patients with HgT | 10 | 5 |
| Patients without HgT | 24 | 11 |

The incidence of large artery infarct is higher among males and hence the incidence of hemorrhagic transformation. The test carries a higher P value and hence is not statistically significant.

ARTERIAL TERRITORY vs HEMORRHAGIC TRANSFORMATION [ P = 0.3813 ] not siginificant

| | MCA territory | PCA terittory | ACA territory |
|---|---|---|---|
| With HgT | 12 | 3 | 0 |
| Without HgT | 29 | 5 | 1 |

MCA territory infarcts are more common and hence the incidence of hemorrhagic transformation. The test carries a higher P value and hence is not statistically significant.

From the above data, it is clear that incidence of hemorrhagic transformation is in no way related to parameters like age, sex or the arterial territory involved.

# CONCLUSION

## ICH mortality:

1. It was found that LDL-C has no statistically significant relationship with ICH mortality in contrast to the studies performed by Ramirez Morino et al and Molina et al.
2. Low total cholesterol to some extent predicts the mortality in ICH patients
3. ICH volume has a very high significant correlation with the ICH mortality
4. The other parameters like HDL-C, Triglycerides, age, sex and site of ICH have no significant correlation with mortality.

## Hemorrhagic transformation:

1. It was found that low LDL-C is directly related to the hemorrhagic transformation of large artery thrombotic infarct with a very low P value and is highly statistically significant. This supports the results found out by Kim et al.
2. Similarly low Total cholesterol also is directly related to the incidence of hemorrhagic transformation.
3. The other parameters like HDL-C, Triglycerides, blood pressure are not significantly related to Hemorrhagic transformation.
4. Age, sex and the arterial territory involved also are not having any significant correlation with the incidence of hemorrhagic transformation.

**Limitations of the study:**

1. The study population is comparatively less
2. Exclusion criteria is broad
3. Only people in and around Chennai were compared
4. MRI detects hemorrhagic transformation better than CT and it is not used in this study due to economical reasons

**FURTHER STUDIES**:

The study has to be conducted in a larger population and the relation of LDL-C to the mortality in ICH patients should be established

Since Low cholesterol patients are prone for hemorrhagic transformation, study has to be conducted whether thrombolysis can be done in patients with lower cholesterol. Clear role of statins in ICH patients and in patients with large artery infarct undergoing thrombolysis should be studied

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# APPENDIX

## ABBREVIATIONS

ACA – Anterior Cerebral Artery

ACEI – Angiotensin Converting Enzyme Inhibitors

AHA – American Heart Association

ASA – American Stroke Association

ATP – Adenosine Triphosphate

BBB – Blood Brain Barrier

BP – Blood Pressure

CBF – Cerebral Blood Flow

CE – CardioEmbolism

CPP – Cerebral Perfusion Pressure

CT – Computed Tomography

CTA – Computed Tomographic Angiography

CVA – Cerebro Vascular Accident

DWI – Diffusion Weighted Imaging

EEG – ElectroEncephaloGram

GCS – Glassgow Coma Scale

HDL-C – High Density Lipoprotein Cholesterol

HTf – Hemorrhagic Transformation

ICH – IntraCerebral Hemorrhage

LAA – Large Artery Atherothrombosis

LDL-C – Low density Lipoprotein Cholesterol

MAP – Mean Arterial Pressure

MCA – Middle Cerebral Artery

MRI – Magnetic Resonance Imaging

MRA – Magnetic Resonance Angiography

NCCT – Non Contrast Computed Tomography

ns – not statistically significant

PCA – Posterior Cerebral Artery

SD – Standard Deviation

SPARCL – Stroke Prevention by Aggressive Reduction in Cholesterol Levels

ss – statistically significant

TC, Total C – Total Cholesterol

TGL – Triglycerides

# PROFORMA

Proforma for Serum LDL-C and its relation to mortality in ICH pts, and risk of Hemorrhagic transformation in atherothrombotic stroke

NAME: AGE/SEX:

OCCUPATION:

ADDRESS AND CONTACT NUMBER:

CLINICAL PRESENTATION:

COMORBID ILLNESS:

SMOKING:

ALCOHOL:

PREVIOUS HISTORY OF STROKE:

PREVIOUS USE OF DRUGS:

1. ANTIHYPERTENSIVES:
2. ANTIDIABETICS:
3. LIPID LOWERING AGENTS:
4. ANTIPLATELETS AND ANTICOAGULANTS:

CLINICAL DIAGNOSIS:

GCS AT ADMISSION:

BP AT ADMISSION:

RBS AT ADMISSION:

LIPID PROFILE AT ADMISSION:

- TOTAL CHOLESTEROL:
- HDL:
- LDL:
- TRIGLYCERIDES:

PT/APTT:

CT BRAIN AT THE TIME OF ADMISSION:

ISCHEMIA – LOCALISATION:

ICH:

- LOCALISATION:
- VOLUME:
- VENTRICULAR EXTENSION:
- INFRATENTORIAL AFFECTATION:

FOUR VESSEL DOPPLER:

CT BRAIN AT 1 WEEK OF ADMISSION:

FOLLOW UP OF THE PATIENT UP TO 30 DAYS