SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM, KERALA

STUDY OF SHORT TERM AND LONG TERM RISK OF VASCULAR EVENTS FOLLOWING EARLY TREATMENT OF TIA AND MINOR STROKE

Thesis submitted in partial fulfilment of the rules and regulations for DM Degree Examination of Sree Chitra Tirunal Institute for Medical Sciences and Technology

BY

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2015-2017
DECLARATION

I, Dr Hemanga Kr Dhing, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, SreeChitra Tirunal Institute for Medical Sciences and Technology.

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INTRODUCTION

Transient ischemic attack and minor ischemic stroke are associated with early recurrence and deterioration respectively. There is a high risk of stroke after TIA ranging between 10—20% in the ensuing 90 days in the various studies. But recent studies have found urgent interventions to be associated with substantial reductions in stroke risk within the first 90 days following TIA (0.6% to 3.1%). There are various clinical and imaging factors which predict the early risk of stroke after a TIA. Identifying the stroke subtype also help in estimating the risk of stroke recurrence and also the risk of deterioration after a minor stroke. Large artery atherosclerosis has been found to be associated with a high risk of stroke after a TIA. A metaanalysis of four population based studies of stroke showed that the risk of recurrent stroke was 4 % (95% CI: 0.2—7.8) at 7 days and 12.6% (95% CI: 5.9—19.3) at 30 days in patients with large artery atherosclerotic aetiology compared to 0 and 2 % (95% CI 0—4.2) respectively in patients with lacunar stroke. In addition to the short-term risk of stroke, these patients are at increased long-term risk of ischemic vascular events. We know that urgent evaluation and treatment of these patients is associated with significant reduction of the short-term risk of stroke, but there was not much literature available about the effect of early treatment and long-term outcome. The purpose of the study is to evaluate short term and long-term outcome and their predictors in patients with TIA or minor ischemic stroke who receive urgent intervention.
Definition of TIA and Minor stroke—

Transient Ischemic Attack is defined by the Ad Hoc Committee on Cerebrovascular Diseases in 1975 defined as “cerebral dysfunction of ischemic nature lasting no longer than 24 hours with a tendency to recur”. WHO defined TIA as “sudden focal cerebral dysfunction lasting less than 24 hours of presumed vascular origin confined to the area of brain or eye perfused by a specific artery”. The arbitrary 24-hour threshold used to distinguish TIA from stroke arose in the mid-1960s. At that time, it was assumed that transient symptoms disappeared completely because no permanent brain injury had occurred. The term TIA was applied to events lasting up to 24 hours, and the term reversible ischemic neurological deficit was applied to events lasting 24 hours to 7 days. Only symptoms enduring 7 days were thought to reliably indicate infarction and received the designation stroke. During the 1970s, it became clear that the great preponderance of events lasting 24 hours to 7 days were associated with infarction, rendering the term reversible ischemic neurological deficit obsolete, and it disappeared from standard nomenclature. More recently, high-resolution CT and especially diffusion-weighted MRI studies have demonstrated that many ischemic episodes with symptoms lasting 24 hours also are associated with new infarction. One third of individuals with traditionally defined TIAs exhibit the signature of new infarction on diffusion-weighted MRI. These findings highlight an inconsistency between the concept of TIA (ischemia causing symptoms, but no infarction) and the traditional definition of TIA. Because of these difficulties Albers and TIA working group have given a tissue-based, rather than time-based, definition of TIA as “a brief episode of neurological dysfunction caused by focal brain or retinal ischemia, with clinical symptoms lasting less than an hour and without neuroimaging evidence of acute infarction”. The writing committee of AHA endorses the following revised definition “Transient ischemic attack (TIA) is a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.” This definition is tissue based, not time based. For diagnosing ischemic stroke requires infarction, whereas TIA is defined by symptomatic ischemia with no evidence of infarction. For those patients in whom a detailed
diagnostic evaluation was not possible, it may be difficult to determine whether stroke or TIA is the most appropriate diagnosis. For these patients, it would be reasonable that a term such as acute neurovascular syndrome should be chosen.

An unanimously agreed definition for minor stroke is lacking. Minor stroke is generally defined as an National Institute of Health Stroke Scale (NIHSS) of 5 or less, which takes into account certain deficits but not the fact that some can have a more profound impact on quality of life than others. Hence, the scale does not linearly correlate deficit and disability. While some studies suggest using an NIHSS of 3 or less to define minor stroke real-world definitions of non-disabling deficits are largely dependent on clinical judgment, which has been shown to vary widely among physicians.

**Epidemiology of TIA and minor stroke**

Stroke is the No. 5 cause of death in the United States, killing nearly 130,000 people a year. That’s 1 in every 20 deaths. Nearly 800,000 (approximately 795,000) people in the United States have a stroke every year, with about three in four being first-time strokes. In population-based studies, approximately two-thirds of ischemic stroke patients found to have mild deficits. The annual incidence of transient ischemic attacks in USA that come to medical attention vary from 200,000 to 500,000 per year and 53 to 91% of all TIA patients presenting to U.S. emergency departments (EDs) are admitted.

In India, the overall age-adjusted prevalence rate for stroke is estimated to lie between 84 and 262/100,000 in rural and between 334 and 424/100,000 in urban areas. However, there was no population based studies were available to look into the incidence of TIA or minor stroke in Indian population.
Evaluation of Patients with TIA and Minor stroke—

HISTORY—

At initial presentation, a comprehensive history should include identification of symptoms consistent with a focal neurologic deficit and the timing of symptom onset and resolution. This is crucial because symptoms often resolve by the time of presentation. Attention should also be given to the presence or absence of nonspecific symptoms common in TIA mimics. Witnesses of the event can also be helpful in describing symptoms not perceived by the patient. The history should elicit risk factors associated with ischemic disease, such as cigarette smoking, obesity, diabetes mellitus, dyslipidaemia, and hypertension, as well as personal or family history of hypercoagulability disorders, stroke, or TIA. The symptoms of a TIA occur suddenly and include a neurological deficit or loss of function. It is imperative to ask about recurrent symptoms of TIA because recent, recurrent TIA (crescendo TIA) requires urgent evaluation.

Mimics are more common in patients with a history of cognitive disorders, seizures with no lateralizing symptoms. Symptoms that generally are not suggestive of TIA include generalized weakness, dizziness, confusion, loss of consciousness, tinnitus, dysphagia, scotoma, eye pain and chest pain. It is important to note that the presence of common mimic symptoms does not exclude TIA from the diagnosis; however, mimics should be considered in the absence of concurrent focal deficits.

Common stroke mimics are—

- Todd’s paralysis (neurologic deficit post seizure)
- Epilepsy
- Complicated migraine
- Multiple sclerosis flare
- Hypoglycaemia
- Syncope from any cause (especially arrhythmia)
• Labyrinthine disorders (Benign positional vertigo (duration of vertigo <1 min), Meniere’s disease, vestibular neuronitis)
• Hyperventilation/panic attack
• Structural brain lesion from tumor, hemorrhage, arteriovenous malformation or aneurysm
• Infection (focal abscess, septic emboli)

PHYSICAL EXAMINATION—

A clinical presentation that demonstrates motor weakness and speech deficits is highly suggestive of TIA, and also may be associated with a higher risk of having an early stroke after TIA.\(^{22}\)

The physical examination should include measurement of vital signs a cardiovascular examination, and a comprehensive neurologic examination. Blood pressure is commonly elevated with cerebral ischemia and should be assessed, along with an evaluation for carotid bruits or cardiac arrhythmias. Careful attention should be given to focal neurologic deficits and their represented neurovascular distribution. Cranial nerve, somatic motor strength, somatic sensory, speech and language, and cerebellar system testing should be performed. The most common findings for TIA in the cranial nerve examination are diplopia, hemianopia, monocular blindness, disconjugate gaze, facial drooping, lateral tongue movement, dysphagia, and vestibular dysfunction.\(^{17,21}\) Cerebellar system testing includes ocular movement and finger-to-nose and heel-to-shin movement, which may reveal nystagmus, pastpointing or ataxia. Motor testing suggestive of TIA may reveal spasticity, clonus, rigidity or unilateral weakness in the upper or lower extremities, face, and tongue. Unilateral weakness and speech disturbance are the most common presenting symptoms in patients with TIA, and these symptoms are more likely to be associated with acute cerebral infarction on MRI.\(^{23}\)
Table 1--Frequency of TIA symptoms in recent clinical studies

<table>
<thead>
<tr>
<th>Patient</th>
<th>Ethnicity</th>
<th>Symptom assessment</th>
<th>Motor symptom (%)</th>
<th>Speech disturbance (%)</th>
<th>Sensory symptoms (%)</th>
<th>Vertebrobasilar symptoms (%)</th>
<th>Gait disturbances (%)</th>
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<td>Jhonston et al 24</td>
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<td></td>
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<td>35.8</td>
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<td>Ay et al 29</td>
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<td>42</td>
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**Imaging**

The AHA/ASA recommends neuroimaging within 24 hours of symptom onset. Diffusion-weighted MRI is the preferred modality because it is more sensitive than computed tomography (CT). However, CT is more commonly used than MRI because of its availability and ability to quickly identify intracerebral hemorrhage. If a patient receives an emergent CT, a follow-up MRI should be performed.
when available because of its superiority in identifying cerebral infarction. The presence of infarction on MRI can have important prognostic implications. Using the new definition, many patients with classically defined TIA would be redefined as having a minor stroke if there is evidence of acute infarction on MRI. For those with evidence of infarction on MRI (now defined as minor stroke), 7.1 percent had a stroke within the next seven days, compared with just 0.4 percent of patients without evidence of infarction. In patients with TIA, imaging the carotids is one of the most important part of the TIA evaluation. This can be done non-invasively using ultrasound, CT angiography (CTA) or MR angiography. CTA compares well with the gold standard digital subtraction angiography. A meta-analysis showed that in case of 70-99% stenosis, CEMRA was the most accurate (sensitivity of 0.94 and specificity 0.93), compared with US (sensitivity 0.89 , specificity 0.84), and CTA( sensitivity 0.77, specificity 0.94). Data for 50-69% stenosis and on combinations of tests were too sparse to be reliable.

**CARDIAC ASSESSMENT—**

Electrocardiography should be performed during the initial evaluation. Transthoracic or transoesophageal echocardiography can be used to look for a cardioembolic source and to determine the presence of patent foramen ovale, valvular disease, cardiac thrombus, and atherosclerosis. Prolonged cardiac monitoring with telemetry in the inpatient setting or Holter monitor in the outpatient setting is reasonable, primarily to evaluate for paroxysmal atrial fibrillation. AHA has advised that for patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event.

**LABORATORY TESTING—**

In the initial evaluation of TIA symptoms, blood glucose and serum electrolyte levels should be measured to help rule out hypoglycaemia or an electrolyte imbalance as the cause of change in mental status. Complete blood count and coagulation studies can help determine the likelihood of hemorrhage and thrombotic disorders. For younger patients and when there is clinical suspicion of central nervous system infection, CNS vasculitis, drug intoxication, or clotting disorders, additional workup to assess
the potential contribution of these disorders should include rapid plasma reagin testing, vasculitic profile, cerebrospinal fluid examination, urine drug screening, and full hypercoagulability workup. A fasting lipid panel should be performed to determine cardiovascular risk and for baseline cholesterol levels, to determine the appropriate starting dose of statin therapy needed to achieve target low-density lipoprotein levels.

**Etiological Classification of TIA –**

Etiological classification is done according to TOAST criteria into following subtypes—

1. Large artery atherosclerosis—

   Clinical and brain imaging findings of either significant (>50%) stenosis or occlusion of a major brain artery or branch cortical artery, presumably due to atherosclerosis

2. Cardioembolic—

   Includes patients with arterial occlusions presumably due to an embolus arising in the heart. Cardiac sources are divided into high-risk and medium-risk groups based on the evidence of their relative propensities for embolism.

3. Lacunar—

   Includes patient who have a normal CT/MRI examination or a relevant brain stem or subcortical hemispheric lesion with a diameter of less than 1.5 cm demonstrated. The patient should have one of the traditional clinical lacunar syndromes and should not have evidence of cerebral cortical dysfunction.
4. Other determined cause—

Includes patient who have clinical and CT or MRI findings of an acute ischemic stroke, regardless of the size or location with diagnostic studies such as blood tests or arteriography should reveal one of these unusual causes of stroke.

5. Undetermined cause— with the subcategories:

- Two or more causes identified,
- Negative and incomplete evaluation

**Treatment of TIA ---**

**Acute Treatment—**

**Thrombolytic Therapy—**

Thrombolytic therapy with intravenous recombinant tissue plasminogen activator (IV rtPA) is an important treatment for patients with acute ischemic stroke.\(^{39}\) Patients with minor deficits are often excluded from such treatment even though they demonstrate a high rate of suboptimal functional outcome. While retrospective studies show no benefit in 3-month outcome between thrombolysed and non-thrombolysed patients with mild deficits,\(^{40}\) these studies are subject to selection bias in favour of treating patients with disabling versus non-disabling deficits. Recent evidence from a stroke registry supports the use of IV rtPA compared with routine medical management in patients with mild deficits.\(^{41}\) In addition, a *post hoc* analysis of the International Stroke Trial-3 (IST-3) found that patients with mild deficits who were treated IV rtPA compared to placebo had a favourable shift in the Oxford Handicap Scale distribution (adjusted odds ratio, 2.38; 95% confidence interval, 1.17–4.85).\(^{42}\) The most feared complication of IV rtPA is symptomatic intracerebral hemorrhage (sICH), which is seen in up to 2% of patients with minor stroke.\(^{43,44}\) Due to the fear of hemorrhagic complications, physicians tend to offer IV rtPA to patients who they consider having a disabling deficit, a highly subjective clinical judgment.
Acute endovascular Therapy—

Several clinical trials recently showed that the addition of mechanical thrombectomy to best medical treatment in patients with acute ischemic stroke and evidence of a large artery occlusion resulted in significant improvement in long-term functional outcomes.\textsuperscript{45} Most of these studies excluded patients with minor stroke leading to variability in the use of mechanical thrombectomy for patients with acute large vessel occlusion and transient or minor deficits. Excluding these patients from endovascular treatment may lead 25% of patients being functionally disabled at 3 months.\textsuperscript{46,47} Recent AHA/ASA guidelines suggest that it is reasonable to consider endovascular treatment for patients with an NIHSS score <6 and evidence of large vessel occlusion. However, clinical trials are needed to prove the efficacy of endovascular treatment in this patient population.\textsuperscript{48}

Secondary stroke prevention—

Recognition and management of TIA offer the greatest opportunity to prevent disabling stroke. TIA should be considered as a medical emergency. Studies have shown up to an 80% reduction in the risk of stroke after TIA with the early implementation of secondary stroke prevention strategies,\textsuperscript{27} including revascularization of patients with symptomatic carotid artery stenosis, anticoagulation of patients with atrial fibrillation, treatment with antiplatelet agent(s), treatment with statins for most patients, management of hypertension, and lifestyle interventions such as smoking cessation or weight loss.

Antiplatelet agents—

Two randomized clinical trials have provided evidence for the short-term use of dual antiplatelet therapy after TIA and minor ischemic stroke. The Fast Assessment of Stroke and Transient Ischemic Attack to Prevent Early Recurrence (FASTER) trial compared the effectiveness of 3 months of treatment with 81 mg aspirin and 75 mg clopidogrel commenced within 24 hours of onset versus
aspirin alone in patients with minor strokes/TIAs. This trial was small and ended early because of slow recruitment; however, there was a suggestion that the combination therapy may reduce recurrent stroke events with a low risk of complications. The Clopidogrel in High-risk Patients with Acute Non-disabling Cerebrovascular Events (CHANCE) trial was performed in China and randomly assigned 5170 high-risk patients with TIA (defined as an ABCD2 score of 4 or higher at assignment) and minor stroke to treatment within 24 hours of onset with either combination therapy with clopidogrel and aspirin (clopidogrel at an initial dose of 300 mg, followed by 75 mg/d for 90 days, plus aspirin at a dose of 75 mg/d for the first 21 days) or placebo plus aspirin (75 mg/d for 90 days). Recurrent stroke was seen in 8.2% of patients in the clopidogrel aspirin group, as compared with 11.7% of those in the aspirin-only group (hazard ratio, 0.68; 95% confidence interval, 0.57–0.81; P<001). The risk of hemorrhage was not different in the two groups. The CHANCE trial has issues with generalizability, including the fact that it was a Chinese-only population, a high proportion of males were included, and the proportion of patients treated with antihypertensive and lipid-lowering medications was less than typically seen in North American populations. In the Stenting vs. Aggressive Medical Management for Preventing Recurrent Stroke in Intracranial Stenosis (SAMMPRIS) study, patients with recently symptomatic severe intracranial stenosis were randomly assigned to intracranial stenting plus aggressive medical management or aggressive medical management alone. The study results showed aggressive medical management alone was superior to stenting in the prevention of recurrent stroke. Medical management included 325 mg aspirin and 75 mg clopidogrel for 90 days, together with intensive medical management of modifiable vascular risk factors. Medical management was superior to stenting because of a combination of higher than expected periprocedural risk and a lower recurrence rate in the medical management arm.

**Statins—**

In addition to their effect on lowering cholesterol, statins have neuroprotective and anti-inflammatory properties that enhance endothelial function and promote blood flow. A small randomized study and a larger retrospective study showed that patients who were continued on a statin acutely after a stroke had a better outcome than those in whom the statin was withdrawn.
Therefore, in patients with minor stroke or TIA, early continuation of statin therapy may improve both short-term and long-term stroke prevention strategies.

**Carotid revascularisation**—

Evaluation for carotid stenosis is a key step in the diagnostic evaluation of patients with TIA and minor stroke. In patients with this disease, carotid endarterectomy (CEA) in addition to best medical therapy is superior to best medical therapy alone, particularly in those with >70% symptomatic stenosis. For patients with ipsilateral moderate (50%–69%) carotid stenosis, CEA is recommended depending on patient-specific factors, such as age, sex, and comorbidities. Since the risk of recurrent stroke in such patients is highest in the first 2 weeks after their initial event, the AHA/ASA recommends urgent surgery within 2 weeks of symptoms. In asymptomatic patients who have more than 70% stenosis of the internal carotid artery if the risk of perioperative stroke, MI, and death is low CEA is indicated.

**Atrial Fibrillation Detection**—

Identifying atrial fibrillation is important in secondary stroke prevention as anticoagulation is superior to antiplatelet agents in reducing the stroke risk of patients with atrial fibrillation. Electrocardiogram and inpatient cardiac telemetry should be part of the diagnostic evaluation of patients admitted with ischemic stroke.

**Outpatient Versus Inpatient Assessment**—

Determining which TIA patients require inpatient hospitalization is largely a factor of institutional resources and the ease of access for patients to receive follow-up care. For stroke prevention, the location of treatment matters less than the speed of the assessment. Stratification into high and low risk status can be done relatively quickly in the emergency room. High risk candidates are admitted for urgent evaluation and treatment and low risk patients triaged to clinic. Hospitalization of the high risk TIAs have potential benefits which include: 1) expedited diagnostic evaluation; 2) monitoring of fluctuating patients with ready access to thrombolysis if they deteriorate.
3) facilitation of early carotid revascularization,\textsuperscript{59} 4) greater opportunity for risk factor modification. For effective secondary stroke prevention, current evidence suggests that patients with high risk TIA require rapid referral and a 24-hour admission.\textsuperscript{58}

Rapid access TIA clinics and ED observation units provide efficient and cost-effective alternatives to hospitalization for many patients. Observation units, typically located within or near the hospital EDs, provide expedited and protocol-driven care and have a proven track record of safety with TIA\textsuperscript{59,60,61,62}. Outpatient clinics, such as the French SOS-TIA and British EXPRESS models, have successfully implemented 24/7 urgent outpatient follow-up for TIA, while reducing 90-day stroke recurrence by 80%\textsuperscript{27,63,64}.

**Early Stroke Risk after TIA**—

Several studies have evaluated the short-term prognosis of TIA. Approximately 15–20\% of ischemic strokes are preceded by a TIA\textsuperscript{65} and the appropriate detection and urgent diagnostic work-up for patients with TIA can avoid a further disabling stroke if the correct treatment is indicated. A retrospective study of consecutive patients attending emergency departments (EDs) within 24 hours after TIA demonstrated that the stroke risk after the index event was higher than previously thought; the stroke rate was 10.5\% at 90 days, with half of the events (5.3\%) occurring within 2 days of symptoms onset.\textsuperscript{24} A further analysis of a population-based TIA incidence study [Oxfordshire Community Stroke Project (OCSP)] also reported a high stroke rate after index TIA, with risks of 8.6\% at 7 days and 12.0\% at 30 days.\textsuperscript{66} Several studies have been published after these publications. With respect to stroke immediately after TIA, in a prospective population-based incidence study of TIA and stroke (OXVASC), in 488 patients with a first TIA the risks of stroke at 6, 12 and 24 hours were 1.2\%, 2.1\% and 5.1\% respectively.\textsuperscript{67} Furthermore, 42\% of all stroke during the 30 days after a first TIA occurred within the first 24 hours.\textsuperscript{67} A metaanalysis of stroke risk after TIA over longer periods of time in 11 studies reported a pooled risk of 8.0\% (5.7-10.2\%) and 9.2\% (6.8-11.5\%) at 30 and 90 days respectively. Intriguingly, this meta-analysis showed that when TIA was prospectively and actively followed, the risk of recurrence was doubled in the 17.3\% range while when outcomes were sought passively using
administrative data, the rate of stroke was approximately 8.7% at 90 days. Another systematic review and meta-analysis of studies reporting the risk of stroke exclusively within 7 days of TIA (total 18 cohorts, n = 10,126 patients) showed pooled risk of stroke of 3.1% at 2 days and 5.2% at 7 days, with a substantial heterogeneity across studies for both pooled risk estimates. The risks of stroke after TIA observed in patients treated urgently by specialist stroke services were 0.6% at 2 days, and 0.9% at 7 days compared with 3.6% at 2 days and 6.0% at 7 days from other cohorts.

Table 2—Stroke recurrence in TIA and minor stroke patients in recent major studies

<table>
<thead>
<tr>
<th>Study ID</th>
<th>Year</th>
<th>Size</th>
<th>Setting</th>
<th>Design</th>
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<td>Population</td>
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<td>315</td>
<td>TIA clinic</td>
<td>Prospective (OXFORD)</td>
<td>5.4(17)</td>
</tr>
<tr>
<td>Lavellee et al</td>
<td>2007</td>
<td>770</td>
<td>Specialist unit</td>
<td>Prospective</td>
<td>1.7(13)</td>
</tr>
<tr>
<td>Study</td>
<td>Year</td>
<td>Sample Size</td>
<td>Setting</td>
<td>Study Type</td>
<td>Follow-Up</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>------</td>
<td>-------------</td>
<td>------------------</td>
<td>--------------------</td>
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<tr>
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<tr>
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<td>89</td>
<td>Hospital</td>
<td>Prospective</td>
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<td>Ois et al 76</td>
<td>2008</td>
<td>221</td>
<td>Hospital</td>
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<td>19(42)77</td>
</tr>
<tr>
<td>Coutts et al 28</td>
<td>2008</td>
<td>134</td>
<td>ED</td>
<td>Prospective</td>
<td>11.1(20)</td>
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<tr>
<td>Chandratheva et al 77</td>
<td>2010</td>
<td>500</td>
<td>Population based</td>
<td>Prospective (OXVASC)</td>
<td>10(50)</td>
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<td>Harrison et al 78</td>
<td>2010</td>
<td>795</td>
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<td>Retrospective</td>
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<td>Merwick et al 79</td>
<td>2010</td>
<td>1232</td>
<td>Population based</td>
<td>Retrospective (OXVASC and Dublin)</td>
<td>7.5(92) 12.0(139)</td>
</tr>
<tr>
<td>Holzer et al 80</td>
<td>2010</td>
<td>173</td>
<td>Specialist unit</td>
<td>Retrospective</td>
<td>5.2(9)</td>
</tr>
<tr>
<td>Nakajima et al 85</td>
<td>2010</td>
<td>113</td>
<td>Hospital</td>
<td>Prospective</td>
<td>8.0(9)</td>
</tr>
<tr>
<td>Puroy et al 82</td>
<td>2010</td>
<td>310</td>
<td>Specialist unit</td>
<td>Prospective</td>
<td>5.8(88)</td>
</tr>
<tr>
<td>Weimer et al 83</td>
<td>2010</td>
<td>1897</td>
<td>Specialist unit</td>
<td>Prospective</td>
<td>5.6(107)</td>
</tr>
<tr>
<td>Yang et al 84</td>
<td>2010</td>
<td>490</td>
<td>Hospital</td>
<td>Retrospective</td>
<td>16(76)</td>
</tr>
<tr>
<td>Meng et al 85</td>
<td>2011</td>
<td>410</td>
<td>Hospital</td>
<td>Prospective</td>
<td>27(111)</td>
</tr>
<tr>
<td>Amarenco et al 86</td>
<td>2012</td>
<td>1679</td>
<td>Specialist unit</td>
<td>Prospective (SOS TIA)</td>
<td>2.0(34)</td>
</tr>
<tr>
<td>Purroy et al 31</td>
<td>2012</td>
<td>1105</td>
<td>Specialist unit</td>
<td>Prospective</td>
<td>2.6(29)</td>
</tr>
<tr>
<td>Ghia et al 87</td>
<td>2012</td>
<td>789</td>
<td>ED</td>
<td>Retrospective</td>
<td>1.9(15)</td>
</tr>
<tr>
<td>Kyohara et al 88</td>
<td>2014</td>
<td>693</td>
<td>Specialist clinic</td>
<td>Prospective</td>
<td>6.9</td>
</tr>
<tr>
<td>Amarenco et al 32</td>
<td>2016</td>
<td>4789</td>
<td>Specialist clinic</td>
<td>Prospective</td>
<td>2.1(10)</td>
</tr>
</tbody>
</table>
Long term risk after TIA—

Both stroke and TIA are sentinel events that confer persistent long-term risks of major adverse outcomes. In one of the earlier population based study Hill et al have reported 15.1% stroke recurrence at 1 year. In a long retrospective follow up study done by Harrison and colleague, the overall absolute risk of stroke in patients who attended an outpatient clinic with a TIA was 7.3% within one year, 16.2% within five years and 28.0% within ten years. A metanalysis which included total of 30,558 participants, published between 2003 and 2011, looked into the long term outcome showed the pooled risk of recurrent stroke at > 90 days to be 11.3%. But a recent (2016) prospective multicentre study published in 2016 by Amarenco et al, showed that the 1 year stroke recurrence rate was 5.1% in 4789 patients, which was lower in comparison to previous studies. Compared to age and sex matched controls, the patients with stroke or TIA who survived initial 90 days without having further events, hazard was highest for recurrent stroke at 1 year (HR 6.8, 95% CI 6.1–7.5), continuing to 5 years (HR 5.1, 95% CI 4.8–5.5). Death, myocardial infarction, or admission to long-term or continuing care was also more than double at 1, 3 and 5 years after the initial event. All these data suggest the need for secondary prevention approaches that not only focus on the management of high short-term risks, but also include strategies for long-term outpatient risk reduction, even when no early adverse complications have occurred.

Non-stroke vascular event after TIA—

Stroke and coronary heart disease (CHD) share common risk factors and pathological mechanisms. Moreover, CHD is an important cause of death in patients with cerebrovascular disease. Autopsy studies have shown that patients with transient ischemic attack (TIA) and stroke have a high prevalence of asymptomatic CHD, which ranges from 15% to 60%. In a meta-analysis, the risk of MI and non-stroke vascular death after stroke or TIA was each 2% per year. In a recent prospective study by Vilanova et al, 628 in TIA patients, incidence of MI found to be 4.5% during the entire follow-up period of 31.2 months. Previous CHD, sex male and positive DWI found to have independent predictor of myocardial infarction. Not only myocardial infarction, other major
cardiovascular events like ventricular arrhythmia also increased in TIA patients. In one large study, 2.6% of TIA patients were hospitalized for major cardiovascular events (myocardial infarction, unstable angina, or ventricular arrhythmia) within 90 days. 99

Risk prediction after TIA -

The risk of stroke after a TIA depends on symptomatology, risk factors, underlying etiology and imaging characteristics. In view of the early risk of stroke after TIA, there is a need for urgent evaluation of these patients. Recently risk prediction tools have been developed which can identify the high-risk patients in the acute phase after TIA.

Clinical predictor —

In literatures, several studies have provided information on the clinical features that identify the patients with TIA at highest risk of stroke. Northern California study demonstrated that simple clinical variables were associated with the risk of stroke at 90 days in patients with a diagnosis of TIA who were initially admitted to an emergency department. Age, presence of diabetes mellitus, duration of episode >10 minutes, weakness and speech impairment during episode were independently associated with the risk of stroke after TIA; the estimated risk of further stroke was 34% in patients presenting with all five predictors.24 In addition, a population-based study conducted in Canada showed that age and diabetes mellitus together with hypertension, were associated with a higher risk of stroke 1 year after TIA. Subsequently, the ABCD score was created to predict the stroke risk during the first week after TIA using those clinical variables that have been independent predictors of stroke.74 Derived from the OCSP population and validated in the OXVASC and local TIA clinic populations, the score showed a fair accuracy in the prediction of stroke risk at 7 days in these patients. A further validation of the ABCD and California scores showed that both had a fair accuracy in the prediction of early recurrent stroke at 2, 7 and 90 days.26 By combing the components of two scores, Jhonston et al generated a uniform prediction tool ABCD2 in 2007 for prediction of early risk of stroke.26
The score classifies TIA or minor stroke patients at low, moderate or high risk using cut-off points of < 4, 4–5 and > 5. In a systematic review and metanalysis, 11 studies were identified which reported the predictive power of these ABCD scores and found them effective in identifying the true TIA patients at highest risk of stroke. But there is no consensus on the best ABCD2 cut-off for stratifying the risk of stroke and select patients for whom an urgent assessment is needed. Clinical guidelines issued by the AHA, for example, advocate admission to hospital and early assessment/treatment for patients with an ABCD2 score of ≥ 3, whereas national guidelines in the UK recommended a specialist assessment and investigation within 24 hours of symptoms for patients with an ABCD2 score of ≥ 4 and within 1 week for those patients with an ABCD2 score of < 4.

But a meta-analysis of 33 studies including 16,070 subjects found that the ABCD2 score performed poorly in patients with high baseline stroke risk, and was only marginally better when applied to low risk patients. Another recent metanalysis concluded the score does not reliably discriminate those at low and high risk of early recurrent stroke, identify patients with carotid stenosis or AF needing urgent intervention, or streamline clinic workload.
There is a small subset of patients with presumed TIA who have a benign prognosis and develop recurrent TIA and not stroke. History of multiple TIAs, duration of spell less than 10 minutes and isolated sensory symptoms alone have been found to follow a benign course. Further, the pattern of recovery from stroke is also important. Patients with rapid early improvement after the onset of neurologic symptoms are at higher risk of subsequent neurological deterioration, indicative of an unstable vasculature.105,106

**Etiology of stroke** –

The underlying cause of the TIA has been shown to be the major factor that predicts the stroke risk after TIA. A meta-analysis of data from 1709 patients showed that the risk of recurrent stroke were 4% and 12.6% at 7 days and 30 days respectively in large artery atherosclerotic aetiology compared to 0% and 2% in patients with lacunar stroke.107 Similarly in different cohorts of patients, where TIA patients were evaluated by a stroke neurologist as in this multicentre registry, the early recurrence risk after TIA is higher in large artery atherosclerosis than in other etiologic subtypes.32,73,76 In patients with small-vessel disease, blood-pressure–lowering therapy is very effective when combined with other risk-factor management and antiplatelet therapy, leading to low recurrence of stroke.108

No studies have looked specifically at TIA associated with atrial fibrillation and recurrence rate, perhaps because such patients are most often anticoagulated straight away, preventing any assessment of the natural history.

These associations subsequently disappeared as time from the index event passed. Moreover, while characteristics of most of the recurrent episodes during the first week were similar to the index event, beyond the first week they were different. If we take into account patients with late stroke recurrence, the proportion of patients with large artery atherosclerosis decreased as the proportion of patients with undetermined cause increased. Late stroke recurrence was also related to previous stroke and coronary heart disease.109
Territory-

Posterior circulation events constitute about 30% of TIA and minor stroke.\textsuperscript{110} Previously, these events were considered to have a better prognosis compared to anterior circulation events, but recent evidence suggests that this is not true. A meta-analysis, of studies that recruited patients in the acute phase after a TIA event, showed a higher risk of stroke after posterior circulation TIA (OR 1.47, 95% CI 1.1-2.0).\textsuperscript{110} Another population-based study of 688 patients with probable or definite TIA (476 carotid and 212 vertebrobasilar) the risk of ischemic stroke during the first year of follow-up was similar after vertebrobasilar or carotid TIA.\textsuperscript{111} Most likely, recurrence depends upon the underlying mechanism of disease. Patient with vertebrobasilar TIA have a high prevalence of vertebrobasilar stenosis, which is associated with a high risk of recurrent stroke.\textsuperscript{111}

Imaging predictor-

Brain imaging has been shown to provide very useful prognostic information, in addition to confirming the diagnosis and giving information on the territory and etiology of TIA. The presence of infarction on computed tomography (CT) brain scanning in patients with TIA has been shown to be associated with an increased risk of stroke.\textsuperscript{112,113} Though the sensitivity of detecting acute infarction on CT brain is low, its presence is associated with a high risk of stroke recurrence and reduced survival.\textsuperscript{114,115} In the study of 322 patients with TIA, new infarct was seen only in 4%, but the risk of stroke during follow-up was substantially higher among those with a new infarct on the head CT(OR,4.06;95% CI.1.16-14.14; \(P=0.028\)).\textsuperscript{115} A recent publication indicated that the addition of CT imaging (old or new infarction or periventricular white matter disease) could increase the predictive value of the ABCD score to better identify high risk TIA patients.\textsuperscript{113}

Diffusion-weighted MRI has been found to be of greater usefulness than CT in patients with TIA. In a study Chatzikonstantinou and colleagues\textsuperscript{116} reported that 1.6% patients had a relevant visible ischemic lesion on CT (1.6%), compared with 17.0% on DWI. In another study Förster and colleagues
found that 4% of patients had a visible ischaemic lesion on CT, compared with 33% on DWI suggestive effectiveness of MRI over CT.117

In a recent metanalysis done by Brazzelli et al, which included 9,078 TIA patients an acute DWI lesion was present in 3,048 patients. (34.3%, 95% CI 5 30.5–38.4%). The frequency of positive DWI findings varied from 9 to 67% (i.e., 7-fold) between studies. 118

Four studies provided data separately for TIA and minor stroke, showed that the proportion of minor stroke patients with visible ischemic lesions on DWI varies from 47% to 100%. 119,120,121,122 Several studies have shown that DWI positivity is associated with early recurrence of stroke in TIA patients. 34, 123, 124, 125 In one of the recent large study, which included 3724 patients with TIA, recurrent stroke risk was higher in patients who were DWI-positive as compared to those who were negative (4.5% vs 1.5%; p =0.001). 126

There are certain factors which decides on the DWI positivity. Symptom duration more than one hour, motor deficits and aphasia are independently correlated with the presence of a DWI lesion.119 But a recent metanalysis found no evidence that DWI-positive rate varied with time between TIA and scanning.118 Eleven studies reported no association between symptom duration and DWI positivity, and 11 other studies reported a positive association; this 50:50 split suggests that symptom duration is a less consistent factor than might be expected. But a very recent study, which focused on Optimal timing of DWI to avoid false-negative findings in patients with TIA found that short latency (≤2 hours) from TIA onset to initial DWI was an independent risk factor related to false-negative findings.127

**Single vs multiple lesion in MRI—**

Presence of multiple infarctions on neuroimaging associated with high risk of recurrent stroke, especially if the lesions were of varying ages.32,126 This finding may be explained by plaque rupture with multiple distal emboli or a cardiac source of embolism. 129
**ABCD2 score and diffusion-weighted imaging or computed tomography finding—**

Several publications assessed the use of MR DWI findings added to the ABCD2 score. In general, the addition of DWI findings to the ABCD2 score improved the risk prediction. A multicentre study assessed the early risk of recurrent stroke after TIA, and performance of ABCD2 score subcategorised as tissue positive or negative on either DWI or CT imaging. Among 3206 patients with DWI, 27.6% had an acute brain infarction. In 1368 patients imaged with CT, 23.9% had an acute or old infarction. For patients with DWI imaging, pooled rates of recurrent stroke at 7 days were 7.1% in those with tissue-positive events compared with 0.4% in those with tissue-negative events (p < 0.0001). For patients imaged with CT, rates were 12.8% and 3.0%, respectively (p < 0.0001). ABCD2 score and presence of infarction on diffusion-weighted imaging or CT were both independently predictive of stroke at 7 days. Incorporation of infarction in the ABCD2I score improved predictive power with an optimal weighting of 3 points for infarction on CT or diffusion-weighted imaging.

**Imaging based scores for prediction of stroke in TIA patients—**

The ABCD2 score uses clinical and ischemic event details to predict clinical outcome and does not include brain imaging. Addition of brain imaging may be a way of improving the prediction of outcome. The score ABCD2 + MRI was created by adding evidence of acute infarct on DWI to the ABCD2 score. The predictive accuracy of the ABCD2 + MRI score was significantly higher than ABCD2 (AUC: 0.88 vs 0.78; p = 0.01). Those with a high score (7–9) had a 90-day recurrent stroke risk of 32.1%, a moderate score (5–6) had a risk of 5.4% and a low score (0–4) had a risk of 0.0%. Unlike the ABCD2 score (p = 0.33), the ABCD2 + MRI score (p = 0.02) predicted functional impairment at 90 days. This was confirmed in a multicentre study that included 4574 patients with TIA and demonstrated a significant improvement in the yield of ABCD2 score in predicting recurrent strokes at day 7 and 90 with addition of brain infarct on NCCT or DWI. To further increase the yield of scoring system, the ABCD3 I score was developed that considered two points for dual TIA, two points for acute infarction on DWI and two points for carotid stenosis of at least 50%. Considering these high-risk features, the predictive value of ABCD2 score significantly improved in
the ABCD3 I score for early recurrent events by day 30 (0.90 at day 2; p = 0.035, 0.92 at day 7; p = 0.001, 0.85 at day 28; p = 0.028 and 0.79 at day 90; p = 0.073).

**Clinical outcome and imaging**

The 90-day clinical outcome is also closely correlated with DWI lesion and occlusion. In a study done by Coutts et al, found that only 2% of DWI negative/ no intracranial occlusion patients were dependent while 26.7% with both findings were dependent at 90 days.123
AIM OF THE STUDY -

1. To evaluate the short term and long term risk of stroke following early treatment of TIA and minor stroke
2. To evaluate the occurrence of nonstroke vascular events following early treatment of TIA and minor stroke.

METHODS AND MATERIALS -

Study design—

The proposed study is a retrospective cohort study of patients with TIA and minor stroke admitted in stroke unit within 48 hours of onset and patients seen as outpatient within 48 hours of symptom onset from 01/01/2010 to 31/12/2014. TIA is defined as sudden focal neurologic deficit of presumed vascular origin lasting less than 24 hours. Minor stroke is defined as an National institute of Health Stroke scale score of ≤5. TIA mimics were excluded from the study. The patients were followed up till 1 year.

The primary outcome is stroke or TIA at 3 months and at one year. In patients with minor stroke, a 2-point worsening in the NIHSS will be considered as an event. The Modified rankin score at 3 months is assessed. The secondary outcome will be any nonstroke vascular events or vascular deaths at 3 months and at one year. Non-stroke vascular event will include any Myocardial infarction, unstable angina and peripheral vascular disease leading to amputation of that limb occurring during follow up.

Clinical and socio demographical data, National Institutes of Health Stroke Scale scores and Modified Rankin Scale scores, as well as data on vascular risk factors were collected from patients. The vascular risk factors include

- Diabetes
- Hypertension
• Age
• Smoking
• Renal dysfunction
• Dyslipidaemia
• Peripheral vascular disease
• Coronary artery disease

Diabetes—

**ADA 2017 criteria for diabetes:**

FPG ≥ 126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.*

Or

2-h PG ≥ 200 mg/dL (11.1 mmol/L) during an OGTT. The test should be performed as described by the WHO, using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.*

Or

HBA1C ≥ 6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is NGSP (National Glycohemoglobin Standardization Program) certified and standardized to the DCCT (Diabetes Control and Complications Trial (DCCT)) assay.*

Or

In a patient with classic symptoms of hyperglycemia or hyperglycaemic crisis, a random plasma glucose ≥ 200 mg/dL (11.1 mmol/L).

*In the absence of unequivocal hyperglycemia, results should be confirmed by repeat testing
Renal dysfunction:

The renal dysfunction is assessed by MDRD formula

\[
GFR = 186 \times (\text{P}_{\text{cr}})^{-1.154} \times \text{(age)}^{-0.203}
\]

(\times 0.742 if female)

(\times 1.210 if African-American ethnicity)

Dyslipidaemia:

It is classified according to the NCEP ATP III guidelines

**Table 4: ATP III Classification of LDL, Total, and HDL Cholesterol (mg/dL)**

| LDL Cholesterol (mg/dl) – Primary Target of Therapy |  
|-------------------------------------------------|---|
| <100                                            | Optimal |
| 100-129                                         | Near optimal/above optimal |
| 130-159                                         | Borderline high |
| 160-189                                         | High |
| ≥190                                            | Very high |

**Total Cholesterol(mg/dl)**

| <200                                            | Desirable |
| 200-239                                         | Borderline High |
| ≥240                                            | High |

**HDL Cholesterol(mg/dl)**

| <40                                             | Low |
| ≥60                                             | High |

Hypertension—

Hypertension is diagnosed according to the JNC 8 classification.
Table 5: JNC 8 Classification of Blood Pressure

<table>
<thead>
<tr>
<th>CATEGORY</th>
<th>SBP mmHg</th>
<th>DBP mmHg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>&lt;120</td>
<td>and</td>
</tr>
<tr>
<td>Pre hypertension</td>
<td>120-139</td>
<td>or</td>
</tr>
<tr>
<td>Hypertension Stage I</td>
<td>140-159</td>
<td>or</td>
</tr>
<tr>
<td>Hypertension Stage II</td>
<td>≥160</td>
<td>or</td>
</tr>
</tbody>
</table>

According to JNC 8 there is strong evidence to support treating hypertensive persons aged 60 years or older to a BP goal of less than 150/90 mm Hg and hypertensive persons 30 through 59 years of age to a diastolic goal of less than 90 mm Hg; however, there is insufficient evidence in hypertensive persons younger than 60 years for a systolic goal, or in those younger than 30 years for a diastolic goal, so the panel recommends a BP of less than 140/90 mm Hg for those groups based on expert opinion. The same thresholds and goals are recommended for hypertensive adults with diabetes or nondiabetic chronic kidney disease (CKD) as for the general hypertensive population younger than 60 years.

**Stroke subtype**—

Stroke subtype is categorized for every patient using Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification.
### Table 6: Stroke subtype according to TOAST classification

<table>
<thead>
<tr>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large-artery atherosclerosis (embolus/thrombosis)*</td>
</tr>
<tr>
<td>Cardioembolism (high-risk/medium-risk)*</td>
</tr>
<tr>
<td>Small-vessel occlusion (lacune)*</td>
</tr>
<tr>
<td>Stroke of other determined etiology*</td>
</tr>
<tr>
<td>Stroke of undetermined etiology*</td>
</tr>
<tr>
<td>a. Two or more causes identified</td>
</tr>
<tr>
<td>b. Negative evaluation</td>
</tr>
<tr>
<td>c. Incomplete evaluation</td>
</tr>
</tbody>
</table>

TOAST, Trial of Org 10172 in Acute Stroke Treatment.
*Possible or probable depending on results of ancillary studies.

**Imaging**

All patients underwent CT scan or MRI with vessel imaging (CT Angiography or MR TOF Angiography) to look for etiology of stroke. Data’s on DWI positivity, single vs multiple infarct, symptomatic vessel stenosis and degree of stenosis were collected for every patient.

ABCD2 and ABCD 3I were calculated for every patient.

Blood samples including creatinine, electrolytes, erythrocytes (RBC), and leukocytes were drawn on admission. Fasting serum samples were collected and high-density lipoprotein, low density lipoprotein, triglycerides, cholesterol, and HbA1c were assessed.
STATISTICAL ANALYSIS:

All statistical analysis was performed using SPSS software. Continuous variables are reported as mean ± SD. Categorical variables were reported as proportions. Baseline characteristics were compared between the 2 groups. Differences in continuous variables were assessed by 1-way analysis of variance and differences between proportions were assessed by the X2 test. Univariate and multivariate analysis was done to identify predictors of new vascular events. Multiple logistic regression model was used to identify independent predictors of new vascular events.
RESULTS

A total 320 patients were analysed. Mean age of the patients was 60.6 years [SD ± 13.6 years]. Out of the patients 20.7% were females.

**Sex distribution**—The gender profile of the study is the as the data represented in table –7 and figure—1.

<table>
<thead>
<tr>
<th>Table 7: Sex distribution of the study group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Female</td>
</tr>
</tbody>
</table>

**Figure 1: Sex distribution of the study group**

TIA and Minor stroke patient proportion--- Out of 320 patients, 78% of patients had minor stroke
Risk Factor associated with TIA and Minor stroke patients – Among the study group, 198 patients (61.9%) had Hypertension, 138 patients (43.1%) had Diabetes, 137 patients (42.8%) had dyslipidaemia and 34 (10.6%) had atrial fibrillation.

Table 8: Risk factors associated with TIA and Minor stroke patients

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>TIA</th>
<th>Minor stroke</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>43(62.3%)</td>
<td>155(61.8%)</td>
<td>198(61.9%)</td>
</tr>
<tr>
<td>DM</td>
<td>23(33.3%)</td>
<td>115(45.8%)</td>
<td>138(43.1%)</td>
</tr>
<tr>
<td>Smoking</td>
<td>19(27.5%)</td>
<td>66(26.3%)</td>
<td>85(26.6%)</td>
</tr>
<tr>
<td>CAD</td>
<td>9(13%)</td>
<td>41(16.3%)</td>
<td>50(15.6%)</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>4(5.8%)</td>
<td>30(12%)</td>
<td>34(10.6%)</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>5(7.2%)</td>
<td>30(12%)</td>
<td>35(10.9%)</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>28(40.6%)</td>
<td>109(43.4%)</td>
<td>137(42.8%)</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (PVD)</td>
<td>0</td>
<td>10(4.1%)</td>
<td>4(3.1%)</td>
</tr>
</tbody>
</table>
Comparison of baseline characteristic between TIA and Minor stroke patients—There is no significant difference between demographic characteristic, risk factor association and clinical characteristic between TIA and minor stroke patients. Limb weakness (63.4%) was the most common in both groups of patients followed by speech impairment (dysarthria in 46.3% and aphasia in 12.8% patients). There is significant association of DWI positivity and minor stroke patients compared to TIA patients (p<0.01).
### Table 9: Comparison between baseline characteristic between TIA and Minor stroke patients

<table>
<thead>
<tr>
<th></th>
<th>TIA</th>
<th>Minor stroke</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>69(21%)</td>
<td>251(79%)</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>62.6 ± 13.8</td>
<td>59.4 ± 13.5</td>
<td>60.6± 13.6</td>
<td>0.13</td>
</tr>
<tr>
<td>Sex (M: F)</td>
<td>51:18</td>
<td>203:48</td>
<td>254:66</td>
<td>0.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43(62.3%)</td>
<td>155(61.8%)</td>
<td>198(61.9%)</td>
<td>0.9</td>
</tr>
<tr>
<td>DM</td>
<td>23(33.3%)</td>
<td>115(45.8%)</td>
<td>138(43%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Smoking</td>
<td>19(27.5%)</td>
<td>66(26.3%)</td>
<td>85(26.6%)</td>
<td>0.83</td>
</tr>
<tr>
<td>CAD</td>
<td>9(13%)</td>
<td>41(16.3%)</td>
<td>50(15.6%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>4(5.8%)</td>
<td>30(12%)</td>
<td>34(10.6%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>5(7.2%)</td>
<td>30(12%)</td>
<td>35(10.9%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>28(40.6%)</td>
<td>109(43.4%)</td>
<td>137(42.8%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Peripheral Vascular Disease (PVD)</td>
<td>0</td>
<td>10(4.1%)</td>
<td>4(3.1%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Limb weakness</td>
<td>45(65.2%)</td>
<td>158(62.98%)</td>
<td>203(63.4%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Dysarthria</td>
<td>31(44.9%)</td>
<td>117(46.6%)</td>
<td>148(46.3%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Aphasia</td>
<td>7(10.1%)</td>
<td>34(13.5%)</td>
<td>41(12.8%)</td>
<td>0.4</td>
</tr>
<tr>
<td>MRI DWI positive</td>
<td>29(48.3%)</td>
<td>169(92.3%)</td>
<td>198(61.8%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>MRI DWI multiple positive</td>
<td>11(18.3%)</td>
<td>53(29.0%)</td>
<td>64(26.3%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Significant vessel stenosis (&gt;50%)</td>
<td>12(15.4%)</td>
<td>66(26.3%)</td>
<td>78(24.4%)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
**Etiologic subtypes of TIA and Minor stroke patients**— According to TOAST classification, in 47 (15%) patients, the cause of stroke was large artery atherosclerosis, in 58 (18.1%) cardioembolism, in 87 (27.2%) lacunar, in 9 (2.8%) other determined etiology and in 119 (37.2%) undetermined cause. There is significant association of lacunar stroke in minor stroke patients (p < 0.01), whereas most TIA patients, etiology remained undetermined. In the large artery atherosclerosis group, 32 (68%) of patients had intracranial atherosclerosis. Carotid endarterectomy was performed in 8 patients.

![Table 10: Distribution of etiologic subtypes of TIA and Minor stroke patients](image)

<table>
<thead>
<tr>
<th>Etiologic subtypes</th>
<th>TIA</th>
<th>Minor stroke</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAA</td>
<td>9 (13%)</td>
<td>38 (15.1%)</td>
<td>47 (15%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Lacunar</td>
<td>6 (8.7%)</td>
<td>81 (32.6%)</td>
<td>87 (27.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Cardioembolism</td>
<td>7 (10.1%)</td>
<td>51 (20.3%)</td>
<td>58 (18.1%)</td>
<td>0.05</td>
</tr>
<tr>
<td>Undetermined</td>
<td>47 (68.1%)</td>
<td>72 (28.6%)</td>
<td>119 (37.2%)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Other determined</td>
<td>0</td>
<td>9 (3.6%)</td>
<td>9 (2.8%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

![Distribution of patients according to stroke subtype](image)

**Fig—4 Etiologic subtype of TIA and minor stroke patients**
New events in TIA and stroke patients at 3 months and 1 year—New cerebrovascular event occurred in 23 (7.7%) and 25 patients (8.5%) at 3 months and 1 year respectively. 14 out of 23 events (60%) occurred within 3 days of occurrence of stroke. There is no significant difference between TIA and minor stroke patients regarding association of new events. In case of cardiovascular event, 7 and 13 patients (2.2% and 4.4%) respectively, had new events at 3 months and 1 year. There were 5 deaths in 3 months of stroke, out of which 2 were vascular death and one patient died due to intracranial hemorrhage who was on anticoagulant. 2 other patient died due to non-vascular causes.

Table 11: New cerebrovascular and cardiovascular events in TIA and Minor stroke patients

<table>
<thead>
<tr>
<th></th>
<th>TIA</th>
<th>Minor stroke</th>
<th>Total</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>No of patients</td>
<td>69 (21%)</td>
<td>251 (79%)</td>
<td>320</td>
<td></td>
</tr>
<tr>
<td>Cerebrovascular event at 3 months</td>
<td>2 (2.9%)</td>
<td>21 (8.4%)</td>
<td>23 (7.2%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Cerebrovascular event at 1 year</td>
<td>3 (4.9%)</td>
<td>22 (9.4%)</td>
<td>25 (8.5%)</td>
<td>0.26</td>
</tr>
<tr>
<td>Cardiovascular event at 3 months</td>
<td>2 (2.9%)</td>
<td>5 (2%)</td>
<td>7 (2.2%)</td>
<td>0.65</td>
</tr>
<tr>
<td>Cardiovascular event at 1 year</td>
<td>4 (6.6%)</td>
<td>9 (3.8%)</td>
<td>13 (4.4%)</td>
<td>0.35</td>
</tr>
</tbody>
</table>

Predictors of recurrence of stroke at 3 months—In univariate analysis both diabetes mellitus and significant vessel stenosis (>50%) were significantly associated with recurrence of stroke. All patients who had recurrent event had ABCD2 score ≥4.
### Table 12: Predictors of recurrence of stroke

<table>
<thead>
<tr>
<th>Factors</th>
<th>Stroke recurrence</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (&gt;60 years)</td>
<td>9(5.3%)</td>
<td>0.16</td>
</tr>
<tr>
<td>Sex</td>
<td>20:3</td>
<td>0.35</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17(8.6%)</td>
<td>0.22</td>
</tr>
<tr>
<td>DM</td>
<td>15(10.9%)</td>
<td>0.01</td>
</tr>
<tr>
<td>Smoking</td>
<td>5(5.9%)</td>
<td>0.59</td>
</tr>
<tr>
<td>CAD</td>
<td>4(8.1%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>4(11.4%)</td>
<td>0.31</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>3(8.8%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>2(20%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Dyslipidaemia</td>
<td>10(7.3%)</td>
<td>0.96</td>
</tr>
<tr>
<td>ABCD (≥ 4)</td>
<td>23(100%)</td>
<td>0.11</td>
</tr>
<tr>
<td>Multiple DWI lesion</td>
<td>4(6.3%)</td>
<td>0.7</td>
</tr>
<tr>
<td>Significant vessel stenosis (&gt;50%)</td>
<td>11(14.1%)</td>
<td>0.01</td>
</tr>
<tr>
<td>LAA</td>
<td>6(12.8%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Lacunar</td>
<td>8(9.2%)</td>
<td>0.4</td>
</tr>
<tr>
<td>CE</td>
<td>7(12.1%)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

In multiple regression analysis, both diabetes [OR 2.6 CI (1.1—6.6), p<0.05] and significant vessel stenosis (>50%) [OR 3.1 CI (1.3—7.6), p<0.05] were found to be an independent predictor of recurrent stroke in TIA and minor stroke patients.

**Outcome of stroke at 3 months** – 14 out of 23 patients (60%) who had recurrence of stroke had significant disability (mRS ≥2), whereas 53 patients (17.8%) who do not have recurrence of stroke had significant disability at 3 months. During these periods only 6 patients received IV thrombolysis, out of which one patient had significant disability (mRS 3), whereas other patient had good outcome (mRS 0 or 1). No patient had symptomatic intracranial hemorrhage.
DISCUSSION

Our study investigated the short term and long-term recurrence of stroke in TIA and minor stroke patients in a tertiary care centre in south India, where round the clock stroke service is available. The study population consisted of 320 patients out of which 21% of patient had TIA.

Patients were classified according to TOAST classification. In our study in TIA group, 13%, 8.7% and 10.1% of patients were having large vessel atherosclerosis, lacunar and cardioembolism as etiology whereas in 68% of patient’s etiology remained undetermined. Levelle et al\textsuperscript{27} in their study showed comparable frequencies [26%,4.1% and 10.5% patients were having large artery atherosclerosis, lacunar and cardioembolism as etiology, whereas in 51% of patient’s etiology remained undetermined]. Similarly, in the minor stroke group, 15.1%, 32.6% and 20.3% of patients were having large vessel atherosclerosis, lacunar and cardioembolism as etiology. In 28.6% of patients the etiology was undetermined. Previous study done by Wu et al\textsuperscript{133} reported 41.8%, 22.4% and 2.8% patients were having large artery atherosclerosis, lacunar and cardioembolism as etiology of stroke. In the study, 28.8% of patients the etiology remained undetermined. Overall in our study, 14.7%, 27.2% and 18.1% of patient had large vessel atherosclerosis, lacunar and cardioembolism as etiology of stroke. These differences can be explained by regional differences in risk factors and different study population.

Hypertension (62.3% in TIA and 61.8% in minor stroke, overall 61.9% of patients), diabetes mellitus (33.3% in TIA and 45.8% in minor stroke, overall 42.2% of patients) and dyslipidaemia (40.6% in TIA and 43.4% in minor stroke, overall 42.8% of patients) were the vascular risk factors most commonly associated with study population. Levelle et al\textsuperscript{27} in their study also reported similar association of risk factors with study population.

In our study limb weakness (63.4%) and speech impairment (55%) were the predominant clinical symptoms presented by the patient which were same as reported by Levelle et al\textsuperscript{27} in their study.

The study showed a recurrence of stroke in 2.9% and 8.4% of patients with TIA and minor stroke at 3 months. Overall, recurrence rate of cerebrovascular event at 3 months is 7.2% which was
similar to the rate of stroke recurrence reported in a recent metaanalysis (6.7% (CI—5.2—8.7%).\textsuperscript{89} The recurrence rate is higher for minor stroke patients compared to TIA patients. Most of the stroke recurrence (60%) occurred within 3 days, suggesting the importance of urgent evaluation and treatment of these patients. In our study, stroke recurrence rate at one year is 8.5% which was lower compared to a metaanalysis which reported risk of recurrent of stroke at > 90 days to be 11.3%( CI 7.5—16.6%).\textsuperscript{89} But a recent study by Amarenco et al, showed that the 3 months and 1 year stroke recurrence rate was 3.7 and 5.1%, which was lower compared to our study.\textsuperscript{32} This may be related to geographic variation, resource availability and health seeking behaviour of peoples of developing countries. The current study showed a decreased trend in stroke recurrence compared to a previous study published from our centre as part of a multicentre study, suggesting improved care in urgent diagnosis and treatment for TIA and minor stroke patients.\textsuperscript{134}

In our study 2.2% and 4.4 % of patients had new cardiovascular event at 3 months and 1-year suggestive high risk of association of cardiovascular event with TIA and minor stroke patients. Previous studies also found similar rate of occurrence of cardiovascular event in TIA and minor stroke patients.\textsuperscript{93,94,95}

All our patients with TIA and minor stroke, who had stroke recurrence had ABCD2 score of 4 or more, suggesting a high sensitivity but poor specificity for prediction of new vascular event. Wardlaw et al in a recent metaanalysis reported similar findings (sensitivity 86.7 % and specificity 35.4%).\textsuperscript{103}

In our study, increasing age was not associated with increased risk of stroke in TIA and minor stroke patients. This contrasts with earlier study by Jhonston et al\textsuperscript{24} where they reported age as a predictor of stroke recurrence. But Ois et al in their study had found age was not significantly associated with further stroke recurrence in both TIA and minor stroke patients.\textsuperscript{76}

Among vascular risk factor, diabetes mellitus was found to be an independent predictor of stroke recurrence in our patient. Similar findings had been reported by Chen et al in their study as both diabetes and metabolic syndrome independently associated with increased stroke risk in TIA and minor
stroke patient. However, in our study we have not evaluated the association of metabolic syndrome with stroke recurrence.

In our study, both intracranial and extracranial significant vessel stenosis (>50%) found to be an independent predictor of stroke recurrence at 3 months, irrespective of the stroke subtype. Coutts et al in their study also reported similar findings as significant vessel stenosis as a strong predictor of stroke recurrence.

Our study reported stroke recurrence rate as 12.8%, 12.1% and 9.2% in Large artery atherosclerosis, cardioembolism and lacunar stroke subtype respectively. We do not find any significant association between stroke recurrence and individual stroke subtype. This contrasts with findings reported by most of the previous studies where a strong association was found with large artery atherosclerosis and early recurrence of stroke. But Ay et al in their study did not find large artery atherosclerosis as independent predictor of recurrent stroke in TIA patients. Previous study done by Lovett et al reported as 19.2%, 11.9% and 3.4% recurrence rate of stroke in LAA, cardioembolism and lacunar etiology. Ohara et al have reported high risk of recurrent stroke (mostly lacunar) in TIA patients without LAA or AF which may be specific to Asian populations compared to western population. In our study also there is higher recurrence of stroke in lacunar group compared to western data. The low risk of recurrent stroke in large artery atherosclerosis in our population may be explained by geographic variation, early intervention in the form of early revascularization surgery and optimum medical management and lower prevalence of intracranial (32%) than extracranial stenosis.

In our study, 60% of patient who had recurrence of stroke had significant disability (mRS ≥2), whereas 17.8% who do not have recurrence of stroke had bad outcome at 3 months. This is in accordance with the study done by Coutts et al, suggesting that a substantial portion of patients remained disabled after TIA and minor stroke. During these periods only 6 patients received IV thrombolysis, out of which one patient had significant disability (mRS 3), whereas rest of the patient had good outcome (mRS 0 or 1). No patients had symptomatic intracranial hemorrhage.
Strength of the study—

The strength of the study is early inclusion of the patient within 48 h of the index event. Acute stroke patients were selected because these are the patients who are likely evaluated in detail in the stroke care unit. Patients were evaluated by stroke neurologist, mimics were excluded from study as far as possible.

Limitation of the study—

It was a retrospective study so chances of bias are high. Moreover, the record for compliance of treatment were not available. Only those patients presented within 48 hours of index event were included in the study, hence patient present late were not studied.
CONCLUSION

Our study showed that urgent treatment after TIA and minor stroke is associated with reduced risk of stroke recurrence. They are also having increased risk of both short term and long term cardiovascular event subsequently. Both diabetes mellitus and significant vessel stenosis are independent predictor of stroke recurrence. We have also found that a substantial portion of patient remained disabled at 3 months. The role of IV thrombolysis in decreasing disability needs to be validated with further study. Patients, who have significant vessel stenosis being at highest risk of disability in view of recurrent event, early intervention will be most beneficial in this group of patients.
REFERENCES


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86. Amarenco P, Labreuche J, Lavallée PC. Patients with transient ischemic attack with ABCD2 <4 can have similar 90-day stroke risk as patients with transient ischemic attack with ABCD2 ≥4. Stroke 2012; 43:863–5.


111. L. Marquardt, W. Kuker, A. Chandratheva, O. Geraghty, P. M. Rothwell; Incidence and prognosis of ≥50% symptomatic vertebral or basilar artery stenosis: prospective population-based study Brain 2009; 132: 982–88.


# ANNEXURE

## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>AHA</td>
<td>American Heart Association</td>
</tr>
<tr>
<td>ASA</td>
<td>American Stroke Association</td>
</tr>
<tr>
<td>CEA</td>
<td>Carotid Endarterectomy</td>
</tr>
<tr>
<td>CHD</td>
<td>Coronary heart disease</td>
</tr>
<tr>
<td>CKD</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>CTA</td>
<td>Computed Tomography Angiography</td>
</tr>
<tr>
<td>DWI</td>
<td>Diffusion-weighted imaging</td>
</tr>
<tr>
<td>ED</td>
<td>Emergency Department</td>
</tr>
<tr>
<td>HTN</td>
<td>Hypertension</td>
</tr>
<tr>
<td>LAA</td>
<td>Large artery atherosclerosis</td>
</tr>
<tr>
<td>MDRD</td>
<td>Modification of Diet in Renal Disease</td>
</tr>
<tr>
<td>MIS</td>
<td>Minor Ischemic Stroke</td>
</tr>
<tr>
<td>MRA</td>
<td>Magnetic Resonance Angiography</td>
</tr>
<tr>
<td>NASCET</td>
<td>North American Symptomatic Carotid Endarterectomy Trial</td>
</tr>
<tr>
<td>NCCT</td>
<td>Non-contrast Computed Tomography</td>
</tr>
<tr>
<td>NIHSS</td>
<td>National Institute of Health Stroke Scale</td>
</tr>
<tr>
<td>OCSF</td>
<td>Oxford community stroke project</td>
</tr>
<tr>
<td>OGTT</td>
<td>Oral Glucose Tolerance Test</td>
</tr>
<tr>
<td>OXVASC</td>
<td>Oxford Vascular Study</td>
</tr>
<tr>
<td>PVD</td>
<td>Peripheral vascular disease</td>
</tr>
<tr>
<td>TIA</td>
<td>Transient Ischemic stroke</td>
</tr>
<tr>
<td>TOAST</td>
<td>Trial of ORG 10172 in Acute Stroke Treatment classification</td>
</tr>
</tbody>
</table>
PROFORMA FOR STUDY ON
“Short term and long term risk of vascular events following early treatment of TIA and minor stroke”

1.1. Patient unique identification number-

1.2. Age --------- years

1.3 Sex ---------- 1. Male 2. female

1.4 Date of admission. ------------- Time ---------

1.5. Date of symptom onset--------- Time---------

1.6 Phone No 1: -------------------------

1.7 Phone No2: -------------------------

2. Risk factors (1=yes, 2=No)

2.1. Hypertension----------- Duration in years -----------

2.2. Diabetes mellitus---------- Duration in years -----------

2.3. Current smoking--------- pack years -----------

2.3a Ex-smoker..............Stopped ------------years back

2.3.b. Drug addiction -----------

2.3. c. Alcoholism-------------

2.4. Coronary artery disease----- Duration in years -----------

2.5. Valvular heart disease------ Duration in years -----------

2.5. a. if yes, Specify -----------

2.5. b. Prosthetic valve -----------

2.5. c. Sick sinus syndrome -----------

2.6. Congestive heart failure ------- Duration in years -----------

2.7. Peripheral vascular disease------
2.8. Hyperlipidaemia---------------- Duration in years----------------

2.9. Atrial fibrillation---------------- Duration in years----------------

2.9.1. If patient on pacemaker ----------------

2.1.1. History of prior stroke --------- 2.1.1. a. Date of ictus---------

2.1.2. History of prior TIA-------- 2.1.2.b. Date of ictus----------

2.1.3. History of migraine ----------------

2.1.4. Known carotid disease------------

2.1.5. Patient on treatment ----------------


2.1.7. History of DVT ---------

2.1.8. Family history of stroke/CAD (first degree relatives) ---------1. Yes 2. No (male<55yrs and female <65 years of age)

2.1.8. Comments----------------------------------------

3. Symptoms (1=yes, 2=No)


3.2. Weakness --------------------- 1. face alone 2. arm 3. leg 4. arm and leg 5. Face arm and leg 6. None

3.3. Numbness/paraesthesia --------


3.5. Vertigo----------------

3.6. Ataxia----------------

3.7. Confusion-------------------- 3.7.a. Loss of consciousness ----------------

3.8. Headache -------------------

3.9. Seizures -------------------

3.10. Symptom recovery after how many hours-----------------

4. Clinical Examination (1=yes, 2=No)

4.1. Pulse rate------------------- (If Regular =1, Atrial fibrillation =2)
4.2. Blood pressure at ER Systolic--------- diastolic ------- (first documented BP)

4.3. Bruit ------------

4.4. Weakness ---------------

4.5. Numbness---------------

4.6. Cerebellar signs-----------

4.7. Aphasia------------

4.8. Dysarthria ------------

4.9. Hemianopia-------------

4.9a. Central retinal artery occlusion---------

4.9.1. Hemi spatial neglect --------

4.9.2. Final impression---------

1. Right hemispheric 2. Left hemispheric 3. Posterior circulation 4. undetermined

4.9.3 NIHSS at admission ----------

4.9.4 mRS at admission------------

4.9.5 GCS on admission-------------

5. Investigations——

5.1. Blood glucose in ER--------

FBS-

PPBS

HbA1c-

5.2. Serum cholesterol-----------

5.3. LDL---------

5.4. HDL---------

5.5. Serum triglycerides. --------


If valve disease, specify ----------------

Done

5.9. Renal function—— Creatinine——- BUN———

5.10.1. ANA —— 1. positive 2. Negative 3. Not done


5.10.3. Homocysteine ————

5.10.4. APLA ———— 1. Positive 2. Negative 3. Not done


5.10.5.a. If done, specify ————

6. Diagnostic imaging——

  Ischaemic changes 5. Not done

6.1. A Territory ———— 1. ICA 2. ACA 3. MCA-complete 4. MCA-Inf div 5. MCA sup div
  6. MCA subcortical 7. Posterior circulation

6.2. CT angio neck ———— 1. Normal 2. abnormal 3. not done

6.2.1. If abnormal, specify ————

6.3. MRI scan ———— 1. DWI negative 2. DWI positive single lesion 3. DWI –
  Multiple lesions 4. Not done

6.3.1. Arterial territory of acute infarct ———— 1. ICA 2. ACA 3. MCA-complete 4. MCA-Inf
  div 5. MCA sup div 6. MCA subcortical 7. Posterior circulation

6.3.1. a. FLAIR —

Fazekas scale of white matter ischaemic changes——

periventricular white matter (PVWM)——
0 = absent, 1 = “caps” or pencil-thin lining, 2 = smooth “halo”, 3 = irregular periventricular signal extending into the deep white matter

Deep white matter (DWM)——
0 = absent, 1 = punctate foci, 2 = beginning confluence, 3 = large confluent areas

6.3.3. SWI ———— 1. microbleeds 2. hemorrhagic transformation of infarct 3. negative 4. Not done

6.4. MRA neck ———— 1. normal 2. abnormal 3. Not done

6.4.1. If abnormal specify ————

6.4.2. MRA intracranial ———— 1. normal 2. abnormal 3. Not done
6.4.3. If abnormal, specify

6.5. Carotid Doppler

1. normal
2. abnormal
3. Not done

6.5.1. If abnormal, specify

6.6. DSA

1. normal
2. abnormal
3. Not done

6.6.1. If abnormal specify

6.7. Final impression on vessel status (symptomatic vessel)

1. <50% stenosis
2. Moderate stenosis (50-69%)
3. severe stenosis (>70%)
4. arterial dissection
5. vessel occlusion
6. Normal

6.7.1. Vessel involved

1. extracranial ICA
2. intracranial ICA
3. MCA M1 M2
4. ACA
5. BA
6. VA
7. PCA
8. SCA
9. PICA
10. ICA

6.7.2. Side of involvement of vessel

1. Right
2. Left
3. Bilateral

6.7. Stroke subtype

1. large artery atherosclerosis
2. Cardioembolic
3. lacunar
4. Other Specific causes
5. Undetermined

6.7. a. If cardioembolic, mention cause

6.7. b. If specific cause

1. Dissection
2. Prothrombotic
3. Vasculitis
4. Moya Moya

6.8. Arterial territory

1. ACA
2. MCA
3. PCA
4. VA
5. BA
6. ICA
7. SCA
8. PICA

7. Prognostic score

7.1—ABCD2 score

7.2—ABCD3—I score

8. Treatment at discharge (1=yes, 2= No)

8.1. Aspirin

8.2. Clopidogrel

8.3. Aggrenox

8.4. Warfarin

8.5. Statins

8.6. Antihypertensive

9. Outcome

9.1. Date of discharge

9.4.1 NIHSS at discharge-------------

9.4.2 Modified Rankin Scale at discharge----------

9.4.3 Any New event during hospital stay Yes/No -------

9.4.4 If Yes
   a. TIA, b. Minor Stroke, c. Other
   a. If TIA
      1. Right hemispheric 2. Left hemispheric 3. Posterior circulation 4. undetermined
   b. If Minor stroke
      1. Right hemispheric 2. Left hemispheric 3. Posterior circulation 4. undetermined

Date of the event----

9.4.5 Any cardiovascular event during hospital stay----Yes/No
   If yes 1. Myocardial infarction 2. CHF 3. Arrhythmia-------

Date of the event---

9.4.6 Any death---yes/no

Cause of death----

10. FOLLOW UP AT 3 MONTHS——

10.1. mRS at 3 months-------------------

10.2 Any New event during 3 months Yes/No -------

   If Yes
   a. TIA, b. Minor Stroke, c. Other
   a. If TIA
      1. Right hemispheric 2. Left hemispheric 3. Posterior circulation 4. undetermined
   b. If Minor stroke
      1. Right hemispheric 2. Left hemispheric 3. Posterior circulation 4. undetermined

Date of the event----

10.3 Any cardiovascular event during 3 month----Yes/No
   If yes 1. Myocardial infarction 2. CHF 3. Arrhythmia-------
Date of the event—

10.4 Any death---yes/no

Cause of death----

**FOLLOW UP AT 1 YEAR----**

11.1. mRS at 1 year-------------

11.2 Any New event during 1 year    Yes/No -------
   If Yes
      a. TIA, b. Minor Stroke, c. Other 
    a. If TIA
       1. Right hemispheric 2. Left hemispheric 3. Posterior circulation4.undetermined 
    b. If Minor stroke
       1. Right hemispheric 2. Left hemispheric 3. Posterior circulation4.undetermined 

Date of the event----

11.3 Any cardiovascular event during 1 year----Yes/No 
   If yes 1. Myocardial infarction---- 2. CHF------ 3. Arrhythmia-------

Date of the event—

11.4 Any death---yes/no

Cause of death----
Institutional Ethics Committee
(IEC Regn No. ECR/189/inst/KL/2013)

Dr. Hemanga Kumar Dhing
Senior Resident
Department of Neurology
SCTIMST, Thiruvananthapuram

Dear Dr. Hemanga Kumar Dhing,

The Institutional Ethics Committee reviewed and discussed your application to conduct the study entitled “SHORT TERM AND LONG TERM RISK OF VASCULAR EVENTS FOLLOWING EARLY TREATMENT OF TIA AND MINOR STROKE” (IEC/879) on 16th April, 2016.

The following documents were reviewed:

1. Covering letter addressed to the Chairperson, IEC, SCTIMST, dated 21.03.2016 with check list
2. TAC Approval Letter
3. IEC Application Form
4. Project Proposal
5. Proforma
6. CV of Principal Investigator and Co- Investigators
The following members of the Ethics Committee were present at the meeting held on 16th April, 2016 at G. Parthasarathi Board Room, AMCHSS, SCTIMST

<table>
<thead>
<tr>
<th>SL. No.</th>
<th>Member Name</th>
<th>Highest Degree</th>
<th>Gender</th>
<th>Scientific/Non Scientific</th>
<th>Affiliation with Institution(s)</th>
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<tbody>
<tr>
<td>1.</td>
<td>Justice Gopinathan, P.S.</td>
<td>BSc, LLB</td>
<td>Male</td>
<td>Legal Expert (Chairperson)</td>
<td>No</td>
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<tr>
<td>2.</td>
<td>Dr. Aasha Kishore</td>
<td>MD, DM</td>
<td>Female</td>
<td>Clinician (Neurologist)</td>
<td>Yes</td>
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<tr>
<td>3.</td>
<td>Shri. O.S. Neelakantan Nair</td>
<td>BE</td>
<td>Male</td>
<td>Engineer</td>
<td>Yes</td>
</tr>
<tr>
<td>4.</td>
<td>Dr. Meenu Hartharan</td>
<td>DM</td>
<td>Female</td>
<td>Clinician (Gastro-Enterologist)</td>
<td>No</td>
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<tr>
<td>5.</td>
<td>Dr. Rema M. N</td>
<td>MD</td>
<td>Female</td>
<td>Pharmacologist</td>
<td>No</td>
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<tr>
<td>6.</td>
<td>Dr. V. Raman Kutty</td>
<td>MPH (Harvard)</td>
<td>Male</td>
<td>Public Health</td>
<td>Yes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>MPhil, MD</td>
<td></td>
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<tr>
<td>7.</td>
<td>Dr. K R S Krishnan</td>
<td>ME, PhD</td>
<td>Male</td>
<td>Biomedical Scientist/Engineer</td>
<td>No</td>
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<tr>
<td>8.</td>
<td>Dr. Kala Kesavan, P</td>
<td>MD</td>
<td>Female</td>
<td>Pharmacologist</td>
<td>No</td>
</tr>
<tr>
<td>9.</td>
<td>Smt. Sathri Nair</td>
<td>MA</td>
<td>Female</td>
<td>Lay Person</td>
<td>No</td>
</tr>
<tr>
<td>10.</td>
<td>Dr. Christina George</td>
<td>MD</td>
<td>Female</td>
<td>Psychiatrist</td>
<td>No</td>
</tr>
<tr>
<td>11.</td>
<td>Dr. Mala Ramanathan</td>
<td>MSc, PhD, MA</td>
<td>Female</td>
<td>Ethicist/Social Scientist (Member Secretary)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

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
“STUDY OF SHORT TERM AND LONG TERM RISK OF VASCULAR EVENTS FOLLOWING EARLY TREATMENT OF TIA AND MINOR STROKE”

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