“A STUDY ON PREDICTORS OF OUTCOME AND RECURRENCE RISK IN EMBOLIC STROKE OF UNDETERMINED SOURCE”

Dr. Jithin George

DM NEUROLOGY THESIS

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A THESIS SUBMITTED BY

Dr. Jithin George

TO

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM.

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

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DECLARATION BY THE STUDENT

CERTIFICATE

I Dr. Jithin George, hereby certify that I had personally carried out the work depicted in the thesis titled, "**A STUDY ON PREDICTORS OF OUTCOME AND RECURRENCE RISK IN EMBOLIC STROKE OF UNDETERMINED SOURCE**". No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

Date: 25/07/2022 *Dr. Jithin George*

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The thesis entitled, "A STUDY ON PREDICTORS OF OUTCOME AND RECURRENCE RISK IN EMBOLIC STROKE OF UNDETERMINED SOURCE." was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

Clearance was obtained from the Institutional Ethics Committee for carrying out the study.

Date 26/07/2022
Dr. Sapna Erat Sreedharan

FORWARDED :-

This is to certify that dissertation entitled "A study on predictors of outcome and recurrence risk in embolic stroke of undetermined source" is a bonafide research work done by **Dr. Jithin George**, Senior Resident In Department of Neurology, in partial fulfillment of the requirement for DM Neurology degree.

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	AAA	Aortic arch atheromas
2	AF	Atrial fibrillation
3	AHA	American Heart Association
4	AIS	Acute ischemic stroke
5	CABG	Coronary Artery Bypass Graft
6	CAD	Coronary Artery Disease
7	CS	Cyptogenic stroke
8	EF	EF: Ejection fraction
9	ESUS	Embolic stroke of undetermined source
10	HDL	High Density Lipoprotein
11	HHC	Hyperhomocysteinemia
12	IHIS	Intraplaque high-intensity signal
13	LDL	Low Density Lipoprotein
14	LMWH	Low-molecular weight Heparin
15	LV	Left ventricle
16	MCA	Middle Cerebral Artery
17	MRA	Magnetic Resonance Angiogram
18	MRI	Magnetic Resonance Imaging
19	mRS	modified Rankin Scale
20	NIHSS	National Institute for Health Stroke Scale

21	PCI	Percutaneous coronary intervention
22	PFO	Patent foramen ovale
23	PTFV1	PTFV1: P wave terminal force in lead V1
24	SD	Standard Deviation
25	TEE	Trans-Esophageal Echocardiography
26	TGL	Triglyceride
27	TIA	Transient Ischemic attack
28	TOAST	Trial of Org 10172 in Acute Stroke Treatment trial
29	TOF	Time of flight
30	TTE	Trans-Thoracic Echocardiography
31	VZV	Varicella Zoster virus
32	WMH	White Matter Hyperintensities

SYNOPSIS

BACKGROUND AND PURPOSE

Around 16-21% of ischemic strokes are embolic strokes from undetermined source(ESUS). Among those with ESUS, annual recurrence is reported in 4.5-5%. Regarding ESUS, studies from India are limited. Here we studied the prevalence of Embolic stroke of undetermined source among stroke subtypes, 1 year outcome and recurrence rate and their predictors

MATERIALS AND METHODS

Ours is a single centre retro-prospective study. Patients above 18 years of age with diagnosis of Cryptogenic ESUS strokes were taken from 1/1/2017-31/12/2020(4 years) and were followed up till 31/12/2021. All patients underwent neuroimaging CT/MRI with angiography, ECG, 2Decho, blood investigations andTransesophageal Echo and holter in select cases. Functional outcome was measured using modified Rankin scale with score 2 or below taken as good outcome.

RESULTS

We had 234 people satisfying criteria for ESUS over the 4 year study period with a mean age 58.2 ± 12.8. 22.6 % had vertebrobasilar strokes. 46 patients had past history of stroke/TIA at admission.. Analyzing the infarct pattern,34.6% had multiple embolic pattern followed bysuperficial watershed infarcts(29.5%), and internal border zone infarcts(22.6%). 12 lead ECG showed atrial ectopics in 7.2% and9.6% had LVH. Holter monitoring showed supraventricular ectopics in 8.3% followed by ventricular ectopics in 6.2%, ,. 4.2% had mild left atrial enlargement. LV systolic dimension was 30-60 in 44%, While LV diastolic dimension was normal for 98.6%. 26 patients (11.3%) had recurrence of vascular events during hospital stay. On followup of 1 year, 8.2% cases had recurrence of stroke on ipsilateral side. 3.8% had stroke in other vascular territories and 2.7% had cardiac events. There was significant correlation between admission blood sugars, total cholestrol, LDL, MRS at discharge, DM, HTN, CAD, PVOD and imaging pattern with recurrence of events at 1 year.

CONCLUSION

We found the prevalence of ESUS to be 11.21 %. Admission blood sugars, total cholesterol, LDL, MRS at discharge, Diabetes Mellitus, Hypertension, Coronary artery

disease, Peripheral vascular occlusive disease and superficial watershed pattern or chronic infarcts, can be considered as predictors of recurrence of ESUS.

Introduction

1. INTRODUCTION

15 million people suffer from stroke worldwide each year as per world health organisation. Among these, 5 million are permanently disabled and another 5 million dies. (1) Among ischemic strokes, 30-40% are cryptogenic stroke while 16-21% account for embolic strokes from undetermined source (2-6), which has an annual recurrence risk of 4.5-5% (7-9). Etiologies and characteristics of strokes in India are different from those from western countries in that stroke and other vascular disease occur at least 1 decade earlier and we have more rheumatic and similar cardioembolic etiologies, in comparison to western population. (10,11)

EMBOLIC STROKE OF UNDETERMINED SOURCE (2, 12)

• Embolic stroke of undetermined source (ESUS) is a subtype of ischemic stroke with an unknown source. It is a non-lacunar infarct without proximal arterial stenosis or cardioembolic sources.

• Diagnostic criteria for ESUS is as follows:

- ✓ Stroke that is not lacunar which is detected by CT or MRI
- ✓ Absence of 50% luminal stenosis in extracranial or intracranial arteries supplying the area of ischaemia
- ✓ No major-risk cardioembolic source of embolism
- ✓ No other specific cause of stroke identified (e.g., migraine/vasospasm, arteritis, drug misuse, dissection.)

Patients with ESUS include a heterogeneous group of patients with an occult embolic source of stroke. These patients include individuals with ESUS related to aortic arch plaque, undetected paroxysmal AF, ESUS related to cardiac valves, ESUS due to patent foramen ovale or related to occult cancer (13-15). On embolic stroke of undetermined source, studies in India are limited. Hence we performed this study to find out the prevalence of ESUS among our hospital cohort of acute ischemic stroke and identify the predictors of outcome and recurrence risks at 1 year.

Review of Literature

2. REVIEW OF LITERATURE

TOAST classification is used for classification of ischemic stroke based on the etiology of the stroke. This is as follows(16).

1. Large artery atherosclerosis
   This can be extracranial or intracranial disease
2. Small artery occlusion (lacunar)
3. Cardioembolism
4. Other demonstrated cause
   Prothrombotic disorders
   Nonatherosclerotic vasculopathies
5. Undetermined cause (cryptogenic)
   ≥2 conflicting causes found
   Diagnostic studies were negative
   Incomplete evaluation for cause

The TOAST definition as stroke of undetermined cause, or cryptogenic stroke: includes three circumstances : the diagnostic assessment is incomplete, no cause can be found despite extensive investigations, or, most likely, a cause cannot be established because more than one cause is there (17).

ESUS is a non-lacunar infarct which is subcortical with a size of ≤1.5 cm on CT or ≤2.0 cm on MRI. The following should be excluded before labelling as ESUS: >50% luminal stenosis in extracranial or intracranial arteries supplying the ischemic region, major cardioembolic sources and other specific cause of stroke (e.g., dissection, arteritis, migraine/vasospasm). Major cardioembolic sources include permanent or paroxysmal atrial fibrillation (AF), sustained atrial flutter, atrial myxoma or other cardiac tumors, prosthetic valve, intracardiac thrombus, left ventricular (LV) ejection fraction <30%, mitral stenosis, myocardial infarction within the past 4 weeks, valvular vegetation's or infective endocarditis (15)

In 2014, the context of "embolic stroke of undetermined source" (ESUS) was introduced. It was mainly to identify patients with nonlacunar cryptogenic ischemic strokes for whom the likely stroke mechanism is embolism. Patients with ESUS are a subset of cryptogenic stroke with embolic strokes and sufficient investigations were done to exclude other etiologies (12).

Percentage of ESUS among ischemic stroke varies between 7% to 42% in the various studies conducted(16).

Frequency of ESUS was almost similar globally. Compared to non ESUS patients, ESUS patients were having lower frequencies of vascular risk factors and younger age (3, 19,20).

PROPOSED MECHANISMS OF ESUS (3)

Minor-risk potential cardioembolic sources

Mitral valve

- Mitral annular calcification
- Myxomatous valvulopathy with prolapse

Aortic valve

- Calcific aortic valve
- Aortic valve stenosis

Left ventricle

- Endomyocardial fibrosis
- Global or regional moderate systolic or diastolic dysfunction
- Ventricular non-compaction

Atrial structural abnormalities

- Atrial septal aneurysm
- Chiari network

Non-atrial fibrillation atrial dysrhythmias and stasis

- Episodes of atrial tachycardia
- Sick-sinus syndrome and atrial asystole
- Atrial appendage stasis with spontaneous echodensities or reduced flow velocities

Covert paroxysmal atrial fibrillation

Arteriogenic emboli

- Cerebral arterial non-stenotic plaques with ulceration
- Aortic arch atherosclerotic plaques

Paradoxical embolism

- Patent foramen ovale
- Atrial septal defect
- Pulmonary arteriovenous fistula

Cancer-associated

• Covert thrombotic endocarditis that is non-bacterial

• Tumour emboli originating from occult cancer

CARDIAC SOURCES

ATRIAL CARDIOPATHY

The ASSERT study demonstrated the role of atrial fibrillation in stroke. They monitored 2580 patients for 2.5 years, who were more than 65 years with hypertension and without known atrial fibrillation who underwent cardiac pacemaker implantation. At 3 months followup, subclinical AF was detected in approximately 10% and only 15% developed clinical AF. As per the study, atrial fibrillation that is subclinical was a predictive factor of ischemic stroke or risk of systemic embolism (adjusted hazard ratio 2.50; 95% CI, 1.28–4.89; $P = 0.008$)

It was also found that, patients with supraventricular tachycardia were having 2 fold raised risk of ischemic stroke when compared to matched controls with a hazard ratio of 2.10 and 95% confidence interval 1.69–2.62. (22). In population-based cohort studies, p-wave dispersion on ECG, was also associated with embolic strokes. (23, 24)

Manhattan Stroke Study showed moderate to severe left atrial enlargement is an associated with recurrent embolic stroke and is independent of Atrial fibrillation (23).

As per various studies, the association between serum NT-proBNP level and ischemic stroke risk (especially embolic subtype), was also found to be significant (25,26). SPOTRIAS study data showed that in around 65% cases of Crytogenic stroke, biomarkers of atrial cardiopathy was present. These inversely associated with other potential stroke mechanisms such as PFO and were associated with vascular risk factors and. (27)

Odds ratio of finding a PFO is 2.9 times higher in patients with Cryptogenic strokes as compared to controls, based on per meta-analysis of 23 studies (28). Characteristics of PFO that is associated with higher probability for thromboembolism is studied. Most commonly reported is Atrial septal aneurysm, and its incidence is higher among both older and younger patients with Cryptogenic strokes(29) Increased risk of recurrent stroke was noticed when

excursion of ≥10 mm of the interatrial septum during the cardiac cycle (30).Also, severe left-to-right shunt and large opening of PFO also been found to be higher risk(31). However, these and other anatomic and physiologic findings such as prominent Eustichian valves , Chiari network , shunting without Valsalva etc, have inconsistent findings regarding recurrence of stroke (30).

Figure 2.1: RISK OF PARADOXICAL EMBOLISM SCORE

Characteristic	Points
No history of hypertension	1
No history of diabetes	1
No history of stroke or TIA	1
Non-smoker	1
Cortical infarct on imaging	1
Age (years)	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0
Total score (sum of individual points)	
Maximum score (a patient <30 years with no hypertension, no diabetes, no history of stroke or TIA, non-smoker, and cortical infarct)	10
Minimum score (a patient ≥70 years with hypertension, diabetes prior stroke, current smoker, and no cortical infarct)	0

Anticoagulation therapy was more effective than antiplatelet therapy in preventing recurrent stroke and/or transient ischemic attack (event rates were 7.7% vs. 9.8%, respectively, $p = 0.03$). But, there was 6 fold increased risk of major bleeding with anticoagulation (7.1 vs. 1.3%; odds ratio 6.49, 95% CI, 3.25–12.99, $P < 0.00001$). PFO closure can reduce stroke /TIA recurrence and the risk of bleeding. PFO closure leads to 50% relative risk reduction of stroke and/or TIA and 82% relative reduction of major bleeding. (32).

Trans-thoracic echocardiography (TTE) and trans-esophageal echocardiography (TEE) are used to detect thrombi from intra-cardiac sources as a part of workup of stroke (33). TEE should

be done in ESUS patients as it has higher detection rate of valvular abnormalities including vegetations, left atrial enlargement , left atrial and ventricular thrombus and aortic arch abnormalities (34). For post Myocardial infarction population, to detect source of LV thrombus, Cardiac MRI has high specificity greater and sensitivity (34).

In NAVIGATE ESUS trial, average dimension of left atrium was 3.7cm (SD, 0.7), and 26% (n=1033) of patients had ipsilateral plaque. About 6% (n=235) had no ipsilateral plaque, but left atrial dimension was ≥4.7 cm and, 24% (n=939) had ipsilateral plaque and no left atrial enlargement, and 2.4% (n=94) had both. Patients with ipsilateral plaque were more likely to be male, white, from eastern Europe, hypertensive, active tobacco users and those having coronary artery disease. These characteristics in addition to heart failure were more in those having left atrial enlargement. Patients with both left atrial enlargement and ipsilateral plaque were having higher prevalence of coronary artery disease and heart failure, in addition to older age of them. When used sex-specific definition of left atrial enlargement, it was found that 24% (n=942) had any left atrial enlargement and no ipsilateral plaque, 17% (n=673) had ipsilateral plaque and no left atrial enlargement, and 9% (n=360) had both.

ARTERIAL CAUSES

ROLE OF NONSTENOTIC PLAQUES

Aortic arch atheromas (AAA) with size > 4 mm, has the greatest risk of stroke (35). Ryoo et al. found that vulnerable AAA can be a causative factor for ESUS in 40 of 321 patients. They defined clinical and radiological features of strokes with aortic arch atheroma of which predominantly were elderly patients with hypertension and those with multiple, small cortical and border zone infarcts. (36) A study conducted by Arun K et al, stated that 15.7% of cryptogenic stroke patients were having significant aortic plaques. They found that higher mean age (68.3 ± 8.3 vs 54.4 ± 13.2, P = 0.0005) and higher risk factors like hypertension (P = 0.025), coronary artery disease (CAD)(P = 0.015), and peripheral vascular disease (POVD) (P = 0.029), were seen in those with significant plaque. At 1 year followup recurrent vascular events/ death was significantly higher in those with significant plaque (19.4% vs 6.2%, P = 0.016). (37)

Similar to that of AAA, nonstenotic carotid plaques also have been hypothesized to have an independent role in patients with ESUS(38, 39). In the metaanalysis by Singh N et al, it was found that, the risk of recurrent stroke/TIA in nonstenotic carotid plaques is not more in the presence of highrisk plaque features (40). The importance of ICAD was also studied extensively. In the comparison between Indian and US patients, was done by Saraf et al found that Indian patients were younger and had more severe strokes compared to US population. However, recurrent strokes were lower in Indian patients which might be because of greater use of dual antiplatelet therapy(41). Recent studies have found that in patients with ESUS, the ultrasound detected nonstenotic carotid plaques is inversely associated with both patent foramen ovale and markers of atrial cardiopathy. This means that they also can be considered as an independent etiology of ESUS (42). 35% of patients in the ESUS Global Registry, had one or more minor-risk potential embolic sources which were excluding carotid artery plaques (43). Also it was found that nonstenotic plaques were seen in 79% of cases in the cervical carotid arteries (43).

Plaque features can describe high risk nature of it which includes intraplaque hemorrhage, plaque neovascularization, fibrous cap thickness, the presence of a lipid-rich necrotic core, plaque ulceration, and plaque inflammatory activity (44). It was also found that type VI American Heart Association (AHA) plaques were seen in 37.5% of carotid arteries ipsilateral to the ischemic stroke. But there were nil AHA type VI plaques contralateral to the side of stroke (45). The most common features that define AHA type VI plaque includes intraplaque hemorrhage (75%), fibrous plaque rupture (50%), and luminal thrombus (33%). In 2015, Gupta et al. used MR TOF imaging and found that 22.2% of patients had intraplaque high-intensity signal (IHIS) ipsilateral to the side of ischemic stroke, while zero patients had IHIS-positive carotid plaques contralateral to the side of stroke. IHIS is a marker for intraplaque hemorrhage, in nonstenosing carotid plaques (46). In 2016, Hyafil et al. combined MRI with 18F-FDG PET imaging and investigated the morphological and biological aspects of nonstenotic carotid artery plaques in cryptogenic stroke in small series of 18 patients (44).

Complicated atherosclerotic plaques were seen in approximately 39% of ipsilateral arteries, while zero complicated plaques were found in contralateral arteries. Those with at least one complicated plaque, had higher18F-FDG uptake in both carotid arteries than in patients with no lesions. This shows there is diffuse inflammatory process associated with that of vulnerable plaques(48).

Plaque thickness of > 5 mm were present in 11% cases ipsilateral to stroke and in 1% cases contralateral to stroke. Plaques with thickness > 4 mm were present in 19% ipsilateral to stroke and contralateral in 5% (49).

In 35% of patients , plaques thickness > 3 mm were seen ipsilateral to stroke and in 15% were seen contralateral to stroke. Ulcerated aortic arch plaques which is covered with thrombi as well as cholesterol plaques can act as a nidus for embolism (49).

The Stroke Prevention in Atrial Fibrillation (SPAF) Echo trial is a meta-analysis of case–control with postmortem series. They stated that a significant risk of stroke in patients with severe AAA with odds of 3.76 and 95% CI, 2.58–5.48 (50). In addition, in patients more than 55 years of age, AAA was found to be more frequent and relatively higher in severity (50).

Other Arterial Causes

Under the age of 45 years , cervicocephalic large vessel dissections cause a quarter of strokes (51). MRA with T1 fat saturation should be done in patients with suspected dissection as it can reveal intramural blood and expansion (52).

Neuroinfectious causes

Varicella Zoster Virus (VZV)-related vasculopathy can involve large and small vessels. It can cause variety of vascular manifestations including TIA, ischemic strokes,aneurysm formation, and intra- parenchymal and subarachnoid hemorrhage (52). In the pediatric population, VZV causes around 40% of transient cerebral arteriopathy and 1/3rd of ischemic arterial strokes(53). In addition, within 1 year of infection by VZV, up to a third of adult may suffer a stroke. Zoster- ophthalmicus can cause large vessel unifocal vasculopathy. But, in immunocompromised patients it can cause both large and small vessel vasculopathy is seen (54). In a study of VZV vasculitis with 30 patients, 97% had abnormal findings in brain MRI with the majority of ischemic changes were involving basal ganglia and other deeper structures (55)

Other infections like neuroborreliosis, syphilis etc also need to be considered as causes for stroke, even though they are rare in patients with ESUS or cryptogenic stroke based on history and clinical findings.

Hypercoagulable states

In ischemic stroke, prevalence of hypercoagulable states is 3–21% (55-57). Inherited coagulopathies most commonly cause venous thrombosis. Compared to other pro-coagulant states, both arterial and venous systems involved in antiphospholipid antibodies and homocystienemia. The prevalence of stroke which is due to acquired and polygenic causes is increasing with age, but it is reversed in monogenetic mutations (58). Positivity of the test was more in those with age <60, positive family history, recurrent unprovoked venous and arterial thrombotic events and nil/ minimal traditional vascular risk factors (58).

Stroke Related to Cancer

In patients with malignancy ,incidence of ischemic stroke can be as high as 15%, out of which only 50% are identified (59). Several biochemical processes have been suggested as the mechanism for the same. These include endothelial cell damage due to procoagulant cytokines which includes TNF-alpha, IL-1, and IL-6, which leads to vWF release, protein C inhibition, platelet activation, release of tissue factors leading to activation of factor VII and X . Also there can be change in the homeostatic property of blood and blood vessels which leads to activation of cell adhesion molecules by mucin secreted from adenocarcinomas, intravascular lymphomatosis. In myeloproliferative disorders, there can be increased viscosity also which can lead to hypercoagulation (60,61).

Trousseau syndrome refers to recurrent / migratory episodes of arterial emboli, venous thrombosis, or both in a patient having malignant neoplasm that is underlying spontaneously In stroke secondary to cancer, there can be 4 fold increase in multiple territory infarcts. Among malignancies, maximum correlation with embolic strokes was found to be gastrointestinal cancer (62). In patients with hypercoagulable state secondary to malignancy, anticoagulation therapy is effective and decreases D-dimer levels over time. If the pattern of strokes resembles small vessel related infarcts, antiplatelet agents instead of anticoagulation also were used in certain studies. However, use of low-molecular Heparin (LMWH) is used for prophylaxis of venous thromboembolic events in cancer patients than warfarin (59, 60, 62).

OTHERS

Triad of encephalopathy, branch retinal artery occlusion and hearing loss constitutes Susac syndromes(63).This occurs more in young women. But the age can range from 7 to 72 years

of age (63). Corpus callosum is the commonest site. SLE has a higher risk of stroke with an odds ratio of 1.5 (64,65).It is seen in 20% of cases. Antiphospholipid antibody syndrome is most frequently associated with arterial hypercoagulability, which manifests with thrombocytopenia, livedo reticularis (Sneddons syndrome), pre-eclampsia, and still birth (63). Other mechanisms of stroke in SLE includes vasculitic mechanisms, libman–Sacks endocarditis, elevated homocysteine and accelerated atherosclerosis (65,66). Other rheumatological diseases can also affect intracranial or extracranial vessels. These includes Giant cell, Takayasu's arteritis, Kawasaki disease, Polyarteritis nodosa, granulomatosis with polyangiits, Sarcoidosis, microscopic polyangiitis, Eosinophilic granulomatosis, Behcets's and Cogan's syndrome(67).

HISTOPATHOLOGY

In ESUS patients, histopathological examination of the thrombi were done. It was found that most of thrombi were erythrocyte-rich (13%) or of mixed composition (80%), while platelet-rich thrombi was present in only 8%. Thrombi extracted from ESUS patients were closely resembling cardioembolic clots than noncardioembolic thrombi. (68)

CLINICAL FEATURES

As per the previous studies in ESUS, the mean age of ESUS patients was 65 years. Among them 58% were males and 42% were females. This shows that ESUS patients are having lower age compared to other etiologies. Median NIHSS was 3 (7). In the study conducted Arauz A et al**,** found MRS of 3-6 in 39.6% on discharge and in 27.5% on followup (69).

ROLE OF RISK FACTORS

ESUS Patients has lower traditional risk factors(7). In the study conducted by Perkins JD et al, it was found that Left ventricular wall motion abnormalities and corresponding changes in left heart function are a potential source of emboli in these patients.Also, aortic arch atherosclerosis was having potential risk of embolization to brain (70).

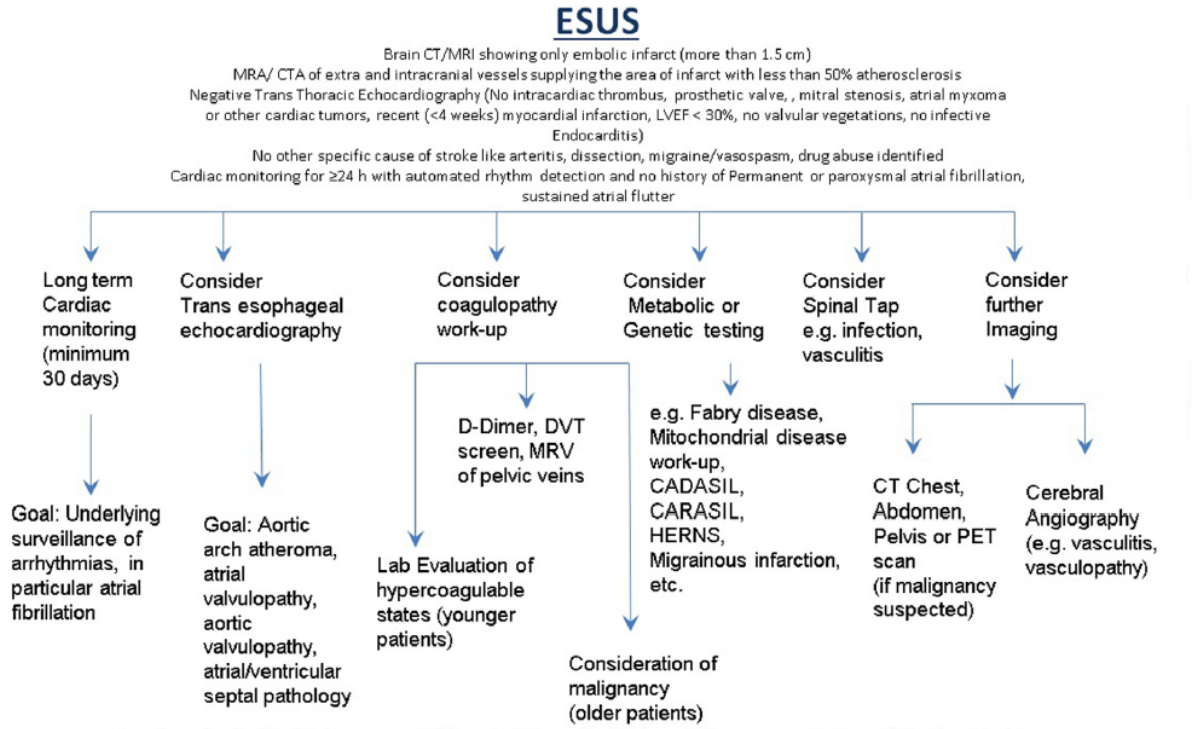
EVALUATION (71)

After the clinical examination, MRI or CT brain needs to be done to know the charcteristics and pattern of infarct. Also CT or MR angiogram needs to be done. Care should be given in identifying the aortic arch plaques and substenotic plaques in the carotid vessels. Plaque characteristics including plaque thickness, plaque localisation (<1 cm proximal or distal to

carotid bifurcation), plaque configuration (eccentric or concentric), echogenicity (hypoechoic, isoechoic or hyperechoic) and stenosis grade. Cardiac examination should include 12-lead

ECG, one day rhythm recording using Holter-ECG or 7 days holter, and a transthoracic echocardiogram. Left atrial dimensions, LVH, Ejection fraction, spontaneous echo contrast should be looked into. TEE should be done to rule out PFO, vegetations, cardiac thrombus etc, if TTE is normal and an underlying cardiac substrate is strongly suspected. ECG parameters should be assessed including abnormal P wave terminal force in lead V1 (PTFV1), PR interval, LVH criteria. Blood tests should include Serum and plasma samples, including markers of inflammation, glycosylated haemoglobin and lipid profile , markers of cardiac congestion (eg, N-terminal prohormone of brain natriuretic peptide (NT-proBNP). Vasculitic markers, Homocysteine are also needs to be included in the evaluation (71, 72).

FIGURE 2.2: EVALUATION OF ESUS



MANAGEMENT

As per ASA/AHA guidelines 2021, In patients with ESUS, treatment with direct oral anticoagulants is not recommended to reduce risk of secondary stroke. In patients with ESUS, treatment with ticagrelor is not recommended to reduce the risk of secondary stroke

(71). This was based on the NAVIGATE ESUS which suggest anticoagulation may benefit in patients with left atrial diameter >4.6 cm, but those with PFO did not (72). SOCRATES trial (Soluble Guanylate Cyclase Stimulator in Heart Failure Studies) did not find reduced vascular event risk with ticagrelor (73).

In WARSS trial, non-cardioembolic stroke prevention was studied comparing effects of warfarin and aspirin, in 2206 subjects. The primary efficacy outcome was recurrent ischemic stroke or death. Safety outcome was major bleeding. Both primary and safety outcome were similar among both groups(74). However, warfarin had increased risk of minor bleeding, compared to aspirin (warfarin, 20.8%; aspirin, 12.9%; $P < 0.001$). A Cochrane meta-analysis showed that warfarin at any dose was not more beneficial compared to antiplatelet therapy in patients with minor stroke or TIA from presumed arterial origin,(75)Also it was found that high intensity warfarin treatment had significantly increased risk of bleeding.

In previous studies, most of the ESUS patients (86%) were on antiplatelet therapy during follow-up, and 13% were on oral anticoagulants.

One study analysed histopathologically the specimens collected from endovascular thrombectomy in 145 patients with acute ischemic stroke. They found that the portions of thrombus collected from patients with cardioembolic stroke or cryptogenic stroke were similar (76). Another study using Gadolinium MRI showed that patients with ESUS has atrial fibrosis similar to those patients who had Atrial fibrillation(77). Crystal-AF trial, was done to detect Atrial fibrillation in patients with cryptogenic stroke, in which long-term cardiac rhythm monitoring was performed with implanted loop recorder. AF was detected in 12.4% of subjects during 1 year and in 30%, during 3-year follow-up (78). All these studies together indicate a strong association between cryptogenic and cardioembolic stroke. This can substantiate the statement that anticoagulants might be effective for secondary treatment in cryptogenic stroke.

A total of 7213 ESUS patients over 50 years old were studied in the NAVIGATE ESUS trial. They were included between 7 days to 6 months post-stroke (72). The primary efficacy outcome of the study was stroke which can be ischemic or hemorrhagic or systemic embolism. Primary safety outcome was major bleeding. The study was predominantly a comparison between rivaroxaban (15 mg once daily) and aspirin (100 mg once daily) groups. Due to more risk of bleeding with rivaroxaban and lack of benefit with regard to stroke risk, the trial was terminated early. After a followup of 11 months, it was found that, the primary efficacy outcome was similar between rivaroxaban and aspirin groups (annualized rate: rivaroxaban,

5.1%; aspirin, 4.8%; P = 0.52). However, rivaroxaban was associated with a higher risk of major bleeding (annualized rate: rivaroxaban, 1.8%; aspirin, 0.7%; P < 0.001) (72).

In RE-SPECT ESUS trial, 5390 ESUS patients were enrolled within 6 months post-stroke(9, 79). This trial was mainly for comparing the safety and efficacy of dabigatran (110 or 150 mg twice daily) with aspirin (100 mg once daily). The primary outcome was recurrent stroke while primary safety outcome was major bleeding. On a median follow-up of 19 months, it was found that both primary efficacy outcome (annualized rate: dabigatran, 4.1%; aspirin, 4.8%; P = 0.1) and safety outcome (annualized rate: dabigatran, 1.7%; aspirin, 1.4%; P = 0.3) were similar between groups. Thus, NAVIGATE –ESUS and RE-SPECT ESUS trials were of the opinion that for stroke prevention, NOACs had similar effect as that of aspirin. But, risk of bleeding was increased in NOAC group when compared with aspirin(72,79).

The Crystal-AF trial stated that about one-third of cryptogenic strokes or ESUS have paroxysmal atrial fibrillation in a period of 3 years (80). Also, AF detection rate was increased to around 50% in those patients with high CHADS2 score (> 4) (80).
The HAVOC score has been used for the prediction of AF after cryptogenic stroke or TIA . It includes 4 points for congestive heart failure ; 2 points each for hypertension, age > 75, valvular heart disease, and coronary artery disease; 1 point each for peripheral vascular disease and obesity(80). In the Crystal-AF trial, during follow-up of 1 year, patients having high HAVOC score (>=4) had higher risk of Atrial fibrillation than those with low score (0- 1) (80).
The results of NAVIGATE ESUS and RE-SPECT ESUS showed that anticoagulation is not superior to antiplatelet therapy in ESUS. In clinically apparent atherosclerotic disease, the combination of low-dose rivaroxaban and aspirin reduced stroke risk, significantly more than aspirin alone , specifically the risk of ESUS and cardioembolic strokes (9,72,79). For long-term secondary stroke prevention after ESUS, in the subset of patient with left atrial enlargement , rivaroxaban was superior to aspirin but not in the subset of patients with ipsilateral nonstenosing plaque (8,9).

PROGNOSIS

Annual recurrence rate of ESUS varies from 2.3-6.8% (3,20). Patent foramen ovale associated young cryptogenic strokes (average age mid-40s) had stroke recurrence rates of 1–2% per year when given aspirin. Also patent foramen ovale associated strokes who are elderly had higher

recurrence rate (14% per year in one report). Thus role of other causes in addition to paradoxical embolism needs consideration in cases of ESUS. (85)

Objectives

3. AIMS AND OBJECTIVES OF THE STUDY

1) To find out the prevalence of Embolic stroke of undetermined source in patients
2) To find out 1 year outcome and Annual recurrence rate of ESUS and to identify any factors that can predict the outcome and recurrence in patients with embolic stroke of undetermined source

Methodology

4. METHODOLOGY

STUDY DESIGN

Single centre retroprospective study

SUBJECT/PARTICIPANT SELECTION

- List of patients from medical records with diagnosis of ESUS / Cryptogenic Stroke satisfying the criteria for ESUS was taken from 1/1/2017-31/12/2020
- Patients were followed up till 31/12/2021 to identify the patients with history of a recurrent stroke or Imaging positive Transient Ischemic Attack

NUMBER:

- Patients admitted in SCTIMST from 1/1/2017 till 31/12/2020 with diagnosis of acute ischemic stroke were 2087. Among them people who were enrolled in the study was 234 patients.
- Prospective arm is included to get adequate samples size

ELIGIBILITY

INCLUSION CRITERIA

- Patients more than 18 years age
- Patients satisfying the diagnostic criteria of embolic stroke of unknown source

EXCLUSION CRITERIA

- Age less than 18 years
- Patients with known stroke etiologies
- Patients who are incompletely evaluated

RECRUITMENT:

Recruitment of patients was done by the principal investigator and co-principal investigator. Hospital records was reviewed for eligibility. All patients who were eligible was recruited for the study.

DATA COLLECTION PROCEDURES

- List of patients from medical records with diagnosis of ESUS / Cryptogenic Stroke satisfying the criteria for ESUS was taken from 1/1/2017-31/12/2020
- Patients were followed up till 31/12/2021 to identify the patients with history of a recurrent stroke or Imaging positive Transient Ischemic Attack. If they didn't come for routine follow up, they were contacted via telephone.
- Consent of patients was obtained for those who were enrolled after the initiation of study
- All the investigations was done as per the standard protocol including Brain imaging CT/MRI with angiography, ECG, 2Decho, blood investigations including vasculitic markers, Transesophageal Echo and 24 hour/7day Holter monitoring (when indicated)
- No additional investigations were done other than the routine hospital protocol done for stroke patients.

DATA ANALYSIS

- Data collected was analysed using SPSS Version 28.
- Frequency of outcome and percentage of outcome was calculated
- Mean, standard deviation for numerical variables and frequency, percentage was calculated for categorical variable
- Mean comparison, cross tabulation was used to explore relationships among the available data
- T test was be used for testing mean comparison and Chi square test for testing association

Results

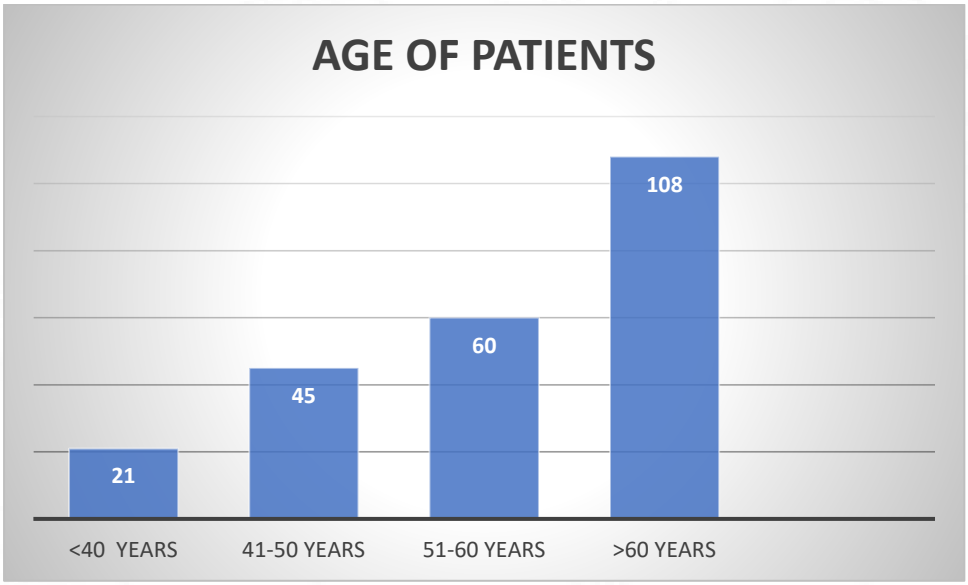
5. RESULTS

We had 234 patients with diagnosis Cryptogenic Stroke satisfying the criteria for ESUS from a cohort of 2087 Acute Ischemic Stroke admitted and evaluated in stroke unit from 1/1/2017-31/12/2020 (11.21%), who were followed up for a minimum duration of 1 year.

1. COHORT CHARACTERISTICS

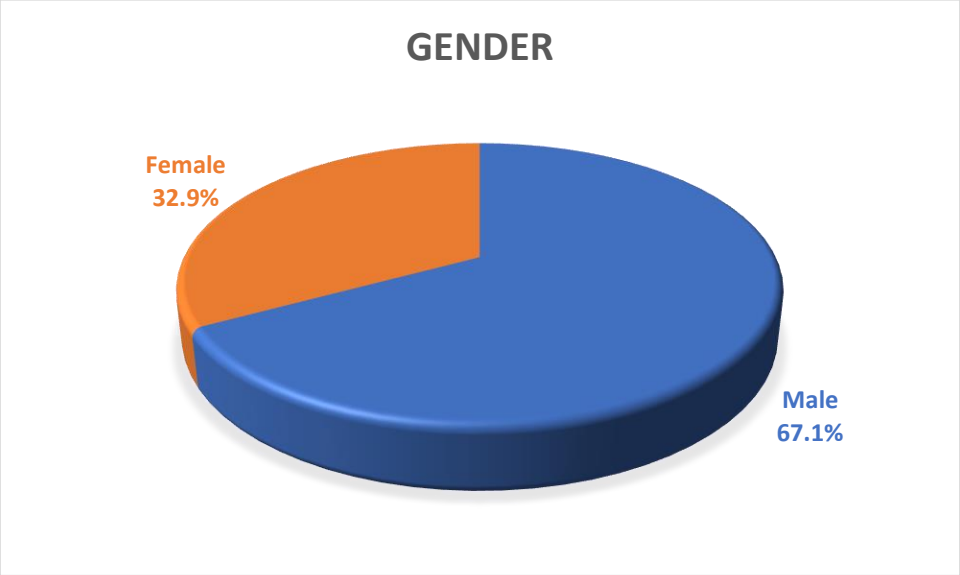
Mean age of the cohort was 58.2 ± 12.8. 126 were below 60 years while 108 people were more than 60 years.

FIGURE 5.1: AGE OF PATIENTS



In our study, there were 157 males and 77 females

FIGURE 5.2: GENDER



Risk factor profile

Among the subjects, 64.1% had hypertension, 52.6% had diabetes, 28.6% had dyslipidemia, 17.1 % had coronary artery disease. 7.7% had PCI and 4.7% had CABG. 5.1 % had PVOD.

TABLE 5.1: COMORBIDITIES

Comorbidities	Frequency	Percent
DM	123	52.6
HTN	150	64.1
DYSLIPIDEMIA	67	28.6
CAD	40	17.1

TABLE 5.2: SMOKING

SMOKING	Frequency	Percent
Current smoker	41	17.5
Non smoker	176	75.2
Ex smoker	17	7.3
Total	234	100

17.5 % were smokers and 7.3% were reformed smokers while 75.2% were non smokers.

TABLE 5.3: ALCOHOLISM

Alcohol	Frequency	Percent
Current	42	17.9
Non alcoholic	182	77.8
Stopped	10	4.3
Total	234	100

TABLE 5.4: CORONARY ARTERY DISEASE

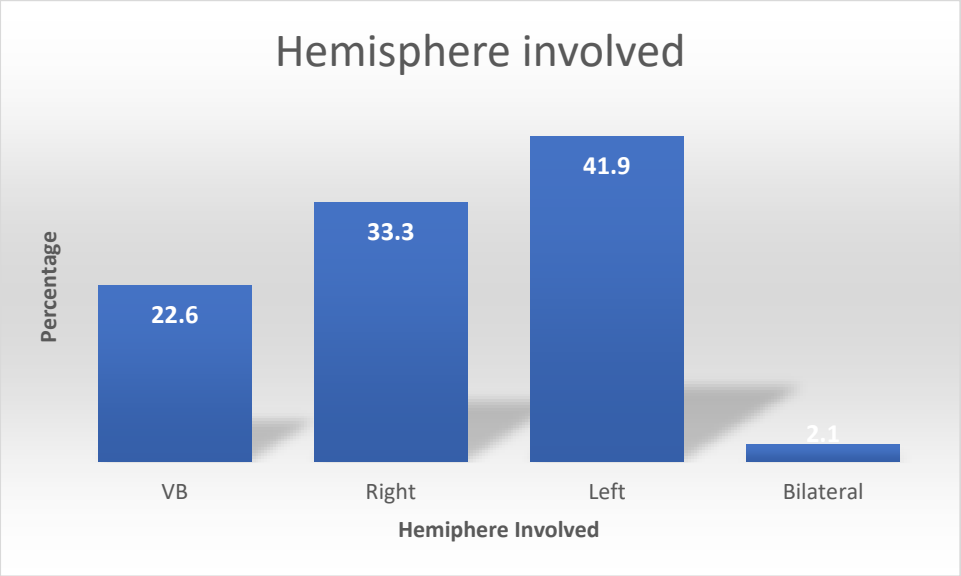
PCI/CABG	Frequency	Percent
PCI	18	7.7
CABG	11	4.7
None	205	87.6
Total	234	100

TABLE 5.5: PERIPHERAL VASCULAR DISEASE

POVD	Frequency	Percent
Yes	12	5.1
No	222	94.9
Total	234	100

Territory involved : 33.3 % had right MCA strokes and 41.9% had left MCA strokes while 2.1 were bilateral and 22.6 % were vertebrobasilar.

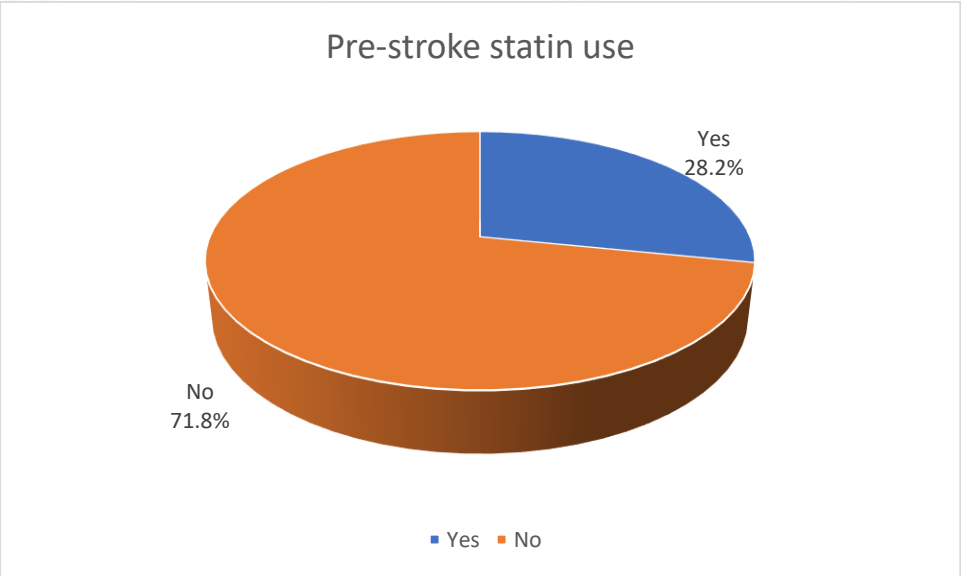
FIGURE 5.3: HEMISPHERE INVOLVED



46 patients had past history of stroke/TIA, of which 16.7% of total cases had TIA and 3% had stroke in the past. Those with past h/o stroke, 19 had left hemispheric, 21 had right hemispheric, 4 had vertebrobasilar and 2 had vertebrobasilar with right MCA stroke.

28.2% had prestroke statin use.

FIGURE 5.4: PRE STROKE STATIN USE



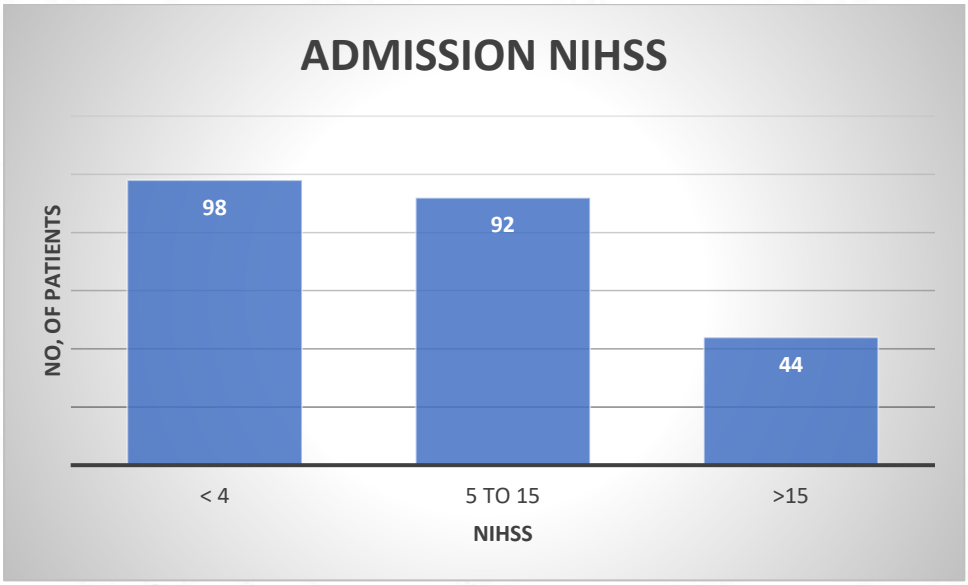
Prestroke antiplatelet use was in 51 patients, of which 42 was on aspirin, while 1 was on clopidogrel and 8 were on dual antiplatelets.

TABLE 5.6: PRESTROKE ANTIPLATELET USE

Prestroke antiplatelet use	Frequency	Percent
Aspirin	42	17.9
None	183	78.2
Clopilet	1	0.4
Both	8	3.4
Total	234	100

Admission NIHSS was ranging from 0-32 with a mean of 8.1± 6.9. Based on NIHSS, minor strokes with NIHSS less than 4 was the most(in 98 patients), moderate strokes of NIHSS 5-15 was seen in 92, and severe strokes with NIHSS >15 were seen in 44 cases only.

FIGURE 5.5: ADMISSION NIHSS



Time between first symptom and admission was ranging between 0.7 hours to 2160 hours with a mean of 102 ± 295 hours.

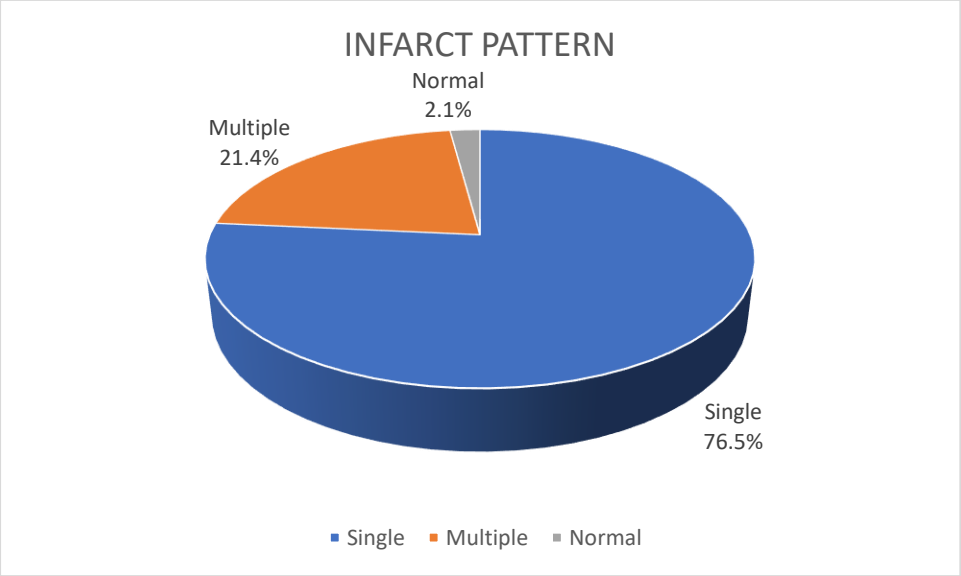
TABLLE 5.7: BIOCHEMICAL PARAMETERS

	N	mean ± sd	Range	Median	IQR
ON ADMISSION					

Admission blood sugar	224	163.7 ± 72.9	76 - 456	139.5	116 - 181.75
HBA1C	220	7.5 ± 2.1	4.5 - 14.4	6.7	5.9 - 8.975
SBP	234	156.2 ± 28.4	96 - 240	150	136 - 180
DBP	234	88.7 ± 16.1	38 - 150	90	80 - 100
Fasting Cholesterol	228	185.8 ± 59.7	72 - 399	180.5	145 - 223
HDL	228	46.7 ± 16.4	14 - 191	45.5	36.25 - 52
LDL	203	119.7 ± 49.5	13 - 276	118	82 - 152
TGL	226	106.1 ± 56.6	32 - 418	89	68 - 129.25
SERUM HOMOCYSTEINE	49	17.7 ± 15.4	4.34 - 75.56	12.83	9.28 - 18.395
ON 1 YEAR FOLLOWUP					
HbA1C	110	7.3 ± 4.2	4.8 - 48	6.6	5.9 - 7.75
F cholesterol	157	141.7 ± 37.2	23 - 322	138	120.5 - 156
LDL	133	81.5 ± 32.6	6 - 231	76	62 - 94.5
HDL	83	47.7 ± 21.9	22 - 214	45	39 - 52
TGL	73	104.4 ± 53.6	24 - 328	93	70 - 125.5

SBP : SYSTOLIC BLOOD PRESSURE, DBP : DIASTOLIC BLOOD PRESSURE, HBA1C: GLYCOSYLATED HEMOGLOBIN

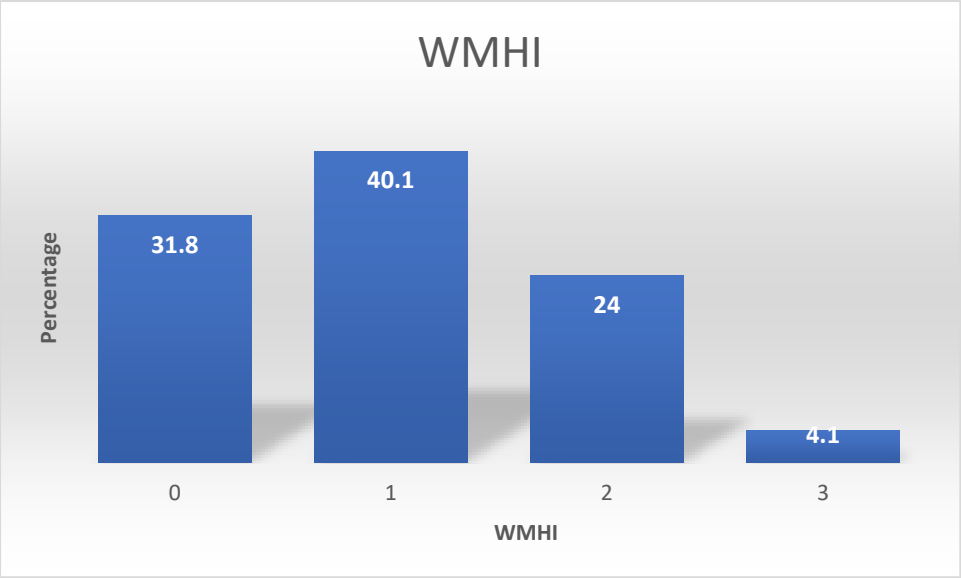
FIGURE 5.6: INFARCT PATTERN



76.5% had single infarct, while 2.4% had multiple infarcts and 2.1 % had MRI normal. Also infarct patterns, 34.6% had multiple embolic pattern, 29.5 % had superficial watershed infarct, 22.6% internal border zone infarct. Among the cohort only 8 had substenotic (30-50%) atherosclerotic disease,

The prevalence of chronic infarcts in the neuroimaging was also studied which showed 17.9% territorial infarcts, 27.8 % lacunar infarcts,16.2% had both territorial and lacunar infracts .40.8 % had Fazekas grade 1, 24% had grade 2 and 4.1 % had grade 3 white matter changes while 31.8% didn't had any white matter ischemic changes.

FIGURE 5.7: GRADING OF WHITE MATTER HYPERINTENSITIES



Cardiovascular parameters including ECG, Echo and holter was also studied. Based on ECG, 7.2% had presence of atrial ectopics, 9.6% had LVH. 24 hour Holter monitoring showed atrial ectopics in 1%, ventricular ectopics in 6.2%, supraventricular ectopics in 8.3%, while it was normal in 84.5%.

FIGURE 5.8 : HOLTER MONITORING

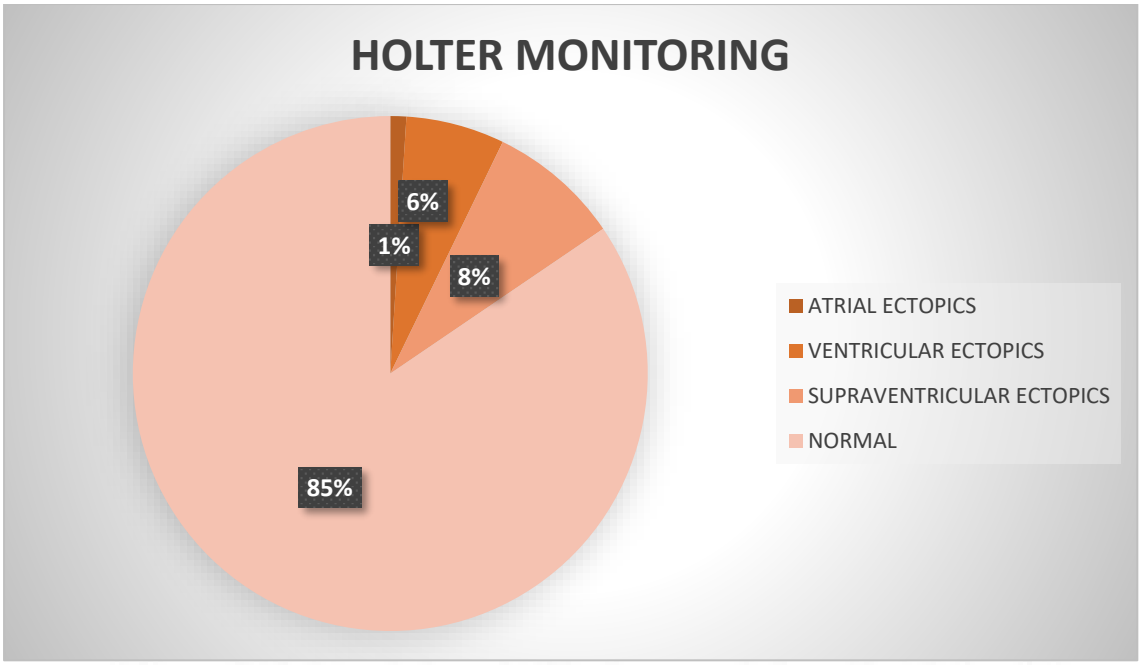


TABLE 5.8 : CARDIAC PARAMETERS

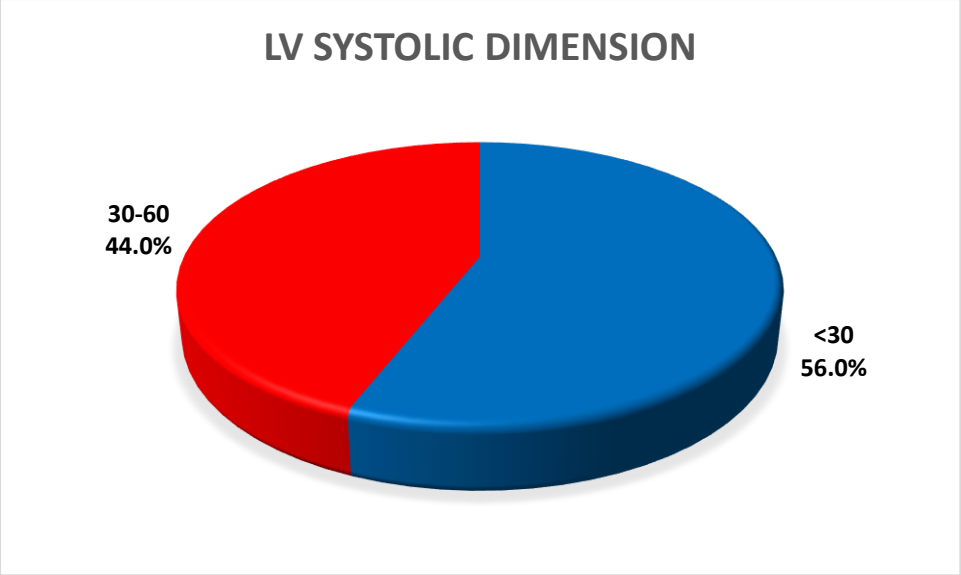
	N	mean ± sd	Range	Median	IQR
Plaque thickness	166	0.26 ± 0.12	0.04 - 0.7	0.24	0.18 - 0.33
PTFV 1	161	0.09 ± 0.09	0.02 - 0.8	0.08	0.04 - 0.08
PR interval	162	0.65 ± 0.79	0.04 - 2	0.22	0.16 - 2
LV dimension systolic	164	29.2 ± 6.4	18 - 54	29	24 - 33
LV dimension diastolic	164	45.1 ± 6.7	32 - 70	45	40 - 49
EF	227	63.1 ± 9.1	36 - 86	64	58 - 69

PTFV1 : P terminal force in lead V1, EF: EJECTION FRACTION

From the Transthoracic Echo, it was found that 95.8% had normal Left atrial diameter and it was <40 for males and <38 or females. But 4.2% had mild left atrial enlargement (males 41-46 and for females 39-42).

LV systolic dimension was 30-60 in 44%, while 56% had <30. LV diastolic dimension was normal for 98.6% and mild increase in 0.9 and moderate increase in 0.5%.

FIGURE 5.9 : LEFT VENTRICULAR SYSTOLIC DIMENSION



In our study 16.3% (38) patients underwent IV thrombolysis and mechanical thrombectomy was done for 8.6% (20) cases.

In our cohort, 26 patients (11.3%) had neurological worsening during hospital stay. Among them 4 had new infarct, 15 had MRI negative TIA and 16 had worsening of the infarct.

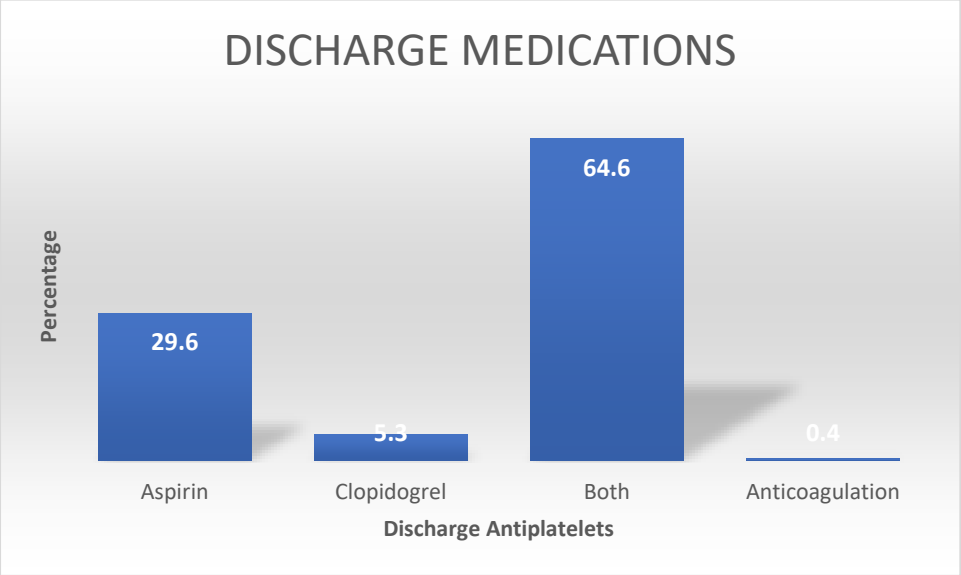
Functional outcome of patients were measured using Modified Rankin scale or MRS. Discharge MRS distribution of our cohort is given in table :

TABLE 5.9 : DISCHARGE MRS

DISCHARGE MRS	PERCENT
0	13.5
1	8.3
2	18.3
3	19.7
4	36.7
5	3.5

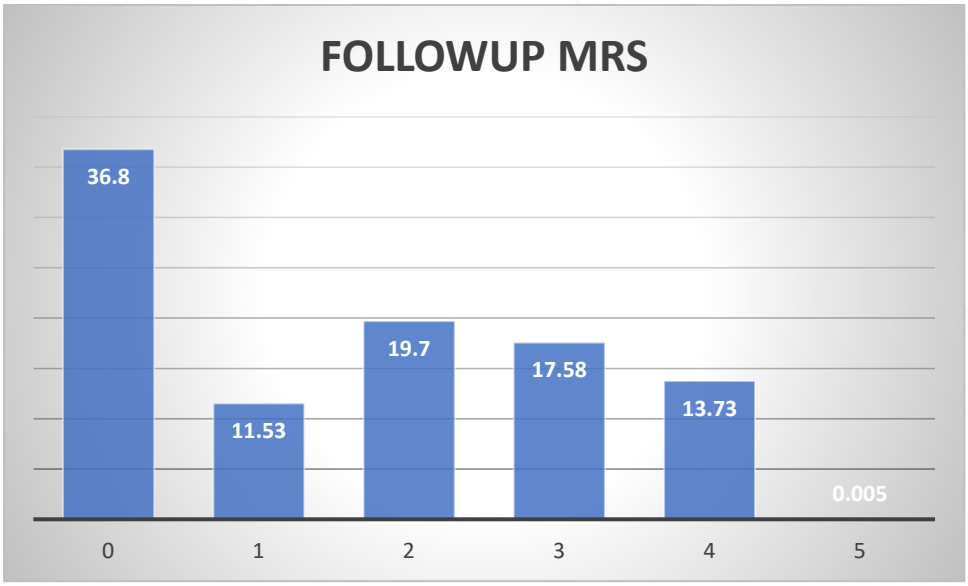
Among discharge medications, 29.6% was on Aspirin, 5.3 % was on Clopidogrel and 64.6% was on both and 0.4% (1) patient was on anticoagulation.

FIGURE 5.10 : DISCHARGE MEDICATIONS



On followup at end of 1 year, the MRS were as in the chart:

FIGURE 5.11 : FOLLOWUP MRS



At end of 1 year, 8.2% cases had recurrence of stroke on ipsilateral side. 3.8% had contralateral or vetebrobasilar strokes. 2.7% had cardiac events.

FIGURE 5.12: IPSILATERAL RECURRENT EVENTS

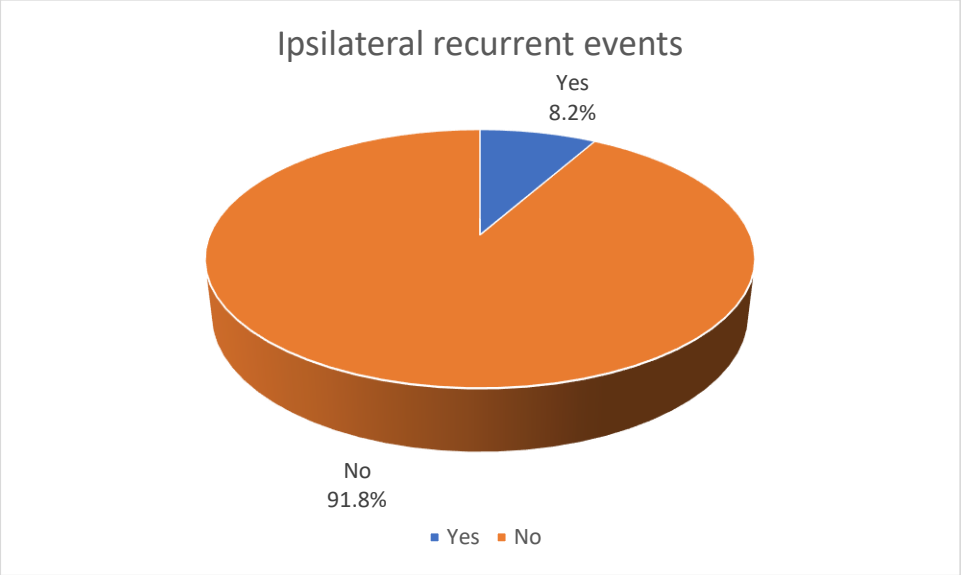


FIGURE 5.13: CONTRALATERAL/VERTEBROBASILAR EVENTS

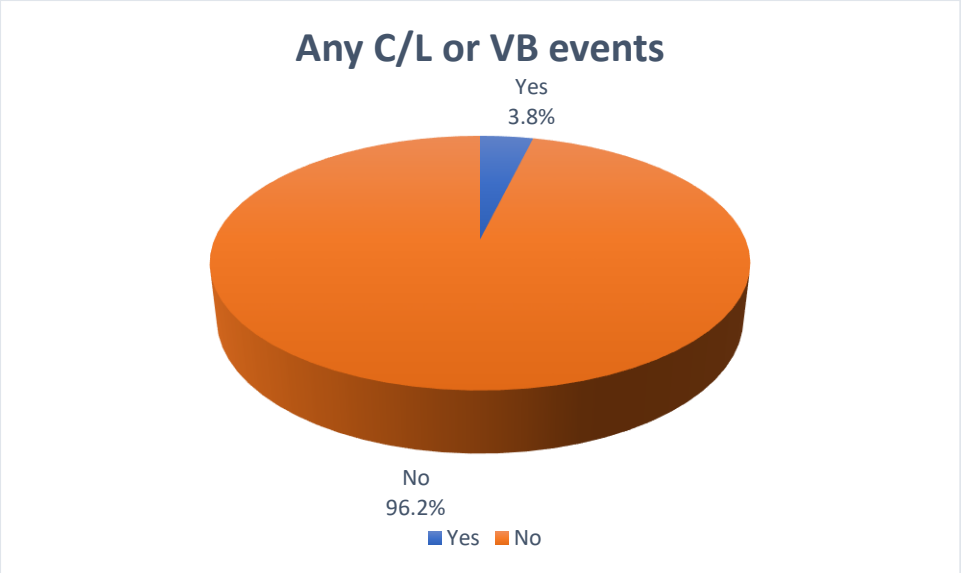
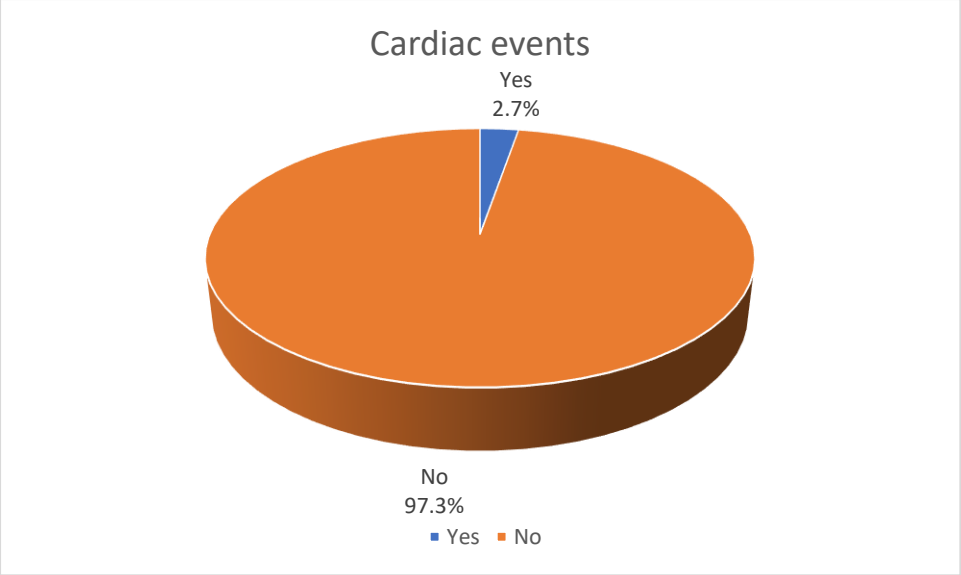


FIGURE 5.14: CARDIAC EVENTS



Various parameters were compared among those who had previous history of stroke/TIA with those who didn't had such past history.

TABLE 5.10 : THOSE WITH PREVIOUS STROKE/TIA AND NOT

	Previous stroke/TIA					
	Yes (n=46)		No (n=188)		t	P
	mean	sd	mean	Sd		
AGE	60.0	12.2	57.8	13.0	1.050	0.295
Admission NIHSS	5.8	5.8	8.7	7.0	2.638	0.009
Time between first symptom and admission	145.3	391.4	91.4	266.5	1.112	0.267
Admission blood sugar	175.0	86.6	161.0	69.3	1.130	0.260
HBA1C	7.3	1.7	7.5	2.2	0.744	0.458
SBP	155.1	30.3	156.4	28.0	0.289	0.773
DBP	90.2	17.3	88.3	15.8	0.696	0.487
Fasting Cholesterol	155.8	61.8	193.0	57.0	3.824	0.000
HDL	48.3	25.7	46.3	13.3	0.739	0.461
LDL	96.7	50.8	125.0	47.8	3.253	0.001
TGL	97.7	42.7	108.1	59.4	1.099	0.273
SERUM HOMOCYSTEINE	17.2	14.8	17.8	15.7	0.114	0.909
Plaque thickness	0.25	0.11	0.26	0.13	0.568	0.571
PTEF-V 1	0.09	0.07	0.09	0.09	0.544	0.587

PR interval	0.92	0.90	0.59	0.75	2.046	0.042
LV dimension systolic	29.2	6.6	29.2	6.4	0.038	0.969
LV dimension diastolic	44.7	6.6	45.2	6.8	0.387	0.699
EF	62.0	11.5	63.4	8.4	0.915	0.361
Discharge NIHSS	4.9	5.2	5.8	6.1	0.821	0.413
NIHSS	2.7	4.6	2.6	3.6	0.142	0.887
HbA1C	7.0	1.9	7.4	4.6	0.438	0.663
F cholesterol	151.3	41.6	139.5	36.0	1.557	0.122
LDL	88.1	35.7	80.1	31.9	1.088	0.279
HDL	48.9	12.8	47.5	23.5	0.235	0.814
TGL	120.2	55.7	100.6	52.9	1.233	0.222

		Previous stroke/TIA				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
GENDER	Male	35	76.1	122	64.9	157	67.1			
	Female	11	23.9	66	35.1	77	32.9	2.1	1	0.148
Hemisphere involved	VB	6	13	47	25	53	22.6			
	Right	16	34.8	62	33	78	33.3			
	Left	22	47.8	76	40.4	98	41.9			
	Bilateral	2	4.3	3	1.6	5	2.1	4.2	3	0.244
DM	Yes	28	60.9	95	50.5	123	52.6			
	No	18	39.1	93	49.5	111	47.4	1.6	1	0.208
HTN	Yes	38	82.6	112	59.6	150	64.1			
	No	8	17.4	76	40.4	84	35.9	8.5	1	0.004
DYSLIPIDEMIA	Yes	13	28.3	54	28.7	67	28.6			
	No	33	71.7	134	71.3	167	71.4	0.0	1	0.950
SMOKING	Yes	11	23.9	47	25	58	24.8			
	No	35	76.1	141	75	176	75.2	0.0	1	0.878
Alcohol	Yes	10	21.7	42	22.3	52	22.2			
	No	36	78.3	146	77.7	182	77.8	0.0	1	0.930
CAD	Yes	14	30.4	26	13.8	40	17.1			
	No	32	69.6	162	86.2	194	82.9	7.2	1	0.007

PCI/CABG	Yes	11	23.9	18	9.6	29	12.4			
	No	35	76.1	170	90.4	205	87.6	7.0	1	0.008
POVD	Yes	10	21.7	2	1.1	12	5.1			
	No	36	78.3	186	98.9	222	94.9	32.5	1	<0.001
	Left	19	41.3	0	0	19	8.1			
OLD STROKE :	Right	21	45.7	0	0	21	9			
HEMISPHERE	None	1	2.2	188	100	189	80.8			
	VB	5	10.9	0	0	5	2.1	227.7	3	<0.001
Pre-stroke statin use	Yes	29	63	37	19.7	66	28.2			
	No	17	37	151	80.3	168	71.8	34.3	1	<0.001
Pre-stroke antiplatelet use	Aspirin	22	47.8	20	10.6	42	17.9			
	None	19	41.3	164	87.2	183	78.2			
	Clopilet	0	0	1	0.5	1	0.4			
	Both	5	10.9	3	1.6	8	3.4	48.0	3	<0.001

		Previous stroke/TIA				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Imaging modality	A	8	17.4	60	31.9	68	29.1			
	B	18	39.1	50	26.6	68	29.1			
	C	20	43.5	78	41.5	98	41.9	4.7	2	0.095
Infarct	Single	27	58.7	152	80.9	179	76.5			
	Multiple	18	39.1	32	17	50	21.4			
	Normal	1	2.2	4	2.1	5	2.1	10.8	2	0.004
OCCLUSION	No	33	71.7	115	61.2	148	63.2			
	Yes	13	28.3	73	38.8	86	36.8	1.8	1	0.183
Superficial watershed	Yes	20	43.5	49	26.1	69	29.5			

	No	26	56.5	139	73.9	165	70.5	5.4	1	0.020
Internal borderzone	Yes	12	26.1	41	21.8	53	22.6			
	No	34	73.9	147	78.2	181	77.4	0.4	1	0.534
Multiple embolic	Yes	16	34.8	65	34.6	81	34.6			
	No	30	65.2	123	65.4	153	65.4	0.0	1	0.979
EC	<30	44	95.7	182	96.8	226	96.6			
	30-40	2	4.3	6	3.2	8	3.4	0.2	1	0.699
IC	<30	45	97.8	181	96.3	226	96.6			
	30-40	1	2.2	7	3.7	8	3.4	0.3	1	0.604
chronic infarcts	Territorial	11	23.9	31	16.5	42	17.9			
	Lacunar	11	23.9	54	28.7	65	27.8			
	Both	11	23.9	27	14.4	38	16.2			
	None	13	28.3	76	40.4	89	38	5.0	3	0.175
WMHI	0	11	25.6	58	33.3	69	31.8			
	1	13	30.2	74	42.5	87	40.1			
	2	14	32.6	38	21.8	52	24			
	3	5	11.6	4	2.3	9	4.1	10.8	3	0.013
Presence of atrial ectopics	Yes	5	16.7	7	5.1	12	7.2			
	No	25	83.3	129	94.9	154	92.8	4.9	1	0.027

		Previous stroke/TIA								
		Yes		No		Total		χ^2	df	p
		N	%	N	%	N	%			
LVH –voltage criteria	Yes	5	16.7	11	8.1	16	9.6			

	No	25	83.3	125	91.9	150	90.4	2.1	1	0.150
AF	Yes	1	3.4	6	4.4	7	4.3			
	No	28	96.6	129	95.6	157	95.7	0.1	1	0.810
24 hour Holter-done	Normal	26	72.2	137	87.3	163	84.5			
	Atrial ectopics	1	2.8	1	0.6	2	1			
	SVT	5	13.9	11	7	16	8.3			
	VENTRICULAR ETCOPIC	4	11.1	8	5.1	12	6.2	5.5	3	0.141
TTE-LA diameter	Normal	27	100	86	94.5	113	95.8			
	Abnormal	0	0	5	5.5	5	4.2	1.5	1	0.213
LV SYSTOLIC DIMENSION	<30	17	54.8	76	56.3	93	56			
	30-60	14	45.2	59	43.7	73	44	0.0	1	0.883
LV DIASTOLIC DIMENSION GRADE	Normal	46	100	168	98.2	214	98.6			
	Mild	0	0	2	1.2	2	0.9			
	Moderate	0	0	1	0.6	1	0.5	0.8	2	0.664
IV THROMBOLYSED	Yes	5	11.1	33	17.6	38	16.3			
	No	40	88.9	155	82.4	195	83.7	1.1	1	0.293
MT	Yes	2	4.4	18	9.6	20	8.6			
	No	43	95.6	170	90.4	213	91.4	1.2	1	0.270
In hospital recurrent events	Yes	5	11.4	21	11.2	26	11.3			
	No	39	88.6	166	88.8	205	88.7	0.0	1	0.980

		Previous stroke/TIA				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Type of recurrent events	Stroke	0	0	4	2.2	4	1.8			
	TIA	3	7.3	12	6.5	15	6.6			
	Nil	36	87.8	156	83.9	192	84.6			

	Worsening	2	4.9	14	7.5	16	7	1.3	3	0.725
Discharge MRS	0	7	16.7	24	12.8	31	13.5			
	1	1	2.4	18	9.6	19	8.3			
	2	10	23.8	32	17.1	42	18.3			
	3	7	16.7	38	20.3	45	19.7			
	4	17	40.5	67	35.8	84	36.7			
	5	0	0	8	4.3	8	3.5	5.6	5	0.346
Discharge antiplatelets	Aspirin	9	22	58	31.4	67	29.6			
	Clopidogrel	2	4.9	10	5.4	12	5.3			
	Both	30	73.2	116	62.7	146	64.6			
	Anticoagulation	0	0	1	0.5	1	0.4	1.8	3	0.613
MRS	0	11	34.4	56	37.3	67	36.8			
	1	4	12.5	17	11.3	21	11.5			
	2	6	18.8	30	20	36	19.8			
	3	6	18.8	26	17.3	32	17.6			
	4	4	12.5	21	14	25	13.7			
	5	1	3.1	0	0	1	0.5	4.9	5	0.431
Ipsilateral recurrent events	Yes	8	24.2	7	4.7	15	8.2			
	No	25	75.8	143	95.3	168	91.8	13.8	1	<0.001
Any C/L or VB events	Yes	4	12.1	3	2	7	3.8			
	No	29	87.9	147	98	176	96.2	7.5	1	0.006
Cardiac events	Yes	0	0	5	3.3	5	2.7			
	No	33	100	145	96.7	178	97.3	1.1	1	0.288

Clinical, risk factors, cardiac and neuroimaging parameters were compared among those who had first stroke versus those who had recurrent strokes. Hypertension was more in those who are having stroke for first time (p value 0.004). Raised PR interval (mean = 0.92 with p value 0.004), Dyslipidemia, CAD (p value 0.007), h/o CABG/PCI (p value 0.008) and PVOD (p value <0.001) were more common in people who had previous h/o stroke /TIA.

Presence of atrial ectopics (p value of 0.027), WMHI (p value = 0.013), superficial watershed infarcts(p value 0.020) , multiple embolic infarcts (p value 0.004) , presence of ipsilateral events or contralateral/vertebrobasilar events were also found be statistically significant among those who had past history of stroke at the time of presentation

TABLE 5.11: THOSE WITH IN HOSPITAL WORSENING VERSUS WITHOUT

		In hospital worsening				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
GENDER	Male	19	73.1	137	66.8	156	67.5			
	Female	7	26.9	68	33.2	75	32.5	0.4	1	0.522
Hemisphere involved	VB	3	11.5	48	23.4	51	22.1			
	Right	14	53.8	63	30.7	77	33.3			
	Left	9	34.6	89	43.4	98	42.4			
	Bilateral	0	0	5	2.4	5	2.2	6.2	3	0.101
DM	Yes	17	65.4	104	50.7	121	52.4			
	No	9	34.6	101	49.3	110	47.6	2.0	1	0.159
HTN	Yes	17	65.4	131	63.9	148	64.1			
	No	9	34.6	74	36.1	83	35.9	0.0	1	0.882
DYSLIPIDEMIA	Yes	5	19.2	60	29.3	65	28.1			
	No	21	80.8	145	70.7	166	71.9	1.2	1	0.284
SMOKING	Yes	10	38.5	47	22.9	57	24.7			
	No	16	61.5	158	77.1	174	75.3	3.0	1	0.083
Alcohol	Yes	8	30.8	44	21.5	52	22.5			
	No	18	69.2	161	78.5	179	77.5	1.1	1	0.284
CAD	Yes	5	19.2	34	16.6	39	16.9			
	No	21	80.8	171	83.4	192	83.1	0.1	1	0.734
PCI/CABG	Yes	4	15.4	25	12.2	29	12.6			
	No	22	84.6	180	87.8	202	87.4	0.2	1	0.644
POVD	Yes	1	3.8	10	4.9	11	4.8			
	No	25	96.2	195	95.1	220	95.2	0.1	1	0.816

	Left	2	7.7	16	7.8	18	7.8			
OLD STROKE :	Right	3	11.5	18	8.8	21	9.1			
HEMISPHERE	None	21	80.8	167	81.5	188	81.4			
	VB	0	0	4	2	4	1.7	0.7	3	0.873
Prestroke statin	Yes	7	26.9	57	27.8	64	27.7			
use	No	19	73.1	148	72.2	167	72.3	0.0	1	0.925
	Aspirin	7	26.9	33	16.1	40	17.3			
Prestroke	None	19	73.1	163	79.5	182	78.8			
antiplatelet use	Clopilet	0	0	1	0.5	1	0.4			
	Both	0	0	8	3.9	8	3.5	2.8	3	0.420

		In hospital recurrent events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Imaging modality	A	13	50	54	26.3	67	29			
	B	3	11.5	63	30.7	66	28.6			
	C	10	38.5	88	42.9	98	42.4	7.5	2	0.023
Infarct	Single	19	73.1	157	76.6	176	76.2			
	Multiple	7	26.9	43	21	50	21.6			
	Normla	0	0	5	2.4	5	2.2	1.0	2	0.592
OCCLUSION	No	11	42.3	135	65.9	146	63.2			
	Yes	15	57.7	70	34.1	85	36.8	5.5	1	0.019
Superficial watershed	Yes	10	38.5	58	28.3	68	29.4			
	No	16	61.5	147	71.7	163	70.6	1.1	1	0.284
Internal borderzone	Yes	4	15.4	49	23.9	53	22.9			
	No	22	84.6	156	76.1	178	77.1	0.9	1	0.331
Lacunar	Yes	2	7.7	39	19	41	17.7			
	No	24	92.3	166	81	190	82.3	2.0	1	0.154

Multiple embolic	Yes	9	34.6	71	34.6	80	34.6			
	No	17	65.4	134	65.4	151	65.4	0.0	1	0.998
EC	<30	25	96.2	198	96.6	223	96.5			
	30-40	1	3.8	7	3.4	8	3.5	0.0	1	0.910
IC	<30	24	92.3	199	97.1	223	96.5			
	30-40	2	7.7	6	2.9	8	3.5	1.6	1	0.211
chronic infarcts	Territorial	8	30.8	33	16.1	41	17.7			
	Lacunar	8	30.8	56	27.3	64	27.7			
	Both	4	15.4	34	16.6	38	16.5			
	None	6	23.1	82	40	88	38.1	4.7	3	0.199
WMHI	0	7	26.9	62	32.8	69	32.1			
	1	13	50	73	38.6	86	40			
	2	6	23.1	45	23.8	51	23.7			
	3	0	0	9	4.8	9	4.2	2.2	3	0.526
Presence of atrial ectopics	Yes	0	0	12	8.2	12	7.3			
	No	19	100	134	91.8	153	92.7	1.7	1	0.194

		In hospital recurrent events				Total				p
		Yes		No						
		N	%	N	%	N	%			
LVH –voltage criteria	Yes	2	10.5	14	9.6	16	9.7			
	No	17	89.5	132	90.4	149	90.3	0.0	1	0.897
AF	Yes	1	5.3	6	4.2	7	4.3			
	No	18	94.7	138	95.8	156	95.7	0.0	1	0.825
24 hour Holter-done	Normal	18	85.7	143	84.1	161	84.3			
	Atrial ectopics	1	4.8	1	0.6	2	1			
	SVT	1	4.8	15	8.8	16	8.4			
	VENTRICULAR ETCOPIC	1	4.8	11	6.5	12	6.3	3.6	3	0.312

TTE-LA diameter	Normal	11	91.7	102	96.2	113	95.8			
	Abnormal	1	8.3	4	3.8	5	4.2	0.6	1	0.457
LV SYSTOLIC DIMENSION	<30	10	66.7	83	55	93	56			
	30-60	5	33.3	68	45	73	44	0.8	1	0.384
LV DIASTOLIC DIMENSION GRADE	Normal	21	95.5	190	99	211	98.6			
	Mild	0	0	2	1	2	0.9			
	Moderate	1	4.5	0	0	1	0.5	9.0	2	0.011
IV THROMMOLYSED	Yes	9	34.6	29	14.1	38	16.5			
	No	17	65.4	176	85.9	193	83.5	7.0	1	0.008
MT	Yes	6	23.1	14	6.8	20	8.7			
	No	20	76.9	191	93.2	211	91.3	7.7	1	0.006

		In hospital recurrent events				Total				p
		Yes		No						
		N	%	N	%	N	%			
Type of recurrent events	Stroke	4	17.4	0	0	4	1.8			
	TIA	0	0	15	7.4	15	6.6			
	Nil	3	13	188	92.6	191	84.5			
	Worsening	16	69.6	0	0	16	7.1	193.7	3	<0.001

Discharge MRS	0	1	4.2	30	14.6	31	13.5			
	1	0	0	19	9.3	19	8.3			
	2	1	4.2	41	20	42	18.3			
	3	1	4.2	44	21.5	45	19.7			
	4	18	75	66	32.2	84	36.7			
	5	3	12.5	5	2.4	8	3.5	27.1	5	<0.001
Discharge antiplatelets	Aspirin	15	62.5	52	25.7	67	29.6			
	Clopidogrel	2	8.3	10	5	12	5.3			
	Both	6	25	140	69.3	146	64.6			
	Anticoagulation	1	4.2	0	0	1	0.4	25.2	3	<0.001
MRS	0	2	10.5	65	39.9	67	36.8			
	1	0	0	21	12.9	21	11.5			
	2	4	21.1	32	19.6	36	19.8			
	3	8	42.1	24	14.7	32	17.6			
	4	5	26.3	20	12.3	25	13.7			
	5	0	0	1	0.6	1	0.5	16.3	5	0.006
Ipsilateral recurrent events	Yes	1	5.3	14	8.5	15	8.2			
	No	18	94.7	150	91.5	168	91.8	0.2	1	0.622
Any C/L or VB events	Yes	0	0	7	4.3	7	3.8			
	No	19	100	157	95.7	176	96.2	0.8	1	0.358
Cardiac events	Yes	0	0	5	3	5	2.7			
	No	19	100	159	97	178	97.3	0.6	1	0.440

	In hospital recurrent events					
	Yes (n=26)		No(n=205)		t	p
	mean	sd	mean	sd		

AGE	57.5	11.1	58.4	13.0	0.366	0.715
Admission NIHSS	10.6	7.6	7.8	6.7	1.959	0.051
Time between first symptom and admission	68.3	135.7	96.9	276.0	0.518	0.605
Admission blood sugar	181.2	77.5	161.6	72.5	1.284	0.200
HBA1C	8.2	2.2	7.4	2.1	1.644	0.102
SBP	153.8	25.4	156.8	28.6	0.509	0.612
DBP	88.0	12.3	89.1	16.5	0.315	0.753
Fasting Cholesterol	176.3	63.1	187.6	59.3	0.908	0.365
HDL	44.9	15.2	47.0	16.6	0.625	0.533
LDL	107.7	55.2	121.3	48.8	1.192	0.235
TGL	106.0	48.7	105.9	57.7	0.003	0.997
SERUM HOMOCYSTEINE	22.6	8.8	17.2	16.1	0.736	0.465
Plaque thickness	0.26	0.12	0.26	0.12	0.004	0.997
PTF-V 1	0.07	0.06	0.09	0.09	0.945	0.346
PR interval	0.57	0.76	0.67	0.79	0.532	0.596
LV dimension systolic	28.5	4.8	29.3	6.5	0.427	0.670
LV dimension diastolic	47.0	8.9	44.9	6.5	1.150	0.252
EF	61.8	8.9	63.4	9.2	0.832	0.406
Discharge NIHSS	11.2	5.7	5.0	5.6	5.140	0.000
NIHSS	5.2	3.3	2.3	3.7	3.197	0.002
HbA1C	7.3	1.2	7.4	4.4	0.023	0.982
F cholesterol	135.5	28.5	142.3	38.1	0.677	0.499
LDL	74.1	19.7	82.5	33.9	0.931	0.354
HDL	45.4	6.2	48.0	22.9	0.318	0.752
TGL	136.0	55.7	101.6	52.9	1.521	0.133

In people with in hospital worsening, terminal branch occlusion was more (n=15) (p value=0.019). 22 patients (91%) in those who had in hospital recurrent events had discharge MRS of 3-5 while 2 had MRS <2.

On followup, it was found that 15 patients had recurrent ipsilateral events of which 11 were males and 4 were females. Smoking and presence of PVOD was associated with recurrence of

events on ipsilateral vascular territory with statistical significance (p value of 0.045 and 0.045 respectively). Pattern of infarcts: superficial watershed infarcts and multiple embolic infarcts showed a statistically significant association with ipsilateral recurrent events. (p value 0.001and 0.019 respectively).

TABLE 5.12: IPSILATERAL RECURRENT EVENTS AT 1 YEAR FOLLOWUP

		Ipsilateral recurrent events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
GENDER	Male	11	73.3	118	70.2	129	70.5			
	Female	4	26.7	50	29.8	54	29.5	0.1	1	0.801
Hemisphere involved	VB	1	6.7	45	26.8	46	25.1			
	Right	4	26.7	56	33.3	60	32.8			
	Left	10	66.7	64	38.1	74	40.4			
	Bilateral	0	0	3	1.8	3	1.6	5.5	3	0.142
DM	Yes	9	60	83	49.4	92	50.3			
	No	6	40	85	50.6	91	49.7	0.6	1	0.432
HTN	Yes	9	60	105	62.5	114	62.3			
	No	6	40	63	37.5	69	37.7	0.0	1	0.848
DYSLIPIDEMIA	Yes	5	33.3	51	30.4	56	30.6			
	No	10	66.7	117	69.6	127	69.4	0.1	1	0.811
SMOKING	Yes	7	46.7	39	23.2	46	25.1			
	No	8	53.3	129	76.8	137	74.9	4.0	1	0.045
Alcohol	Yes	5	33.3	36	21.4	41	22.4			
	No	10	66.7	132	78.6	142	77.6	1.1	1	0.289
CAD	Yes	3	20	28	16.7	31	16.9			
	No	12	80	140	83.3	152	83.1	0.1	1	0.742
PCI/CABG	Yes	3	20	21	12.5	24	13.1			
	No	12	80	147	87.5	159	86.9	0.7	1	0.410
POVD	Yes	2	13.3	5	3	7	3.8			
	No	13	86.7	163	97	176	96.2	4.0	1	0.045

	Left	4	26.7	9	5.4	13	7.1			
OLD STROKE :	Right	1	6.7	14	8.3	15	8.2			
HEMISPHERE	None	8	53.3	143	85.1	151	82.5			
	VB	2	13.3	2	1.2	4	2.2	19.8	3	<0.001
Prestroke statin	Yes	8	53.3	45	26.8	53	29			
use	No	7	46.7	123	73.2	130	71	4.7	1	0.030
Prestroke antiplatelet use	Aspirin	7	46.7	27	16.1	34	18.6			
	None	8	53.3	134	79.8	142	77.6			
	Both	0	0	7	4.2	7	3.8	8.8	2	0.012

		Ipsilateral recurrent events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Imaging modality	A	3	20	51	30.4	54	29.5			
	B	8	53.3	44	26.2	52	28.4			
	C	4	26.7	73	43.5	77	42.1	5.0	2	0.082
Infarct	Single	10	66.7	129	76.8	139	76			
	Multiple	5	33.3	34	20.2	39	21.3			
	Normal	0	0	5	3	5	2.7	1.7	2	0.419
OCCLUSION	No	10	66.7	108	64.3	118	64.5			
	Yes	5	33.3	60	35.7	65	35.5	0.0	1	0.854
Superficial watershed	Yes	10	66.7	45	26.8	55	30.1			
	No	5	33.3	123	73.2	128	69.9	10.4	1	0.001
Internal borderzone	Yes	3	20	36	21.4	39	21.3			
	No	12	80	132	78.6	144	78.7	0.0	1	0.897
Multiple embolic	Yes	9	60	51	30.4	60	32.8			
	No	6	40	117	69.6	123	67.2	5.5	1	0.019
EC	<30	15	100	162	96.4	177	96.7			
	30-50	0	0	6	3.6	6	3.3	0.6	1	0.457

IC	<30	15	100	160	95.2	175	95.6			
	30-50	0	0	8	4.8	8	4.4	0.7	1	0.387
chronic infarcts	Territorial	4	26.7	31	18.5	35	19.1			
	Lacunar	4	26.7	50	29.8	54	29.5			
	Both	3	20	23	13.7	26	14.2			
	None	4	26.7	64	38.1	68	37.2	1.4	3	0.705
WMHI	0	5	33.3	57	35.6	62	35.4			
	1	7	46.7	67	41.9	74	42.3			
	2	3	20	29	18.1	32	18.3			
	3	0	0	7	4.4	7	4	0.8	3	0.855
Presence of atrial ectopics	Yes	0	0	9	7	9	6.5			
	No	11	100	119	93	130	93.5	0.8	1	0.363

		Ipsilateral recurrent events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
LVH –voltage criteria	Yes	1	9.1	10	7.8	11	7.9			
	No	10	90.9	118	92.2	128	92.1	0.0	1	0.880
24 hour Holter-done	Normal	9	75	126	85.1	135	84.4			
	Atrial ectopics	0	0	2	1.4	2	1.3			
	SVT	2	16.7	11	7.4	13	8.1			
	VENTRICULAR ETCOPIC	1	8.3	9	6.1	10	6.3	1.6	3	0.670
TTE-LA diameter	Normal	7	100	88	94.6	95	95			
	Abnormal	0	0	5	5.4	5	5	0.4	1	0.529
LV SYSTOLIC DIMENSION	<30	6	50	74	56.1	80	55.6			
	30-60	6	50	58	43.9	64	44.4	0.2	1	0.686
LV DIASTOLIC DIMENSION GRADE	Normal	15	100	153	98.1	168	98.2			

	Mild	0	0	2	1.3	2	1.2			
	Moderate	0	0	1	0.6	1	0.6	0.3	2	0.863
IV THROMMOLYSED	Yes	3	20	29	17.3	32	17.5			
	No	12	80	139	82.7	151	82.5	0.1	1	0.789
MT	Yes	1	6.7	16	9.5	17	9.3			
	No	14	93.3	152	90.5	166	90.7	0.1	1	0.715

		Ipsilateral recurrent events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Type of recurrent events	Stroke	0	0	3	1.8	3	1.6			
	TIA	2	13.3	12	7.2	14	7.7			
	Nil	12	80	140	83.8	152	83.5			
	Worsening	1	6.7	12	7.2	13	7.1	1.0	3	0.807
Discharge MRS	0	2	13.3	24	14.3	26	14.2			
	1	3	20	14	8.3	17	9.3			
	2	3	20	33	19.6	36	19.7			
	3	1	6.7	36	21.4	37	20.2			
	4	6	40	59	35.1	65	35.5			
	5	0	0	2	1.2	2	1.1	3.8	5	0.581
Discharge antiplatelets	Aspirin	2	14.3	51	30.5	53	29.3			
	Clopidogrel	2	14.3	7	4.2	9	5			
	Both	10	71.4	108	64.7	118	65.2			
	Anticoagulation	0	0	1	0.6	1	0.6	4.0	3	0.263
MRS	0	3	20	63	38.4	66	36.9			
	1	1	6.7	20	12.2	21	11.7			
	2	4	26.7	32	19.5	36	20.1			
	3	2	13.3	29	17.7	31	17.3			
	4	4	26.7	20	12.2	24	13.4			

	5	1	6.7	0	0	1	0.6	15.2	5	0.010
Any C/L or VB events	Yes	2	13.3	5	3	7	3.8			
	No	13	86.7	163	97	176	96.2	4.0	1	0.045
Cardiac events	Yes	0	0	5	3	5	2.7			
	No	15	100	163	97	178	97.3	0.5	1	0.498

	Ipsilateral recurrent events					
	Yes(n=15)		No (n=168)		t	p
	mean	sd	mean	sd		
AGE	58.5	13.3	58.0	12.0	0.151	0.880
Admission NIHSS	8.3	7.2	7.7	6.7	0.335	0.738
Time between first symptom and admission	159.8	398.8	73.4	243.2	1.239	0.217
Admission blood sugar	187.1	87.3	164.2	72.9	1.073	0.285
HBA1C	7.3	2.5	7.3	2.1	0.009	0.993
SBP	150.9	31.3	157.9	27.4	0.930	0.353
DBP	85.6	13.9	89.7	16.4	0.939	0.349
Fasting Cholesterol	177.8	51.3	188.9	57.2	0.681	0.496
HDL	48.9	12.1	47.2	16.5	0.372	0.711
LDL	112.5	47.3	121.3	47.5	0.620	0.536
TGL	89.9	18.2	103.3	55.5	0.866	0.388
SERUM HOMOCYSTEINE	12.9	4.9	17.4	14.2	0.539	0.593
Plaque thickness	0.28	0.12	0.26	0.12	0.747	0.456
PTF-V 1	0.06	0.03	0.09	0.09	0.909	0.365
PR interval	1.01	0.95	0.62	0.77	1.600	0.112
LV dimension systolic	29.0	5.9	29.2	6.3	0.084	0.933
LV dimension diastolic	44.3	6.9	45.2	6.9	0.450	0.653
EF	64.7	9.4	63.5	9.0	0.520	0.603
Discharge NIHSS	5.6	5.9	5.2	5.4	0.301	0.764
NIHSS	6.1	7.0	2.3	3.2	3.923	0.000
HbA1C	7.5	2.4	7.4	4.4	0.073	0.942
F cholesterol	168.7	39.9	139.8	36.9	2.385	0.018

LDL	89.3	26.1	81.1	33.2	0.680	0.497
HDL	48.4	8.3	47.4	23.1	0.094	0.925
TGL	146.4	70.2	101.5	52.0	1.819	0.073

TABLE 5.13: CONTRALATERAL/VERTEBROBASILAR RECURRENT EVENTS AT 1 YEAR FOLLOWUP

		Any C/L or VB events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
GENDER	Male	7	100	122	69.3	129	70.5			
	Female	0	0	54	30.7	54	29.5	3.0	1	0.081
Hemisphere	VB	4	57.1	42	23.9	46	25.1			
involved	Right	1	14.3	59	33.5	60	32.8			
	Left	2	28.6	72	40.9	74	40.4			
	Bilateral	0	0	3	1.7	3	1.6	4.1	3	0.251
DM	Yes	4	57.1	88	50	92	50.3			
	No	3	42.9	88	50	91	49.7	0.1	1	0.711
HTN	Yes	5	71.4	109	61.9	114	62.3			
	No	2	28.6	67	38.1	69	37.7	0.3	1	0.611
DYSLIPIDEMIA	Yes	2	28.6	54	30.7	56	30.6			
	No	5	71.4	122	69.3	127	69.4	0.0	1	0.905
SMOKING	Yes	4	57.1	42	23.9	46	25.1			
	No	3	42.9	134	76.1	137	74.9	4.0	1	0.047
Alcohol	Yes	4	57.1	37	21	41	22.4			
	No	3	42.9	139	79	142	77.6	5.1	1	0.025
CAD	Yes	1	14.3	30	17	31	16.9			
	No	6	85.7	146	83	152	83.1	0.0	1	0.849
PCI/CABG	Yes	1	14.3	23	13.1	24	13.1			
	No	6	85.7	153	86.9	159	86.9	0.0	1	0.925
POVD	Yes	1	14.3	6	3.4	7	3.8			
	No	6	85.7	170	96.6	176	96.2	2.2	1	0.141
OLD STROKE :	Left	0	0	13	7.4	13	7.1			
HEMISPHERE	Right	2	28.6	13	7.4	15	8.2			

	None	3	42.9	148	84.1	151	82.5			
	VB	2	28.6	2	1.1	4	2.2	28.8	3	<0.001
Prestroke statin use	Yes	5	71.4	48	27.3	53	29			
	No	2	28.6	128	72.7	130	71	6.4	1	0.012
Prestroke antiplatelet use	Aspirin	4	57.1	30	17	34	18.6			
	None	3	42.9	139	79	142	77.6			
	Both	0	0	7	4	7	3.8	7.2	2	0.027

		Any C/L or VB events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Imaging modality	A	1	14.3	53	30.1	54	29.5			
	B	1	14.3	51	29	52	28.4			
	C	5	71.4	72	40.9	77	42.1	2.6	2	0.276
Infarct	Single	4	57.1	135	76.7	139	76			
	Multiple	3	42.9	36	20.5	39	21.3			
	Normla	0	0	5	2.8	5	2.7	2.1	2	0.346
OCCLUSION	No	6	85.7	112	63.6	118	64.5			
	Yes	1	14.3	64	36.4	65	35.5	1.4	1	0.231
Superficial watershed	Yes	4	57.1	51	29	55	30.1			
	No	3	42.9	125	71	128	69.9	2.5	1	0.111
Internal borderzone	Yes	0	0	39	22.2	39	21.3			
	No	7	100	137	77.8	144	78.7	2.0	1	0.160
Multiple embolic	Yes	2	28.6	58	33	60	32.8			

	No	5	71.4	118	67	123	67.2	0.1	1	0.809
EC	<30	7	100	170	96.6	177	96.7			
	30-40	0	0	6	3.4	6	3.3	0.2	1	0.619
IC	<30	7	100	168	95.5	175	95.6			
	30-40	0	0	8	4.5	8	4.4	0.3	1	0.564
chronic infarcts	Territorial	4	57.1	31	17.6	35	19.1			
	Lacunar	1	14.3	53	30.1	54	29.5			
	Both	1	14.3	25	14.2	26	14.2			
	None	1	14.3	67	38.1	68	37.2	7.1	3	0.069
WMHI	0	2	28.6	60	35.7	62	35.4			
	1	2	28.6	72	42.9	74	42.3			
	2	2	28.6	30	17.9	32	18.3			
	3	1	14.3	6	3.6	7	4	2.8	3	0.428
Presence of atrial ectopics	Yes	0	0	9	6.6	9	6.5			
	No	3	100	127	93.4	130	93.5	0.2	1	0.645

		Any C/L or VB events				Total				
		Yes		No				χ^2	df	p
		N	%	N	%	N	%			
LVH –voltage criteria	Yes	1	33.3	10	7.4	11	7.9			
	No	2	66.7	126	92.6	128	92.1	2.7	1	0.099
24 hour Holter-done	Normal	6	100	129	83.8	135	84.4			
	Atrial ectopics	0	0	2	1.3	2	1.3			
	SVT	0	0	13	8.4	13	8.1			
	VENTRICULAR ETCOPIC	0	0	10	6.5	10	6.3	1.2	3	0.764
TTE-LA diameter	Normal	2	100	93	94.9	95	95			

	Abnormal	0	0	5	5.1	5	5	0.1	1	0.743
LV SYSTOLIC DIMENSION	<30	1	25	79	56.4	80	55.6			
	30-60	3	75	61	43.6	64	44.4	1.6	1	0.212
LV DIASTOLIC DIMENSION GRADE	Normal	7	100	161	98.2	168	98.2			
	Mild	0	0	2	1.2	2	1.2			
	Moderate	0	0	1	0.6	1	0.6	0.1	2	0.937
IV THROMMOLYSED	Yes	1	14.3	31	17.6	32	17.5			
	No	6	85.7	145	82.4	151	82.5	0.1	1	0.820
MT	Yes	0	0	17	9.7	17	9.3			
	No	7	100	159	90.3	166	90.7	0.7	1	0.388

		Any C/L or VB events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Type of recurrent events	Stroke	0	0	3	1.7	3	1.6			
	TIA	0	0	14	8	14	7.7			
	Nil	7	100	145	82.9	152	83.5			
	Worsening	0	0	13	7.4	13	7.1	1.4	3	0.697
Discharge MRS	0	1	14.3	25	14.2	26	14.2			
	1	0	0	17	9.7	17	9.3			
	2	2	28.6	34	19.3	36	19.7			

	3	1	14.3	36	20.5	37	20.2			
	4	3	42.9	62	35.2	65	35.5			
	5	0	0	2	1.1	2	1.1	1.3	5	0.936
Discharge antiplatelets	Aspirin	1	14.3	52	29.9	53	29.3			
	Clopidogrel	0	0	9	5.2	9	5			
	Both	6	85.7	112	64.4	118	65.2			
	Anticoagulation	0	0	1	0.6	1	0.6	1.4	3	0.698
MRS	0	1	14.3	65	37.8	66	36.9			
	1	0	0	21	12.2	21	11.7			
	2	3	42.9	33	19.2	36	20.1			
	3	2	28.6	29	16.9	31	17.3			
	4	1	14.3	23	13.4	24	13.4			
	5	0	0	1	0.6	1	0.6	4.3	5	0.505
Cardiac events	Yes	0	0	5	2.8	5	2.7			
	No	7	100	171	97.2	178	97.3	0.2	1	0.651

	Any C/L or VB events					
	Yes (n=7)		No (n=176)		t	p
	mean	sd	mean	sd		
AGE	62.0	9.2	57.9	12.1	0.892	0.374
Admission NIHSS	5.0	4.0	7.8	6.8	1.092	0.276
Time between first symptom and admission	61.7	122.1	81.3	263.1	0.196	0.845
Admission blood sugar	170.9	81.5	165.7	74.0	0.181	0.857
HBA1C	7.5	2.0	7.3	2.1	0.197	0.844
SBP	162.9	38.4	157.1	27.3	0.540	0.590
DBP	97.0	18.2	89.1	16.1	1.276	0.203
Fasting Cholesterol	181.9	67.8	188.4	56.5	0.297	0.767
HDL	42.0	9.4	47.5	16.4	0.881	0.379
LDL	123.5	41.4	120.6	47.7	0.148	0.883
TGL	140.0	126.2	100.8	48.8	1.907	0.058

SERUM HOMOCYSTEINE	11.6	3.0	17.4	14.1	0.568	0.573
Plaque thickness	0.24	0.19	0.26	0.12	0.350	0.727
PTEF-V 1	0.08	0.07	0.09	0.09	0.123	0.903
PR interval	0.21	0.10	0.66	0.79	0.981	0.328
LV dimension systolic	31.0	5.4	29.1	6.3	0.596	0.552
LV dimension diastolic	45.3	7.0	45.1	6.9	0.043	0.966
EF	64.2	8.2	63.6	9.0	0.164	0.870
Discharge NIHSS	4.4	4.2	5.2	5.5	0.376	0.707
NIHSS	3.0	2.7	2.6	3.8	0.286	0.775
HbA1C	6.9	1.5	7.4	4.3	0.182	0.856
F cholesterol	145.8	25.9	141.6	38.0	0.248	0.805
LDL	54.0	33.7	82.5	32.6	1.720	0.088
HDL	48.5	29.0	47.5	22.4	0.065	0.948
TGL	241.0	.	102.7	51.9	2.644	0.010

7 patients had contralateral or vertebrobasilar events. Any contralateral or vertebrobasilar events were more common in those with smoking, alcohol intake and raised triglyceride levels (p values 0.045, 0.025, 0.010 respectively.). the history of prestroke statin and antiplatelet use was more in people with recurrent use. However the risk of stroke is a confounding factor in this.

TABLE 5.14: CARDIAC EVENTS AT 1 YEAR FOLLOWUP

		Cardiac events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
GENDER	Male	4	80	125	70.2	129	70.5			
	Female	1	20	53	29.8	54	29.5	0.2	1	0.636
Hemisphere	VB	3	60	43	24.2	46	25.1			
involved	Right	0	0	60	33.7	60	32.8			
	Left	2	40	72	40.4	74	40.4			
	Bilateral	0	0	3	1.7	3	1.6	4.3	3	0.235
DM	Yes	2	40	90	50.6	92	50.3			
	No	3	60	88	49.4	91	49.7	0.2	1	0.641
HTN	Yes	3	60	111	62.4	114	62.3			

	No	2	40	67	37.6	69	37.7	0.0	1	0.914
DYSLIPIDEMIA	Yes	1	20	55	30.9	56	30.6			
	No	4	80	123	69.1	127	69.4	0.3	1	0.602
SMOKING	Yes	1	20	45	25.3	46	25.1			
	No	4	80	133	74.7	137	74.9	0.1	1	0.788
Alcohol	Yes	1	20	40	22.5	41	22.4			
	No	4	80	138	77.5	142	77.6	0.0	1	0.896
CAD	Yes	2	40	29	16.3	31	16.9			
	No	3	60	149	83.7	152	83.1	1.9	1	0.163
PCI/CABG	Yes	1	20	23	12.9	24	13.1			
	No	4	80	155	87.1	159	86.9	0.2	1	0.644
POVD	Yes	0	0	7	3.9	7	3.8			
	No	5	100	171	96.1	176	96.2	0.2	1	0.651
	Left	0	0	13	7.3	13	7.1			
OLD STROKE :	Right	0	0	15	8.4	15	8.2			
HEMISPHERE	None	5	100	146	82	151	82.5			
	VB	0	0	4	2.2	4	2.2	1.1	3	0.780
Prestroke statin	Yes	2	40	51	28.7	53	29			
use	No	3	60	127	71.3	130	71	0.3	1	0.581
	Aspirin	1	20	33	18.5	34	18.6			
Prestroke antiplatelet use	None	3	60	139	78.1	142	77.6			
	Both	1	20	6	3.4	7	3.8	3.7	2	0.155

		Cardiac events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Imaging modality	A	1	20	53	29.8	54	29.5			
	B	0	0	52	29.2	52	28.4			
	C	4	80	73	41	77	42.1	3.4	2	0.185
Infarct	Single	4	80	135	75.8	139	76			
	Multiple	1	20	38	21.3	39	21.3			
	Normla	0	0	5	2.8	5	2.7	0.2	2	0.925

OCCLUSION	No	2	40	116	65.2	118	64.5			
	Yes	3	60	62	34.8	65	35.5	1.3	1	0.246
Superficial watershed	Yes	2	40	53	29.8	55	30.1			
	No	3	60	125	70.2	128	69.9	0.2	1	0.623
Internal borderzone	Yes	0	0	39	21.9	39	21.3			
	No	5	100	139	78.1	144	78.7	1.4	1	0.238
Multiple embolic	Yes	2	40	58	32.6	60	32.8			
	No	3	60	120	67.4	123	67.2	0.1	1	0.728
EC	<30	5	100	172	96.6	177	96.7			
	30-40	0	0	6	3.4	6	3.3	0.2	1	0.676
IC	<30	5	100	170	95.5	175	95.6			
	30-40	0	0	8	4.5	8	4.4	0.2	1	0.628
chronic infarcts	Territorial	0	0	35	19.7	35	19.1			
	Lacunar	1	20	53	29.8	54	29.5			
	Both	1	20	25	14	26	14.2			
	None	3	60	65	36.5	68	37.2	2.0	3	0.576
WMHI	0	2	50	60	35.1	62	35.4			
	1	2	50	72	42.1	74	42.3			
	2	0	0	32	18.7	32	18.3			
	3	0	0	7	4.1	7	4	1.2	3	0.749
Presence of atrial ectopics	Yes	0	0	9	6.7	9	6.5			
	No	5	100	125	93.3	130	93.5	0.4	1	0.549

		Cardiac events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
LVH –voltage criteria	Yes	1	20	10	7.5	11	7.9			
	No	4	80	124	92.5	128	92.1	1.0	1	0.308

24 hour Holter-done	Normal	2	50	133	85.3	135	84.4			
	Atrial ectopics	0	0	2	1.3	2	1.3			
	SVT	1	25	12	7.7	13	8.1			
	VENTRICULAR ETCOPIC	1	25	9	5.8	10	6.3	4.4	3	0.224
TTE-LA diameter	Normal	4	100	91	94.8	95	95			
	Abnormal	0	0	5	5.2	5	5	0.2	1	0.640
LV SYSTOLIC DIMENSION	<30	2	40	78	56.1	80	55.6			
	30-60	3	60	61	43.9	64	44.4	0.5	1	0.476
LV DIASTOLIC DIMENSION GRADE	Normal	4	80	164	98.8	168	98.2			
	Mild	1	20	1	0.6	2	1.2			
	Moderate	0	0	1	0.6	1	0.6	15.8	2	<0.001
IV THROMMOLYSED	Yes	0	0	32	18	32	17.5			
	No	5	100	146	82	151	82.5	1.1	1	0.297
MT	Yes	0	0	17	9.6	17	9.3			
	No	5	100	161	90.4	166	90.7	0.5	1	0.468

		Cardiac events				Total		χ^2	df	p
		Yes		No						
		N	%	N	%	N	%			
Type of recurrent events	Stroke	0	0	3	1.7	3	1.6			
	TIA	0	0	14	7.9	14	7.7			
	Nil	5	100	147	83.1	152	83.5			
	Worsening	0	0	13	7.3	13	7.1	1.0	3	0.798
Discharge MRS	0	0	0	26	14.6	26	14.2			
	1	1	20	16	9	17	9.3			
	2	1	20	35	19.7	36	19.7			

	3	2	40	35	19.7	37	20.2			
	4	1	20	64	36	65	35.5			
	5	0	0	2	1.1	2	1.1	2.8	5	0.736
Discharge antiplatelets	Aspirin	1	20	52	29.5	53	29.3			
	Clopidogrel	0	0	9	5.1	9	5			
	Both	4	80	114	64.8	118	65.2			
	Anticoagulation	0	0	1	0.6	1	0.6	0.6	3	0.895
MRS	0	1	25	65	37.1	66	36.9			
	1	1	25	20	11.4	21	11.7			
	2	1	25	35	20	36	20.1			
	3	1	25	30	17.1	31	17.3			
	4	0	0	24	13.7	24	13.4			
	5	0	0	1	0.6	1	0.6	1.5	5	0.910

	Cardiac events					
	Yes (n=5)		No (n=178)		t	p
	mean	sd	mean	sd		
AGE	63.4	9.6	57.9	12.1	1.013	0.312
Admission NIHSS	4.0	2.1	7.8	6.8	1.258	0.210
Time between first symptom and admission	25.1	24.3	82.1	262.4	0.484	0.629
Admission blood sugar	146.8	40.7	166.3	74.7	0.522	0.603
HBA1C	7.5	2.8	7.3	2.1	0.123	0.902
SBP	155.0	29.4	157.4	27.7	0.188	0.851
DBP	81.8	15.1	89.6	16.2	1.060	0.291
Fasting Cholesterol	159.2	60.6	188.9	56.6	1.157	0.249
HDL	50.0	7.7	47.2	16.4	0.375	0.708
LDL	100.3	45.6	121.2	47.5	0.873	0.384
TGL	89.0	27.2	102.7	54.2	0.502	0.617
SERUM HOMOCYSTEINE	22.6	.	17.0	13.9	0.402	0.690
Plaque thickness	0.24	0.05	0.26	0.12	0.341	0.733
PTEF-V 1	0.08	0.05	0.09	0.09	0.053	0.958

PR interval	0.26	0.05	0.67	0.80	1.131	0.260
LV dimension systolic	32.8	14.1	29.0	5.9	1.325	0.187
LV dimension diastolic	49.6	11.7	44.9	6.6	1.500	0.136
EF	65.4	14.8	63.5	8.8	0.460	0.646
Discharge NIHSS	1.8	0.4	5.3	5.5	1.411	0.160
NIHSS	0.5	1.0	2.7	3.8	1.118	0.265
HbA1C	7.3	1.9	7.4	4.3	0.025	0.980
F cholesterol	120.0	16.2	142.3	37.9	1.170	0.244
LDL	62.0	6.6	82.1	33.1	1.046	0.298
HDL	75.5	33.2	46.8	21.9	1.820	0.073
TGL	68.5	13.4	105.7	54.5	0.957	0.342

Among 5 with cardiac events, LV diastolic dimesion was normal in 4 and 1 person had mild dysfunction. Among them, 2 had normal holter, and 1 had SVT and 1 had ventricular ectopic. LVH was present in 1 and normal cardiac chambers in other 4.

All the parameters were compared with those who had any history of recurrent strokes (previous TIA/Stroke, ipsilateral, contralateral or vertebrobasilar strokes/TIA. It was found that blood sugar at admission, fasting total cholestrol were statistically significant with p values 0.021, 0.002, 0.003 respectively. Males were found to have more recurrence. Diabetes, Coronary artery disease, superficial watershed infarcts, territorial infarcts were also associated with recurrence of strokes.

TABLE 5.15: SINGLE VERSUS RECURRENT STROKES : A

PARAMETER	SINGLE ESUS	MORE THAN ONE EVENT	P VALUE
AGE	57.3	60.17	0.11
TIME BETWEEN 1ST SYMPTOM AND ADMISSION	100.35	105.52	0.901
BLOOD SUGAR ADMISSION	156.01	180.01	0.021

HBA1C DISCHARGE	7.413	7.625	0.49
HBA1C FOLLOWUP	7.477	7.07	0.644
SBP	155.34	157.87	0.526
DBP	87.82	90.53	0.23
FASTING CHOLESTROL	194.34	167.68	0.002
FASTING CHOLESTROL FOLLOWUP	139.41	147.13	0.238
HDL DISCHARGE	46.35	47.29	0.689
HDL FOLLOWUP	47.93	47.14	0.884
LDL DISCHARGE	126.68	104.78	0.003
LDL FOLLOWUP	81.17	82.32	0.853
TGL DISCHARGE	109.13	99.74	0.245
TGL FOLLOWUP	97.26	123.3	0.064
HOMOCYSTEINE	17.42	18.43	0.841
PLAQUE THICKNESS	0.264	0.2595	0.834
PTET V1	0.0885	0.087	0.731
PR INTERVAL	0.607	0.756	0.265
LV SYSTOLIC DIMENSION	29.23	29.15	0.937
LV DIASTOLIC DIMENSION	45.22	44.79	0.709
EF	63.51	62.33	0.364
NIHSS ADMISSION	8.32	7.75	0.554
NIHSS DISCHARGE	4.95	7.1	0.011
NIHSS FOLLOWUP	1.99	3.93	0.001

TABLE 5.16: SINGLE VERSUS RECURRENT STROKES: B

PARAMETER		SINGLE	RECURRENT	P VALUE
GENDER	MALE	63.5	74.7	0.09
	FEMALE	36.5	25.3	
HEMISPHERE	VB	27	13.3	
	RIGHT	30.8	38.7	
	LEFT	40.3	45.3	
	B/L	1.9	2.7	

DM		46.5	65.3	0.007
HTN		59.7	73.3	0.043
DYSLIPIDEMIA		29.6	26.7	0.648
SMOKING		22.6	29.3	0.269
ALCOHOL		21.4	24	0.653
CAD		11.3	29.3	0.001
PCI/CABG		6.9	24	0
POVD		0.6	14.7	0
OLD STROKE	LEFT	0	25.3	
	RIGHT	0	28	
	VB	0	6.7	
PRESTROKE STATIN		18.2	49.3	0
Prestroke_antiplatelet_use	1. ASPRIRIN	8.2	38.7	
	2. NONE	89.3	54.7	
	3. CLOPILET	6	0	
	4. BOTH	1.9	6.7	
Imaging	CT	28.9	29.3	0.97
	MRI	29.6	28	
	BOTH	41.5	42.7	
INFARCT SINGLE/MULTIPLE	SINGLE	84.3	66.7	
	MULTIPLE	15.7	33.3	
OCCLUSION		37.7	34.7	0.65
Superficial_watershed		23.9	41.3	0.006
Internal_borderzone		22	24	0.735
MUTIPLE EMBOLIC		17	20	0.574
EC	<30	96.9	96	0.713
	30-50	3.1	4	
IC	<30	96.9	96	0.713
	30-50	3.1	4	
CHRONIC INFARCTS	TERRITORIAL	13.8	26.7	0.045
	LACUNAR	28.3	26.7	

	BOTH	15.1	18.7	
	NONE	42.8	28	
WMHI	0	34.5	26.4	0.294
	1	40.7	38.9	
	2	22.1	27.8	
	3	2.8	6.9	
ATRIAL ECTOPIC ECG		6.1	9.8	0.516
LVH VOLTAGE		7.8	13.7	0.26
24 HOLTER	NORMAL	8708	77.4	
	ATRIAL ECTOPIC	0	3.2	
	SVT	6.9	11.3	
	VENTRICULAR ECTOPIC	5.3	8.1	
TTE LA	MILD LA ENLARGE	5.1	2.6	0.526
LV SYSTOLIC	<30	54.7	59.2	0.596
	30-60	45.3	40.8	
LV_DIASTOLIC_DIMENSION	0	98.6	98.6	
	1	1.4	0	
	2	0	1.4	
IVTHROMBOLYSIS		15.7	17.6	0.723
MT		8.8	8.1	0.86
MRS DISCHARGE	0	14.6	11.3	0.031
	1	10.1	4.2	
	2	19.6	15.5	
	3	22.8	12.7	
	4	29.7	52.1	
	5	3.2	4.2	
MRS FOLLOWUP	0	42.4	24.6	0.035
	1	13.6	7	

	2	18.4	22.8	
	3	15.2	22.8	
	4	10.4	21.1	
	5	0	1.8	

TABLE 5.17: BIVARIATE ANALYSIS

PARAMETER	**AMONG THOSE WITH > 1 EVENT**	**P VALUE**
GENDER		0.090
MALE	63.5%	
FEMALE	36.5%	
DIABETES MELLITUS	65.4%	0.007
NON DIABETIC		
HYPERTENSION	73.3%	0.043
NON HYPERTENSIVE		
CAD	29.3%	0.001
NON CAD		
MUTIPLE EMBOLIC PATTERN	65.3%	0.006
WITHOUT MULTIPLE EMBOLIC PATTERN	34.7%	
SUPERFICIAL WATERSHED INFARCT	41.3%	0.006
NON SUPERFICIAL WATERSHED INFARCT	58.7%	
MRS ON FOLLOWUP <=2	54.4%	0.007
MRS ON FOLLOWUP >=3	45.6%	

TABLE 5.18 : MULTIVARIATE ANALYSIS

	P value	Odds Ratio		95% C.I.for Odds Ratio
Gender	0.528	0.780	Lower	Upper
DM	0.764	0.891	0.420	1.891
HTN	0.628	0.831	0.394	1.755
CAD	0.012	0.296	0.115	0.762
Infarct_pattern	0.014	2.710	1.227	5.988
Superficial_watershed	0.076	0.515	0.247	1.072
MRS Followup	0.138	2.091	0.788	5.545
NIHSS at Discharge	0.486	1.029	0.949	1.116

Multivariate analysis showed statistical significance between recurrence of stroke and history of coronary artery disease and multiple embolic pattern of infarct.

Discussion

6. DISCUSSION

PREVALENCE

We had 234 cases of ESUS/cryptogenic strokes satisfying criteria of ESUS, out of total 2087 cases of stroke admitted during the study period, which accounts for 11.21% of cases. Percentage of ESUS among ischemic stroke varies between 7% to 42% in the various studies conducted(7).

CLINICAL FEATURES

Our study had a total of 234 patients and mean age was 58.2 ± 12.8. There were total 8 studies about the features of ESUS (7)Study by Ntaios et al was the highest with 1095 patients (3). But in NAVIGATE ESUS study, 7213 patients were included(72). Mean age of the patients in the previous studies were varies from 44-73 years (7).

In the previous studies, the prevalence of risk factors- hypertension ranged from 25-74% (7) and Diabetes was 7 -32% (7) Our cohort had a high prevalence of vascular risk factors and coronary disease also. This finding has been noticed in most of the studies on risk factor profile and etiology of AIS from India. As per the study from Calcutta by Das et al, hypertension rate was higher in the community including unrecognised hypertension (86). In Trivandrum stroke registry study by Sapna et al, it was found that around 90% had risk factors (87). Among our subjects, hypertension and diabetes were the predominant risk factors and 88% had atleast 1 risk factor.

17.5 % were smokers and 7.3% were reformed smokers in our study. This is similar to the study conducted by Sapna et al which stated that 26.8% had history of smoking (87). 22.2 % were alcoholic in our cohort, which was higher than the study conducted by Scavasine et al (88).

In our study, predominantly was hemispheric strokes (left more than right) while 2.1 were bihemispheric strokes. This is comparison to the study conducted by Veltkamp et al, where 44% of ESUS were left hemisphere, 33% right hemisphere , and 8% vertebrobasilar stroke. But they had 15% multiple artery territory strokes while in our study it was lesser (89).

In the systematic review by Hart G et al, it was found that he recurrence of stroke in ESUS cases are around 4-4.5% (7). RE-SPECT ESUS trial reported that recurrent strokes was having association with past cerebrovascular events.(9) In our study, we found 46 patients had past history of stroke/TIA. Among those with past h/o stroke, it was predominantly hemispheric strokes (19 had left hemispheric, 21 had right) than vertebrobasilar and multiple territorial. .

In our cohort, we found that 28.6% had dyslipidemia and mean LDL was 119.7 ± 49.5. In RESPECT ESUS study also the role of dyslipidemia was proven (9). The increased rate in our cohort can be due to early onset of metabolic syndrome or due to the genetic predisposition in Asian population. In the study conducted by Pandit K et al, it was found that in south Asians the risk of metabolic syndrome and risk factors were found to be more (90).

In our study, Prestroke antiplatelet use was in 21.8% cases, among which predominantly were on aspirin. Jung JM et al, it was found that strokes caused by Small vessel disease was more in those having prestroke antiplatelet use than large artery atherosclerosis (91). Our patients were not on anticoagulation at the time of presentation.

In ESUS cases, usually strokes are milder and Median NIHSS score was 5 as per study conducted by Ntaios et al, while the one conducted by Arauz et al was 7. (3, 72, 89). The mean NIHSS was 7 in the brazilean cohort of ESUS(92). This was comparable with the mean NIHSS of our study which was 8.1± 6.9 at admission and 5.6 ± 5.9 at the time of discharge.

NEUROIMAGING PARAMETERS

In NAVIGATE ESUS trial, 93% had recent or chronic brain infarcts of which multiple infarcts seen in 70% and multiple arterial territories in 62 and 68% had silent infarcts. Also it was predominately cortical infarcts than subcortical. Among those with multiple large and/or cortical infarcts, 57% had infarcts of ESUS(72). In our study, 61.9% had chronic infarcts. Out of which, 17.9% territorial infarcts, 27.8 % lacunar infarcts,16.2% had both territorial and lacunar infarcts. In the FIND AF trial, multiple embolic pattern was seen in ESUS cases of 42.3% and 30.8% had multiple arterial territory (93). In our study, 76.5% had single infarct, while 2.4% had multiple infarcts and 2.1 % had MRI normal. Also infarct patterns, 34.6% had multiple embolic pattern, 29.5 % had superficial watershed infarct, 22.6 internal border zone infarct. The difference in the infarct pattern from the previous studies could be due to difference in demographic features and risk factors.

In the study conducted by Siegler et al, it was found that substenotic plaques were more in people <65 years in those with ESUS (48% in <65 year) (94). Kamtchum-Tatuene studied the importance of high risk plaque characteristics in ESUS (95). In our study, among 3.4% had 30-50% stenosis. However, the plaque characteristics were not studied in our study.

In the study conducted by Guo et al stated, that most of cardioembolic cases had mild to moderate degree of white matter ischemic changes. Also it was found that lesser the white matter ischemic changes, better the prognosis (96). In our study we found that there is 40.8 % had Fazekas grade 1, 24% had grade 2 and 4.1 % had grade 3 white matter changes while 31.8% didn't had any white matter ischemic changes. However in our study, there was no statistical significance for white matter changes regarding the recurrence of events.

CARDIAC PARAMETERS

The role of atrial cardiopathy in ESUS were studied in few trials (97, 98, 99). Atrial cardiopathy is defined as NT-proBNP > 250 pg/mL, or P wave terminal force in lead V1 PTFV1 > 5,000 μV·ms, or severe LAE) , and atrial cardiomyopathy is defined as LA > 38 mm for women and >40mm for men or if supraventricular extrasystoles was present in nearly 45% ESUS patients. In our study, mean PTFV1 was 0.09 ± 0.09 and was raised in 39% of the cohort. . PR interval was raised in 17.1 % cases. There was atrial arrhythmias in 15.5% cases including atrial and supraventricular ectopics. From the Transthoracic Echo, it was found that 4.2% had mild left atrial enlargement. LV systolic dimension was 30-60 in 44%, while 56% had <30. LV diastolic dimension was normal for 98.6% and mild increase in 0.9 and moderate increase in 0.5%. A total of 46.5% cases had some of the markers of atrial cardiopathy. This was similar to the prevalence found in other studies. This was similar to the previous trial in which it was found that about 6% had a left atrial dimension ≥4.7 cm and no ipsilateral plaque, 24% had ipsilateral plaque and no left atrial enlargement, and 2.4% had both. Patients with left atrial enlargement were more likely to be male, white, enrolled in Europe, and have hypertension. 63% cryptogenic stroke patients have an increased prevalence of markers of atrial cardiomyopathy (97). In the study conducted by Lotlikar et al, recurrence of large vessel atherosclerotic disease and cryptogenic strokes were studied and it was found that atrial cardiopathy is having significant role in prediction of recurrence (100).

OUTCOME AND RECURRENCE

In the study conducted by Arauz A et al, stroke recurrence was similar between ESUS and CS patients (5.4% vs. 9.8% respectively, p = 0.12). Death occurred in 30 CS cases (12.8%). Stroke recurrence was similar between ESUS and CS patients (5.4% vs. 9.8% respectively, p = 0.12). Death occurred in 30 CS cases (12.8%) (101). In our cohort,11.3% had worsening during hospital stay. On followup of 1 year, 8.2% cases had recurrence of stroke on ipsilateral side. 3.8% had contralateral or vetebrobasilar strokes. 2.7% had cardiac events. In the study

conducted by Ntaios et al, 6.8% was recurrence rate, 9.0% risk of other vascular events. (3, 72) Recurrence rate was higher in our cohort which might be due to the higher incidence of risk factors and poor control of the same.

Zivozonic et al opined that IV thrombolysis has better outcome in ESUS group than cryptogenic strokes. Out of 394 cases thrombolysed, 62 were satisfying criteria of ESUS. After 24h, neurological improvement was similar in both groups (59.7% in ESUS group versus 51.3% in Cryptogenic stroke group, *p*= 034). But favorable outcome (mRS 0–2) at discharge and at 3 months was more common in ESUS group (102). In our study 16.3% (38) patients underwent IV thrombolysis and 8.6% (20) underwent mechanical thrombectomy as well,which is similar to the overall thrombolysed patients among hospital admissions for AIS.

Outcome of cohort on followup based on MRS was studied. In our study MRS <2 was seen in 40.1% at the time of discharge. 68.4% had MRS <2 on 1 year followup. This was comparable with the outcome of the cases as per study conducted Arauz A et al**,** found MRS of <2 in 72.5% on followup (101).

Among discharge medications, 34.9 % was on single antiplatelet and 64.6% was on dual antiplatelets and 0.4% was on anticoagulation. The discharge medications used were in parallel with the other trials on ESUS and as per AHA guidelines. The role of oral anticoagulants dabigatran, rivaroxaban and apixaban were studied in RE-SPECT ESUS, NAVIGATE ESUS, ATTICUS trials (8,72, 103). But significant benefit could not be found over antiplatelets in them.

Cardiac and neuroimaging parameters were compared among those who had stroke in the past and those who having stroke for first time. 0.92 was the mean PR interval for those who had past h/o stroke. There was statistical significance for the same with p value 0.042. Hypertension was more in those who are having stroke for first time (p value 0.004). Dyslipidemia, CAD, h/o CABG/PCI and PVOD were more common in people who had previous h/o stroke /TIA.

Presence of atrial ectopics were more in patients with previous stroke/TIA (16.7%) than those presenting as first episode of stroke (5.1%) with p value of 0.027.

In people with in hospital recurrent events, terminal branch occlusion was more (n=15) than those who didn't (n=11) (p value=0.019). 22 patients (91%) in those who had in hospital recurrent events had discharge MRS of 3-5 while 2 had MRS <2. 56.1% of those who didn't had recurrent events had MRS 3-5 while 43.9% had discharge MRS of <2.

In the RE-SPECT ESUS trial, it was found that independent predictors for recurrent stroke were previous stroke/ TIA before the index event (HR, 2.2 [95% CI, 1.83–2.82]), creatinine clearance <50 mL/min (HR, 1.69 [95% CI, 1.23–2.32]), male sex (HR, 1.60 [95% CI, 1.27–2.02]), and CHA2DS2-VASc ≥4 (HR, 1.55 [95% CI, 1.15–2.08] and HR, 1.66 [95% CI, 1.21–2.26 for scores of 4 and ≥5, respectively) . (8).

NAVIGATE ESUS trial showed factors associated with recurrent ischemic stroke by bivariate analysis. They were older age (68.4 in recurrence versus 66.9 years). Other features significantly associated with recurrent ischemic stroke were current tobacco use, stroke or TIA prior to the qualifying stroke, diabetes mellitus, Asian race, multiple acute infarcts on neuroimaging, time from qualifying stroke to randomization, and aspirin use prior to the qualifying stroke (72).

Ntaois et al, stated that age, is a strong predictor of stroke recurrence and death in ESUS. However sex is not a predictor. The risk is 3 and 8 fold higher in patients >80 years compared with those > 60 years of age, respectively. Ischemic stroke/TIA recurrences and deaths per 100 patient-years were 2.46 and 1.01 in patients <60 years old, 5.76 and 5.23 in patients 60 to 80 years old, 7.88 and 11.58 in those >80 years old, 3.53 and 3.48 in women, and 4.49 and 3.98 in men, respectively. (3, 72)

In our study, on followup, it was found that 15 patients had recurrent events on ipsilateral side. of which 11 were males and 4 were females. Smoking was associated with recurrence of events on ipsilateral vascular territory with statistical significance (p value of 0.045). PVOD was also found to have statistically significant with a p value of 0.045 . Pattern of infarcts with superficial watershed infarct was having statistical significance in patients with ipsilateral recurrent events. (p value 0.001). Also those with multiple embolic pattern was also having statistical significance. (p value 0.019).

7 patients had contralateral or vertebrobasilar events. Any contralateral or vertebrobasilar events were more common in those with smoking, alcohol intake and raised triglyceride levels (p values 0.045, 0.025, 0.010 respectively.).The history of prestroke statin and antiplatelet use was more in people with recurrent use. However it might be due to the confounding factors.

Multivariate analysis showed statistical significance between recurrence of stroke and history of coronary artery disease and multiple embolic pattern of infarct. This was in comparison with the multivariate Cox proportional hazard analyses conducted by Nezu T et al, which showed that multiple infarcts were independently associated with recurrent stroke and all-cause mortality (hazard ratio, 3.79; 95% confidence interval, 2.24–6.37; P<0 (104). In the study

conducted by Hou Y et al, comparing young and older ESUS cases, the role of multiple cardiac diseases was also found to be related to recurrence of stroke in older patients, while in younger it was only unclosed PFOs (105).

Conclusion

7. CONCLUSION

- Prevalence of ESUS was 11.21%in our cohort of acute ischemic stroke.
- Our patients had a mean age was 58.2 ± 12.8 and a high prevalence of vascular risk factors.
- While any of the atrial cardiopathy markers were present in 46.5% of ESUS patients, atherosclerotic plaques causing 30-50% stenosis cases were seen in 3.8%
- Our cohort had an annual recurrence risk of 9.4%.
- There was significant correlation between risk factors-total cholesterol, LDL, Diabetes Mellitus, Hypertension, Coronary artery disease, Peripheral Vascular Occlusive Disease and functional status at discharge with recurrence of events in patients with ESUS
- Imaging pattern of superficial watershed infarcts had a significant association with recurrence risk at 1 year.
- Multivariate analysis showed statistical significance between recurrence of stroke and history of coronary artery disease and multiple embolic pattern of infarct.
- At end of 1 year, on followup, most patients had good outcome with 36.8% had MRS 0 while 68.03% had MRS less than or equal to 2.
- High prevalence of vascular risk factors and its association with recurrence risk reiterates the importance of risk factor in the population of ESUS as well.

Bibliography

8. REFERENCES

1. World health report 2002
2. Perera et al, Embolic strokes of undetermined source : Prevalence and patient features in the ESUS Global registry, International Journal of Stroke, 2016; 11(5)
3. Ntaios G, Papavasileiou V, Milionis H, Makaritsis K, Manios E, Spengos K, et al. Embolic strokes of undetermined source in the Athens stroke registry: a descriptive analysis. Stroke. 2015;46:176–181
4. Mahagne MH, Lachaud S, Suissa L. Letter by Mahagne et al regarding article, "Embolic strokes of undetermined source in the athens stroke registry: a descriptive analysis". Stroke. 2015;46:e69
5. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al; Oxford Vascular Study. Incidence, outcome, risk factors, and longterm prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. Lancet Neurol. 2015;14:903–913.
6. Putaala J, Nieminen T, Haapaniemi E, Meretoja A, Rantanen K, Heikkinen N, et al. Undetermined stroke with an embolic pattern–a common phenotype with high early recurrence risk. Ann Med. 2015; 47:406– 413.
7. Hart RG, Catanese L, Perera KS, et al. Embolic stroke of undetermined source: systematic review and clinical update. Stroke 2017;48:867-872.
8. Hart RG, Sharma M, Mundl H, et al. Rivaroxaban for stroke prevention after embolic stroke of undetermined source. N Engl J Med 2018;378:2191-2201.
9. Diener H-C, Sacco RL, Easton JD, et al. For the RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906-1917
10. Banerjee TK, Das SK. Fifty years of stroke researches in India. *Ann Indian Acad Neurol*. 2016;19(1):1-8

11. Subhash K. "Stroke in India: Are we Different from the World". Pak J Neurol Sci 2007; 2(3):158-164

12. Hart RG, Diener HC, Coutts SB, Easton JD, Granger CB, O'Donnell MJ, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* (2014) **13**(4):429–38.

13. Eckerle B, Massaro A. Lumpers or splitters: evaluation and management of embolic stroke of undetermined source. Neurology. 2016;87:972–3.

14. Dennis M. Embolic stroke of undetermined source: a therapeutic target? Lancet Neurol. 2014;13:344–6.

15. Katsanos AH, Bhole R, Frogoudaki A, Giannopoulos S, Goyal N, Vrettou AR, et al. The value of transesophageal echocardiography for embolic strokes of undetermined source. Neurology. 2016;87:988–95.

16. Harold P. Adams Jr, Biller J. History of the TOAST Scale. Stroke. 2015; 46:e114-e117.

17. Adams Jr HP, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35e41.

18. Hart RG, Catanese L, Kanjana S, Ntaios G, Connolly SJ. Embolic Stroke of Undetermined Source. A Systematic Review and Clinical Update. Stroke. 2017;48:867-872

19. Li L, Yiin GS, Geraghty OC, Schulz UG, Kuker W, Mehta Z, et al; Oxford Vascular Study. Incidence, outcome, risk factors, and longterm prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol*. 2015;14:903–913.

20. Putaala J, Nieminen T, Haapaniemi E, Meretoja A, Rantanen K, Heikkinen N, et al. Undetermined stroke with an embolic pattern–a common phenotype with high early recurrence risk. *Ann Med*. 2015;47:406– 413.

21. Gladstone DJ, Dorian P, Spring M, Panzov V, Mamdani M, Healey JS, et al. Atrial premature beats predict atrial fibrillation in cryptogenic stroke: results from the embrace trial. *Stroke* (2015) **46**:936–41.

22. Kamel H, Elkind MS, Bhave PD, Navi BB, Okin PM, Iadecola C, et al. Paroxysmal supraventricular tachycardia and the risk of ischemic stroke. *Stroke* (2013) **44**:1550–4.

23. Yaghi S, Moon YP, Mora-McLaughlin C, Willey JZ, Cheung K, Di Tullio MR, et al. Left atrial enlargement and stroke recurrence: the Northern Manhattan Stroke Study. *Stroke* (2015) **46**:1488–93.

24. Kamel H, O'Neal WT, Okin PM, Loehr LR, Alonso A, Soliman EZ. Electrocardiographic left atrial abnormality and stroke subtype in atheroscle-rosis risk in communities study. *Ann Neurol* (2015) **78**(5):670–8.

25. Folsom AR, Nambi V, Bell EJ, Oluleye OW, Gottesman RF, Lutsey PL, et al. Troponin t, n-terminal pro-b-type natriuretic peptide, and incidence of stroke: the atherosclerosis risk in communities study. *Stroke* (2013) **44**:961–7.

26. Cushman M, Judd SE, Howard VJ, Kissela B, Gutierrez OM, Jenny NS, et al. N-terminal pro-b-type natriuretic peptide and stroke risk: the reasons for geographic and racial differences in stroke cohort. *Stroke* (2014) **45**:1646–50

27. Yaghi S, Boehme AK, Hazan R, Hod EA, Canaan A, Andrews HF, et al. Atrial cardiopathy and cryptogenic stroke: a cross-sectional pilot study. *J Stroke Cerebrovasc Dis* (2015) **25**(1):110–4.

28. Alsheikh-Ali AA, Thaler DE, Kent DM. Patent foramen ovale in cryptogenic stroke incidental or pathogenic? *Stroke* (2009) **40**(7):2349–55.

29. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Eng J Med* (2007) **357**(22):2262–8.

30. Wessler BS, Thaler DE, Ruthazer R, Weimar C, Di Tullio MR, Elkind MS, et al. Transesophageal echocardiography in cryptogenic stroke and patent foramen ovale analysis of putative high-risk features from the risk of par-adoxical embolism database. *Circ Cardiovasc Imaging* (2014) **7**(1):125–31.

31. Overell JR, Bone I, Lees KR. Interatrial septal abnormalities and stroke: a meta-analysis of case-control studies. *Neurology* (2000) **55**(8):1172–9.

32. Patti G, Pelliccia F, Gaudio C, Greco C. Meta-analysis of net long-term benefit of different therapeutic strategies in patients with cryptogenic stroke and patent foramen ovale. *Am J Cardiol* (2015) **115**(6):837–43.

33. Cheitlin MD, Armstrong WF, Aurigemma GP, Beller GA, Bierman FZ, Davis JL, et al. *ACC/AHA/ASE 2003 Guideline for the Clinical Application of Echocardiography* (2006).

34. Baher A, Mowla A, Kodali S, Polsani VR, Nabi F, Nagueh SF, et al. Cardiac MRI improves identification of etiology of acute ischemic stroke. *Cerebrovasc Dis* (2014) **37**(4):277–84.

35. Viedma-Guiard E, Guidoux C, Amarenco P, Meseguer E. Aortic Sources of Embolism. Front Neurol. 2021 Jan 15;11:606663.

36. Ryoo S, Chung JW, Lee J, Kim SJ, Lee J, Kim GM, et al. An Approach to Working Up Cases of Embolic Stroke of Undetermined Source. J Am Heart Assoc. 2016;5:e002975

37. Arun K, Nambiar PN, Kannath SK, Sreedharan SE, Sukumaran S, Sarma S, Sylaja PN. Prevalence of Aortic Plaques in Cryptogenic Ischemic Stroke: Correlation to Vascular Risk Factors and Future Events. Neurol India. 2022 Jan-Feb;70(1):182-187.

38. Kamtchum-Tatuene J, Nomani AZ, Falcione S, Munsterman D, Sykes G, Joy T, Spronk E, Vargas MI, Jickling GC. Non-stenotic Carotid Plaques in Embolic Stroke of Unknown Source. Front Neurol. 2021 Sep 22;12:719329.

39. Siegler JE, Thon JM, Woo JH, Do D, Messé SR, Cucchiara B. Prevalence of Nonstenotic Carotid Plaque in Stroke Due to Atrial Fibrillation Compared to Embolic Stroke of Undetermined Source. J Stroke Cerebrovasc Dis. 2019 Oct;28(10):104289

40. Singh N, Marko M, Ospel JM, Goyal M, Almekhlafi M. The Risk of Stroke and TIA in Nonstenotic Carotid Plaques: A Systematic Review and Meta-Analysis. *AJNR Am J Neuroradiol*. 2020;41(8):1453-1459.

41. Saraf U, Prabhakaran S, Arun K, et al. Comparison of Risk Factors, Treatment, and Outcome in Patients with Symptomatic Intracranial Atherosclerotic Disease in India and the United States. *Ann Indian Acad Neurol*. 2020;23(3):265-269.

42. A. Jaffre, B. Guidolin, J.B. Ruidavets, N. Nasr, V. Larrue, Non-obstructive carotid atherosclerosis and patient foramen ovale in young adults with cryptogenic stroke, Eur. J. Neurol. 24 (2017) 663–666.

43. K.S. Perera, T. Vanassche, J. Bosch, et al., Embolic strokes of undetermined source: prevalence and patients features in the ESUS global registry, Int. J. Stroke 11 (2016) 526–533.

44. Vedre A, Pathak DR, Crimp M, Lum C, Koochesfahani M, Abela GS. Physical factors that trigger cholesterol crystallization leading to plaque rupture. Atherosclerosis. 2009; 203(1):89–96.

45. Freilinger TM, Schindler A, Schmidt C, Grimm J, Cyran C, Schwarz F et al, Prevalence of Nonstenosing, Complicated Atherosclerotic Plaques in Cryptogenic Stroke. J Am Coll Cardiol Img 2012;5:397–405

46. Gupta A, Gialdini G, Lerario MP, et al. Magnetic resonance angiography detection of abnormal carotid artery plaque in patients with cryptogenic stroke. *J Am Heart Assoc*. 2015;4(6):e002012.

47. Hyafil F, Schindler A, Sepp D, Obenhuber T, Bayer-Karpinska A, Boeckh-Behrens T, Höhn S, Hacker M, Nekolla SG, Rominger A, Dichgans M, Schwaiger M, Saam T, Poppert H. High-risk plaque features can be detected in non-stenotic carotid plaques of patients with ischaemic stroke classified as cryptogenic using combined (18)F-FDG PET/MR imaging. Eur J Nucl Med Mol Imaging. 2016;43(2):270-279

48. Aizaz M, Moonen RPM, van der Pol JAJ, Prieto C, Botnar RM, Kooi ME. PET/MRI of atherosclerosis. *Cardiovasc Diagn Ther*. 2020;10(4):1120-1139.

49. Coutinho JM, Derkatch S, Potvin AR, et al. Nonstenotic carotid plaque on CT angiography in patients with cryptogenic stroke. *Neurology*. 2016;87(7):665-672.

50. Macleod MR, Amarenco P, Davis SM, Donnan GA. Atheroma of the aortic arch: an important and poorly recognised factor in the aetiology of stroke. *Lancet Neurol* (2004) 3:408–14.

51. Nedeltchev K, der Maur TA, Georgiadis D, Arnold M, Caso V, Mattle HP, et al. Ischaemic stroke in young adults: predictors of outcome and recur-rence. *J Neurol Neurosurg Psychiatry* (2005) **76**(2):191–5.

52. Gilden D, Cohrs RJ, Mahalingam R, Nagel MA. Varicella zoster virus vasculopathies: diverse clinical manifestations, laboratory features, pathogenesis, and treatment. *Lancet Neurol* (2009) **8**:731–40

53. Askalan R, Laughlin S, Mayank S, Chan A, MacGregor D, Andrew M, et al. Chickenpox and stroke in childhood: a study of frequency and causation. *Stroke* (2001) **32**:1257–62

54. Nagel MA, Cohrs RJ, Mahalingam R, Wellish MC, Forghani B, Schiller A, et al. The *Varicella zoster* virus vasculopathies: clinical, CSF, imaging, and virologic features. *Neurology* (2008) **70**:853–60.

55. Bushnell CD, Goldstein LB. Diagnostic testing for coagulopathies in patients with ischemic stroke. *Stroke* (2000) **31**(12):3067–78.

56. Lane DA, Grant PJ. Role of hemostatic gene polymorphisms in venous and arterial thrombotic disease. *Blood* (2000) **95**(5):1517–32.

57. Hart RG, Kanter MC. Hematologic disorders and ischemic stroke. A selective review. *Stroke* (1990) **21**(8):1111–21.

58. Chan MY, Andreotti F, Becker RC. Hypercoagulable states in cardio-vascular disease. *Circulation* (2008) **118**(22):2286–97.

59. Graus F, Rogers LR, Posner JB. Cerebrovascular complications in patients with cancer. *Medicine* (1985) **64**(1):16–35.

60. Varki A. Trousseau's syndrome: multiple definitions and multiple mecha-nisms. *Blood* (2007) **110**(6):1723–9. doi:10.1182/blood-2006-10-053736

61. Caine GJ, Stonelake PS, Lip GY, Kehoe ST. The hypercoagulable state of malignancy: pathogenesis and current debate. *Neoplasia* (2002) **4**(6):465

62. Seok JM, Kim SG, Kim JW, Chung CS, Kim GM, Lee KH, et al. Coagulopathy and embolic signal in cancer patients with ischemic stroke. *Ann Neurol* (2010) **68**(2):213–9.

63. Susac JO, Hardman JM, Selhorst JB. Microangiopathy of the brain and retina. *Neurology* (1979) **29**:313–6.

64. Futrell N, Millikan C. Frequency, etiology, and prevention of stroke in patients with systemic lupus erythematosus. *Stroke* (1989) **20**:583

65. Mikdashi J, Handwerger B, Langenberg P, Miller M, Kittner S. Baseline disease activity, hyperlipidemia, and hypertension are predictive factors for ischemic stroke and stroke severity in systemic lupus erythematosus. *Stroke* (2007) **38**:281.

66. Liang MH, Karlson E. Neurologic manifestations of lupus. 2nd ed. In: Schur PH, editor. *The Clinical Management of Systemic Lupus Erythematosus*. Philadelphia: Lippincott (1996).

67. Nouh A, Carbunar O, Ruland S. Neurology of rheumatologic disorders. *Curr Neurol Neurosci Rep* (2014) **14**(7):1–13

68. Niesten JM, van der Schaaf IC, van Dam L, et al. Histopathologic composition of cerebral thrombi of acute stroke patients is correlated with stroke subtype and thrombus attenuation. *PLoS One*. 2014;9(2):e88882.

69. Nouh A, Hussain M, Mehta T, Yaghi S. Embolic Stroke of Unknown Source and cryptogenic stroke : Implications in clinical practice. *Front. Neurol.* 2016. *7:37.*

70. Feil K, Heinrich J, Küpper C, et al. Catch-up-ESUS - follow-up in embolic stroke of undetermined source (ESUS) in a prospective, open-label, observational study: study protocol and initial baseline data. *BMJ Open*. 2019;9(12):e031716.

71. Kleindorfer DO, Towfighi A, Chaturvedi S, Cockroft KM, Gutierrez J, Lombardi-Hill D, et al. 2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack: A Guideline From the American Heart Association/American Stroke Association. Stroke .2021 ;52(7).

72. Ntaios G, Pearce LA, Veltakamp R, Sharma M, Kasner LE, Korompokki E et al. Potential Embolic Sources and Outcomes in Embolic Stroke of Undetermined Source in the NAVIGATE-ESUS Trial Stroke. 2020;51:1797-1804

73. Amarenco P, Albers GW, Denison H, Easton JD, Evans SR, Held P, Hill MD, Jonasson J, Kasner SE, Ladenvall P, et al; SOCRATES Steering Committee and Investigators. Ticagrelor versus aspirin in acute embolic stroke of undetermined source. *Stroke.* 2017;48:2480–2487.

74. Mohr JP, Thompson JL, Lazar RM, Levin B, Sacco RL, Furie KL, et al. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med 2001;345:1444e51.

75. De Schryver EL, Algra A, Kappelle LJ, van Gijn J, Koudstaal PJ. Vitamin K antagonists versus antiplatelet therapy after transient ischaemic attack or minor ischaemic stroke of presumed arterial origin. Cochrane Database Syst Rev 2012;9:Cd001342.

76. Boeckh-Behrens T, Kleine JF, Zimmer C, Neff F, Scheipl F, Pelisek J, et al. Thrombus histology suggests cardioembolic cause in cryptogenic stroke. Stroke 2016;47: 1864e71.

77. Tandon K, Tirschwell D, Longstreth Jr WT, Smith B, Akoum N. Embolic stroke of undetermined source correlates to atrial fibrosis without atrial fibrillation. Neurology 2019; 93:e381e7.

78. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med 2014;370:2478e86.

79. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906e17.

80. Zhao SX, Ziegler PD, Crawford MH, Kwong C, Koehler JL, Passman RS. Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study.

81. Kamel H, Merkler AE, Iadecola C, Gupta A, Navi BB. Tailoring the approach to embolic stroke of undetermined source: a review. JAMA Neurol 2019;76:855e61.

82. Diener HC, Sacco RL, Easton JD, Granger CB, Bernstein RA, Uchiyama S, et al. Dabigatran for prevention of stroke after embolic stroke of undetermined source. N Engl J Med 2019;380:1906e17.

83. Zhao SX, Ziegler PD, Crawford MH, Kwong C, Koehler JL, Passman RS. Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study.

84. Verma N, Ziegler PD, Liu S, Passman RS. Incidence of atrial fibrillation among patients with an embolic stroke of undetermined source: insights from insertable cardiac monitors. Int J Stroke 2019;14:146e53

85. Mazzucco S, Li L, Rothwell PM. Prognosis of Cryptogenic Stroke With Patent Foramen Ovale at Older Ages and Implications for Trials: A Population-Based Study and Systematic Review. JAMA Neurol. 2020 Oct 1;77(10):1279-1287

86. Das SK, Banerjee TK, Biswas A, Roy T, Raut DK, Mukherjee CS, Chaudhuri A, Hazra A, Roy J. A prospective community-based study of stroke in Kolkata, India. Stroke. 2007 Mar;38(3):906-10.

87. Sridharan SE, Unnikrishnan JP, Sukumaran S, et al. Incidence, types, risk factors, and outcome of stroke in a developing country: the Trivandrum Stroke Registry. *Stroke*. 2009;40(4):1212-1218

88. Scavasine VC, Ribas GC, Costa RT, Ceccato GHW, Zétola VHF, Lange MC. Embolic Stroke of Undetermined Source (ESUS) and Stroke in Atrial Fibrillation Patients: not so Different after all?. Int. J. Cardiovasc. Sci. 2021;34(5):517-22.

89. Veltkamp R, Pearce LA, Korompoki E, et al. Characteristics of Recurrent Ischemic Stroke After Embolic Stroke of Undetermined Source: Secondary Analysis of a Randomized Clinical Trial . *JAMA Neurol.* 2020;77(10):1233–1240.

90. Pandit K, Goswami S, Ghosh S, Mukhopadhyay P, Chowdhury S. Metabolic syndrome in South Asians. *Indian J Endocrinol Metab*. 2012;16(1):44-55.

91. Jin-Man Jung, Jungsoon Choi, Mi-Yeon Eun, Woo-Keun Seo, Kyung-Hee Cho, Sungwook Yu, Kyungmi Oh, Soonwoong Hong, Kwang-Yeol Park, Neurology Mar 2015, 84 (11) 1080-1089

92. Modolo GP, Souza JT, Winckler FC, et al. Embolic stroke of undetermined source (ESUS) cohort of Brazilian patients in a university hospital. *Arq Neuropsiquiatr*. 2019;77(5):315-320.

93. Weber-Krüger M, Gelbrich G, Stahrenberg R, Liman J, Kermer P, Hamann GF, Seegers J, Gröschel K, Wachter R; Find-AF(RANDOMISED) investigators. Finding atrial fibrillation in stroke patients: Randomized evaluation of enhanced and prolonged Holter monitoring--Find-AF(RANDOMISED) --rationale and design. Am Heart J. 2014 Oct;168(4):438-445.e1

94. Siegler JE, Thon JM, Woo JH, Do D, Messé SR, Cucchiara B. Prevalence of Nonstenotic Carotid Plaque in Stroke Due to Atrial Fibrillation Compared to Embolic Stroke of Undetermined Source. *J Stroke Cerebrovasc Dis*. 2019;28(10):104289.

95. Kamtchum-Tatuene J, Wilman A, Saqqur M, Shuaib A, Jickling GC. Carotid Plaque With High-Risk Features in Embolic Stroke of Undetermined Source. Stroke. 2020;51:311–314.

96. Guo Y, Chen Z, Wang Q, et al. Influence of white matter lesions on the prognosis of acute cardioembolic stroke without reperfusion therapy. *BMC Neurol*. 2021;21(1):364.

97. Yaghi S, Boehme AK, Hazan R, Hod EA, Cannan R, Andrews H. Atrial Cardiopathy and Cryptogenic Stroke: A Cross-sectional Pilot Study. *J Stroke Cerebrovasc Dis*. 2016 January ; 25(1): 110–114.

98. Ntaios G, Perlepe K, Lambrou D, Sirimarco D, Strambo D, Eskandari A.. Prevalence and Overlap of Potential Embolic Sources in Patients With Embolic Stroke of Undetermined Source. J Am Heart Assoc. 2019;8: e012858
99. Ning Y, Tse G, Luo G and Li G (2021). Atrial Cardiomyopathy: An Emerging Cause of the Embolic Stroke of Undetermined Source. Front. Cardiovasc. Med. 8:674612
100. Lotlikar RS, Saikiran K, George J, Namboodiri N, Sylaja PN, Sreedharan SE. Predictors of Recurrence in Symptomatic Large Artery Atherosclerosis and Cryptogenic Strokes—A Comparative Study. *Journal of Stroke Medicine*. 2022;5(1):21-25
101. Arauz A, Morelos E, Colín J, Roldán J, Barboza MA. Comparison of functional outcome and stroke recurrence in patients with Embolic Stroke of Undetermined Source (ESUS) vs. cardioembolic stroke patients. PLoS One. 2016;11:e0166091
102. Zivanovic Z, Ostojic Z, Rajic S, Vlahovic D, Mijajlovic M, Jovicevic M. Outcome after intravenous thrombolysis in embolic stroke of undetermined source compared to cardioembolic stroke. Wien Klin Wochenschr, 2020: 132:515–5
103. Geisler T, Poli S, Meisner C, Schreieck J, Zuern CS, Nägele T, et al. Apixaban for treatment of embolic stroke of undetermined source (ATTICUS randomized trial): Rationale and study design. Int J Stroke. 2017 Dec;12(9):985-990.
104. Nezu T, Mukai T, Uemura J, et al. Multiple Infarcts Are Associated With Long-Term Stroke Recurrence and All-Cause Mortality in Cryptogenic Stroke Patients. *Stroke*. 2016;47(9):2209-2215..
105. Hou Y, Elmashad A, Staff I, Alberts M, Nouh A. Potential Embolic Sources Differ in Patients With Embolic Stroke of Undetermined Source According to Age: A 15-Year Study. *Front Neurol*. 2022;13:860827.

PROFORMA

Baseline data

1A	SERIAL NO	
1B	AGE	
1C	GENDER	
1D	Date of first event	
1E	Type of event	Stroke/TIA
1Fa	Hemisphere involved	
1G	Time between first symptom and admission	
1H	Admission NIHSS	
1I	DM	
1J	HYPERTENSION If yes-medications Betablockers CCB Alpha blockers ACE-I ARB Diuretics More than one	
1K	DYSLIPIDEMIA	
1L	SMOKING	Current/ex->3 months/never

1M	Alcohol	
1N	CAD	
1O	PCI/CABG done	
1P	POVD	
1p1	Prestroke statin use	
1p2	Prestroke antiplatelet use	Aspirin Clopidogrel Both none
1Q	Admission blood sugar	
1R	HBA1C	
1S	Admission BP	
1T	Fasting Cholesterol	
1U	HDL	
1V	LDL	
1W	TAG	
1X	Serum Homocysteine	
1y	Vasculitic workup	

Imaging data

2a	Type of imaging	CT/MRI
2b	Infarct pattern Single versus multiple arterial territories	 Y/N

	Territorial Main artery/Branch occlusion Superficial watershed Internal borderzone Lacunar Multiple embolic	
2c	Ipsilateral vessel involvement EC IC	<30% 30-49% 50-69% 70-99% Occlusion
2f	Plaque thickness	<2mm 2-3mm 3-4mm 4-5 mm >5mm
2g	chronic infarcts territorial lacunar both	
2h	WMHI Fazekas grade 0/1/2/3	

Cardiac investigations-ECG

3a	PTEF-V 1 >4000microvolt*duration in ms >5000 microvol*ms	
3b	INTERATRIAL BLOCKS P wave duration >110 ms	
	PR interval Duration>200 ms	
3c	Presence of SVT	
3d	Presence of atrial ectopics	
3e	LVH –voltage criteria	
3f	AF <30 seconds >30 seconds	
3g	24 hour Holter-done Atrial ectopics	

	SVT Atrial fibrillation Burden	
3h	7 day holter Atrial ectopics SVT Atrial fibrillation Burden	

Cardiac investigations-ECHO

3a	TTE-LA diameter Normal Male ≤ 40 Female ≤ 38 Mild LAE Male 41-46 Female 39-42 Moderate LAE Male 47-51 Female 43-46 Severe LAE Male ≥52 Female ≥47	
3b	LA volume >34 ml/m2	
3c	Spontaneous echo contrast	
3d	LV dimension systolic	

3e	LV dimension diastolic	
3f	EF	

Outcome data-discharge

3a	In hospital recurrent events	
3b	Type of recurrent events	Stroke/TIA
3c	Discharge NIHSS	
3d	Discharge MRS	
3e	Discharge antiplatelets	Aspirin Clopidogrel Both Anticoagulation
3f	Discharge diagnosis-TOAST 1.LAA 2.Cardioembolic 3.lacunar 4.other determined causes-specify 5.cryptogenic	

1 year followup

4a	NIHSS	
4b	MRS	
4c	Any ipsilateral recurrent events	TIA Stroke None
4d	Any C/L or VB events	
4e	Any cardiac events	
4f	HBA1C	
4g	F cholesterol	
4h	LDL	
4i	HDL	
4j	TAG	
	Etiology	

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-16)

SCT/IEC/1564/OCTOBER-2020 30.10.2020

Dr. Jithin George
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Jithin George,

Thank you for submitting documents related to your proposal titled "**A STUDY ON PREDICTORS OF OUTCOME AND RECURRENCE RISK IN EMBOLIC STROKE OF UNDERTERMINED SOURCE** (IEC/1564)" to the IEC for review.

The following documents were reviewed:

Original submission

1. *Check list*
2. *Covering letter from PI addressed to Chairman, IEC dated 12/08/2020*
3. *Covering letter addressed to Chairman dated 12/08/2020 from Dr.Sanjeev Thomas HOD, Dept of Neurology*
4. *Thesis Proposal*
5. *IEC Application*
6. *Co .PI's (Dr.Sapna Erat Sreedharan) letter to Chairman IEC*
7. *Proforma*
8. *TAC Approval dated 07/07/2020*
9. *TAC-Submission endorsed by HOD, Dept of Neurology*
10. *Patient Information Sheet in English*
11. *Patient information sheet in Malayalam*
12. *Informed consent form in English*
13. *Informed consent form in Malayalam*
14. *CV of PI Dr.Jithin George with TCMC registration*
15. *CV of Co-PI Dr.Sapna Erat Sreedharan with TCMC registration*

Revised submission on 14/11/2020

1. *Check list*
2. *Thesis proposal*
3. *IEC Application form*
4. *Covering letter addressed to Chairman dated 12/08/2020 from Dr.Sanjeev Thomas HOD, Dept of Neurology*
5. *Co .PI's (Dr.Sapna Erat Sreedharan) letter to Chairman IEC(undated)*
6. *Proforma*
7. *TAC clearance dated07/07/2020 with comments received*
8. *TAC certification by DEAN*
9. *Revised patient information sheet in English*
10. *Revised patient information sheet in Malayalam*
11. *Informed consent form in English*
12. *Informed consent for in Malayalam*
13. *Telephone consent form in English(new)*
14. *Telephone consent form in Malayalam(new)*
16. *CV of PI Dr.Jithin George with TCMC registration*
17. *CV of Co-PI Dr.Sapna Erat Sreedharan with TCMC registration*
15. *Covering letter addressed to IEC Chairman dated 13/11/2020*

The following members of the Students Sub-Committee of the Institutional Ethics Committee participated in the discussions held between August 23-October29, 2020 at the offices and residences of the members

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Dr. R V G Menon	M Tech, PhD	Male	Lay Person (Chairman)	No
2.	Dr. Harikrishnan S	MD, DM (Cardiology) DNB (Cardiology)	Male	Clinician	Yes
3.	Dr. Kala Kesavan. P	MBBS, MD	Female	Basic Medical Scientist	No
4.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
5.	Dr. Rema M. N	MD	Female	Basic Medical Scientist	No
6.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
7.	Dr. Mala Ramanathan	PhD	Female	Social Scientist (Member Secretary)	Yes

IEC Decision

The IEC approved the conduct of the study in the present form.

Remarks:
The Institutional Ethics Committee expects to be informed about the progress of the study, any SAE occurring in the course of the study, any changes in the protocol and patient information/informed consent and asks to be provided a copy of the final report.

There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,

Mala Ramanathan
Member Secretary, IEC

Plagiarism Checker X - Report

Originality Assessment

Overall Similarity: **3%**

Date: Jul 27, 2022

Statistics: 461 words Plagiarized / 15192 Total words

Remarks: Low similarity detected, check your supervisor if changes are required.