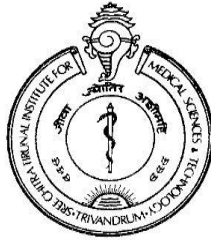


**SREE CHITRA TIRUNAL INSTITUTE
FORMEDICAL SCIENCES AND TECHNOLOGY
THIRUVANANTHAPURAM, KERALA**



**CAROTID ENDARTERECTOMY FOR SYMPTOMATIC
CAROTID STENOSIS: DIFFERENCES IN PATIENT
PROFILE IN A LOW-MIDDLE INCOME COUNTRY**

*Project work submitted in partial fulfilment of the rules and regulations for
the degree of Post Doctoral Fellow in Stroke of
Sree Chitra Tirunal Institute for Medical Sciences and Technology*

By

Dr. Naveen Kumar. P

PDF in Stroke

Month and Year of Submission: November 2022

Department of Neurology

Sree Chitra Tirunal Institute for Medical Sciences and Technology

Thiruvananthapuram

2022

DECLARATION

I, Dr.Naveen Kumar. P, hereby declare that this project was undertaken by me under the supervision of the faculty, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology.

Thiruvananthapuram,
Date: 28-11-2022

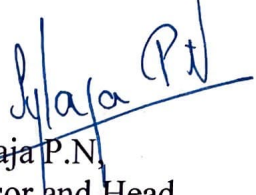


Dr. Naveen Kumar. P

Forwarded :

The candidate, Dr Naveen Kumar. P, has completed the project under my guidance.

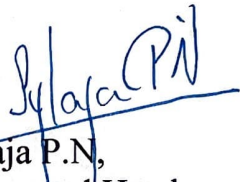
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Dr. Naveen Kumar. P

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SYNOPSIS

Introduction:

Carotid Endarterectomy (CEA) is the standard treatment for patients with symptomatic carotid stenosis. Data from Low- and Middle-Income Countries (LMIC) is sparse on CEA and its outcomes. We aimed to describe the profile of our patients, and factors associated with periprocedural cerebral ischemic events in patients with symptomatic carotid stenosis who underwent CEA in our institute.

Methods:

Retrospective review of patients with symptomatic carotid stenosis(50-99%) who underwent CEA between January 2011 and December 2021 was done. Clinical and imaging parameters and their influence on periprocedural cerebral ischemic events were analysed.

Results:

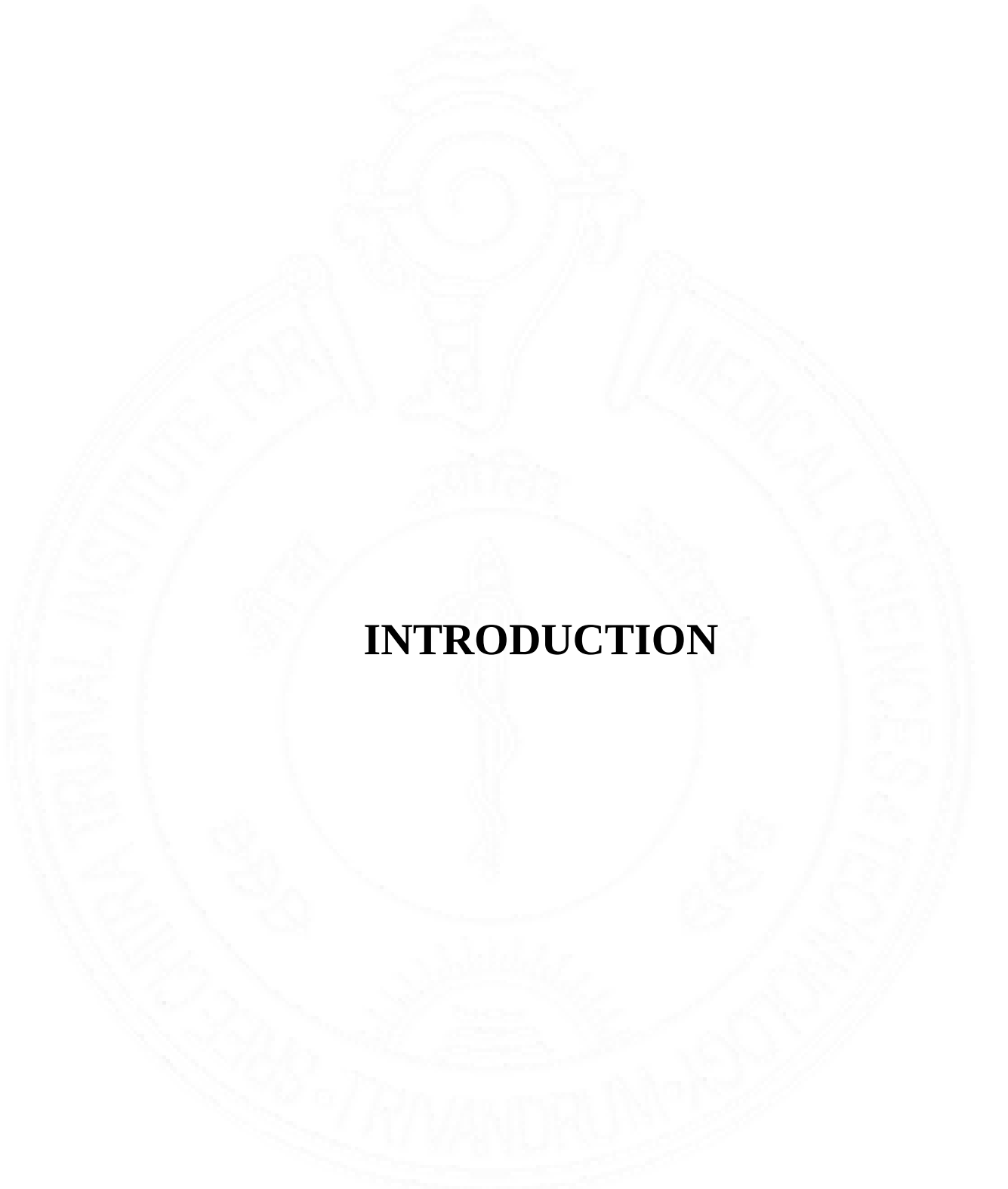
Of the 319 patients (77% males) with a mean age of 64 years (SD ± 8.6), 207 (65%) presented only after a stroke. Majority (85%) had high grade stenosis ($\geq 70\%$) of the symptomatic carotid. The mean time to CEA was 50 days (SD ± 36), however only 26 patients (8.2%) underwent surgery within 2 weeks. Minor strokes and TIA occurred in 2.2%, while major strokes and death occurred in 4.1% patients. None of the clinical or imaging parameters predicted the periprocedural cerebral ischemic events. The presence of co-existing significant ($\geq 50\%$) tandem intracranial atherosclerosis (n=77,

24%) or contralateral occlusion (n=24, 7.5%) did not influence the periprocedural stroke risk.

Conclusion:

There is a delay in patients undergoing CEA for symptomatic carotid stenosis.

Majority have high grade stenosis and present late only after a stroke reflecting a lack of awareness. CEA can be performed safely even in patients with significant intracranial tandem stenosis and contralateral carotid occlusion.



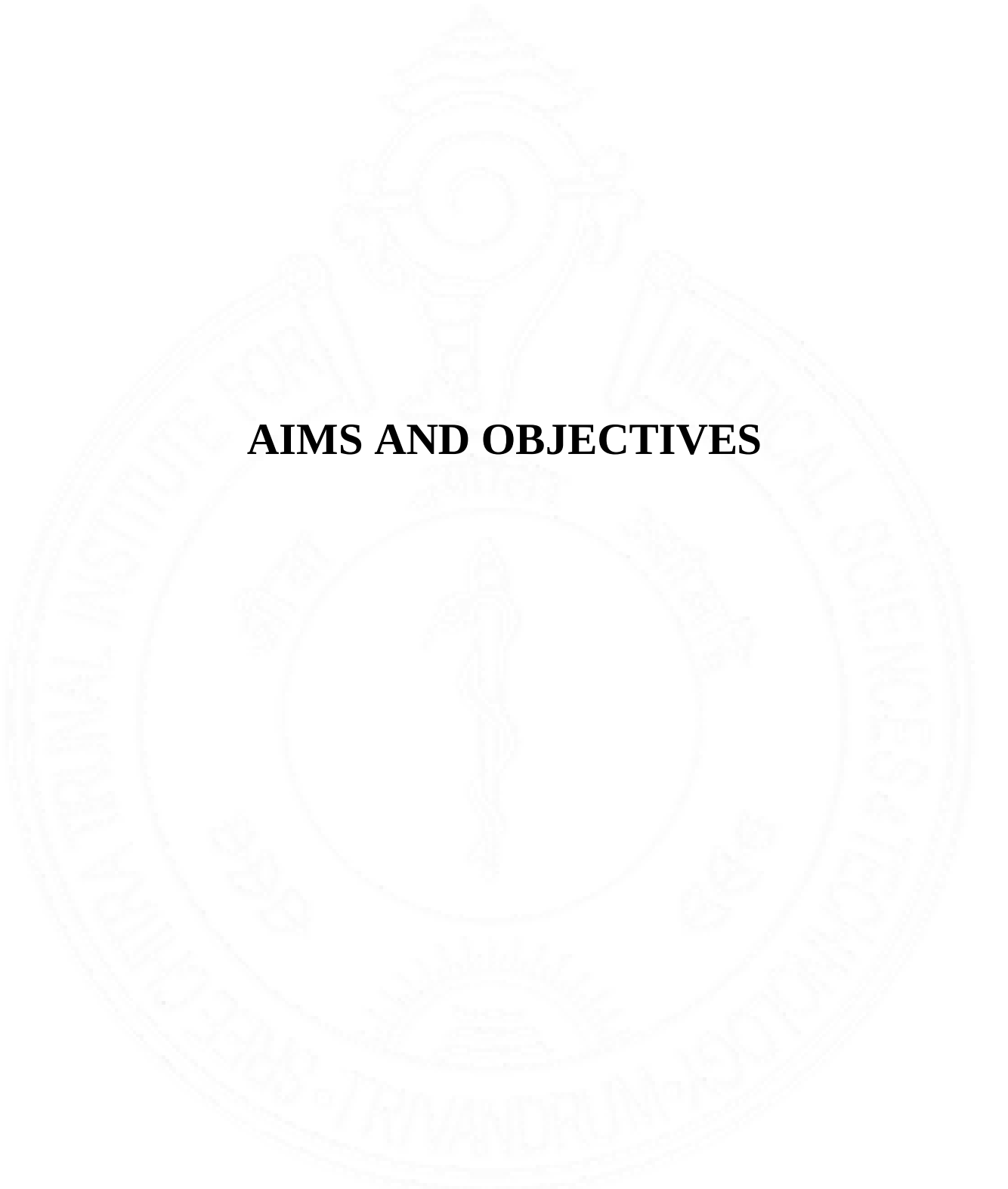
INTRODUCTION

Introduction

Large vessel atherosclerotic disease constitutes approximately 20% to 30% of all ischemic strokes[1]. Based on the three major trials (The North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST) and Veteran Affairs Trial 309) [2–4] and a pooled analysis of the same[5], the current recommendation is to perform carotid endarterectomy (CEA) in patients with symptomatic carotid stenosis ($\geq 50\%$) in centers with perioperative morbidity and mortality less than 6%[6]. Recent trials also affirm that CEA is the standard of care with a lower incidence of periprocedural stroke[7].

However, randomized controlled trials (RCTs) include large volume centers with highly specialized surgeons and their results may not be replicable in all patient populations. While the majority of patients in the western world undergo CEA even after a Transient Ischemic Attack (TIA)[8–11], it is the reverse in low and middle income countries (LMIC) where CEA is done most often after a stroke[12–14] and tend to be delayed compared to the guideline recommended timing within 2 weeks.

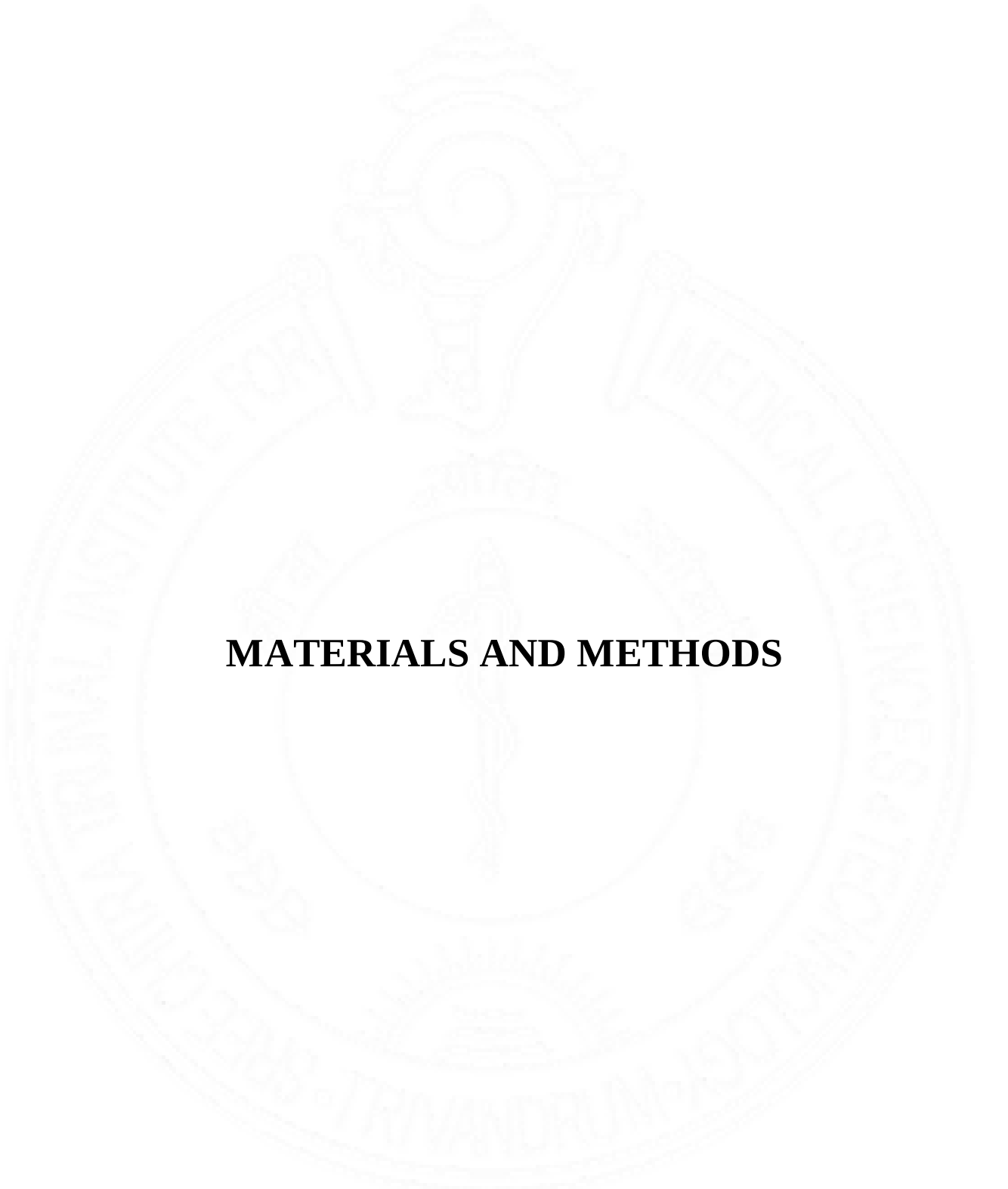
In this background, the application of these guidelines in LMIC requires an understanding of the profile of patients who undergo carotid revascularization. There is lack of data on the clinical profile, imaging characteristics, timing and outcome of CEA in patients who present with symptomatic carotid stenosis from a country like India.



AIMS AND OBJECTIVES

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1. We aimed to describe the clinical profile of patients with symptomatic carotid stenosis who underwent CEA in our institute and analysed the factors associated with perioperative vascular events.
2. The primary outcome was the occurrence of perioperative cerebral ischemic events that included TIA and stroke.
3. Secondary outcome included a composite of stroke, TIA, cardiac events or death perioperatively.



MATERIALS AND METHODS

METHODS

This study was a retrospective review of prospectively collected data of all patients aged >18 years with symptomatic carotid artery stenosis ($\geq 50\%$) who underwent carotid endarterectomy in the Comprehensive stroke care centre, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala, between 2011 and 2021. The clinical profile of the patients, including the vascular risk factors, clinical characteristics, the admission stroke severity assessed using the National Institute of Health Stroke Scale (NIHSS), disability status assessed using modified Rankin Scale (mRS) were collected. The imaging characteristics such as the pattern of infarcts were assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the brain. The vessels affected both ipsilateral and contralateral, percentage of luminal stenosis both extra and intracranial were assessed through imaging modalities like CT angiography (CTA), MR angiography (MRA), Digital Subtraction Angiography (DSA) or neck vessel doppler. In patients with more than one vascular imaging assessments, DSA was chosen as the modality of review whenever available. When DSA was unavailable, CT angiogram or Contrast enhanced MRA were used with equal weightage given to both. MR TOF angiogram was taken for assessment only when other modalities of vessel assessment were unavailable. The NASCET method for estimating the percentage of stenosis was used in the study. An extracranial carotid stenosis $\geq 70\%$ was taken as high grade. Both intracranial and extracranial stenosis as well as the presence or absence of ulcer or thrombus of ipsilateral and contralateral vessels were noted. The presence of intracranial stenosis $\geq 50\%$ was considered significant. The patterns of infarcts were classified as embolic or hemodynamic or a

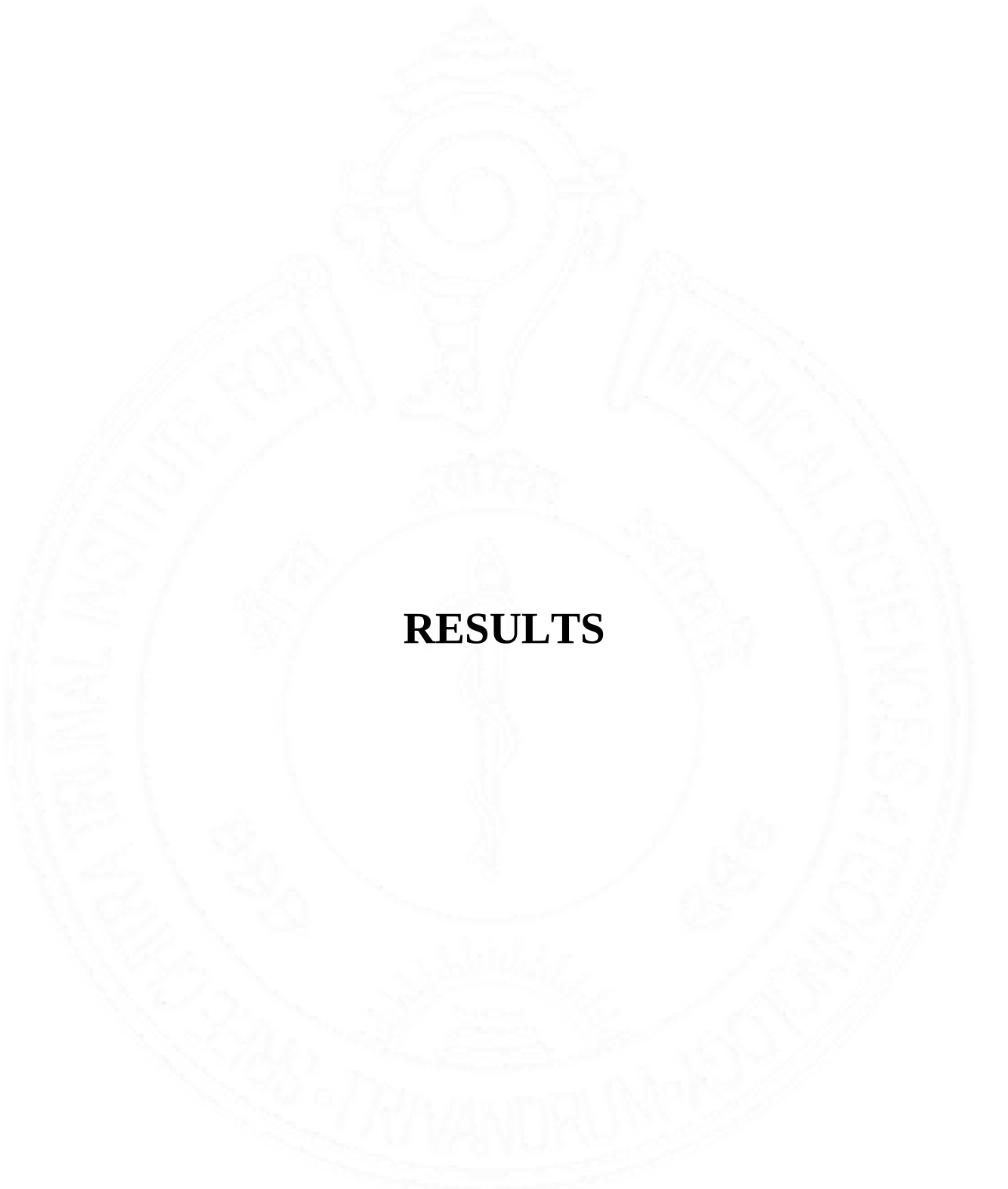
combination of both. Territorial infarcts with or without fragmentation, multiple small infarcts in ICA territory were taken as embolic pattern and those infarcts in cortical watershed and internal watershed areas were included under hemodynamic pattern. The timing of CEA from the onset of the symptoms and periprocedural TIA/stroke, cardiac events or any other procedural complications including reperfusion injury, wound hematoma or cranial neuropathy were also collected. Post procedural cardiac events were defined by presence of typical cardiac chest pain, with rise in troponins or dynamic changes in electrocardiogram or new onset regional wall motion abnormalities in echocardiogram. The primary outcome was the occurrence of perioperative cerebral ischemic events that included TIA and stroke. Secondary outcome included a composite of stroke, TIA, cardiac events or death perioperatively.

Statistical analysis:

The statistical analysis was performed using Intercooled STATA 14.1 software package (StataCorp, Texas, USA). The timing of CEA was divided into early (≤ 14 days) and late (>14 days) after the onset of symptoms, for analysing the relationship to perioperative events. The association of demographic, clinical and radiological characteristics of the patients with perioperative cerebral ischemic events were assessed using Chi-square test or Fisher's exact test as appropriate. A p value <0.05 was deemed significant.

Ethical considerations:

The study protocol was reviewed and approved by the Institutional Ethics Committee, approval number: SCT/IEC/1896/AUGUST/2022. The study was granted an exemption from requiring informed consent by our Institutional Ethics Committee as it was a review of retrospective data.



RESULTS

RESULTS

Between 2011 and 2021, there were 472 patients who were taken up for carotid revascularisation. Of these, 61 underwent carotid stenting while 411 had carotid endarterectomy. Among 411 patients, we excluded those who underwent the procedure for asymptomatic carotid stenosis and those with remote symptomatic carotid stenosis, defined by last symptom onset more than 6 months ago.

There were 319 patients of whom 247 (77%) were males. The mean age of the patients was 64 years (SD ± 8.6). The most common presentation was stroke ($n=208, 65\%$). Of those who had presented with stroke, 40% had prior TIAs. The median time to undergo CEA was 39 days (range 4-180), and 26 patients (8.2%) underwent surgery within 2 weeks.

Majority of the patients ($n=270, 85\%$) had high grade stenosis ($\geq 70\%$) of the symptomatic carotid, while 77 (24%) had co-existent tandem significant ($>50\%$) intracranial stenosis.

About 63 patients (19.75%) had an ulcerated plaque in ipsilateral carotid while 24 patients (7.5%) had a contralateral carotid artery occlusion.

The demographic, clinical, risk factor profile and imaging patterns of our patients are shown in Table 1.

Table 1: Clinical and imaging characteristics of the study population

Characteristics	Number (N=319)
Mean age (SD)	64 ($\pm$ 8.6)
Males (%)	247 (77%)
Hypertension (%)	269 (84.3%)
Diabetes (%)	198 (62%)
Smoking (%)	71 (22.2%)
Coronary artery disease (%)	70 (21.9%)
Post Coronary artery Bypass Surgery (%)	18 (5.6%)
Dyslipidemia (%)	99 (31%)
Peripheral vascular disease (%)	33 (10.3%)
Renal dysfunction (%)	51 (15.9%)
Initial Event	
Retinal TIA	20 (6%)
Hemispheric TIA	117 (37%)
Stroke	183 (57%)
Presenting event	
Retinal TIA	16 (5%)
Hemispheric TIA	93 (29%)
Stroke	208 (65%)
Median NIHSS prior to surgery (IQR)	1 (0-3)
Median duration of timing of procedure from the initial event in days (range)	39 (4-180)
Underwent surgery within 2 weeks (%)	26 (8.2%)
Median duration of hospital stay in days(SD)	9 ($\pm$ 4.9)
Side of surgery	
Left CEA	161 (50.5%)
Right CEA	158 (49.5%)
Infarcts	
Single	47 (15%)

Multiple	230 (72%)
Pattern of infarcts	
Embolic	211 (66%)
Hemodynamic	195 (61%)
Combination of embolic and hemodynamic	129 (40%)
Contralateral infarcts	46 (14%)
Vessel imaging	
Digital Subtraction Angiography	23 (7.2%)
Computed Tomography angiography	258 (80.8%)
Magnetic Resonance Angiography	104 (32.6%)
Neck vessel Doppler	230 (72.1%)
High grade ($\geq 70\%$) stenosis of symptomatic carotid	270 (85%)
Ulcerated plaque	63 (20%)
Tandem Intracranial ($\geq 50\%$) stenosis of symptomatic side	77 (24%)
Contralateral carotid occlusion	24 (7.5%)

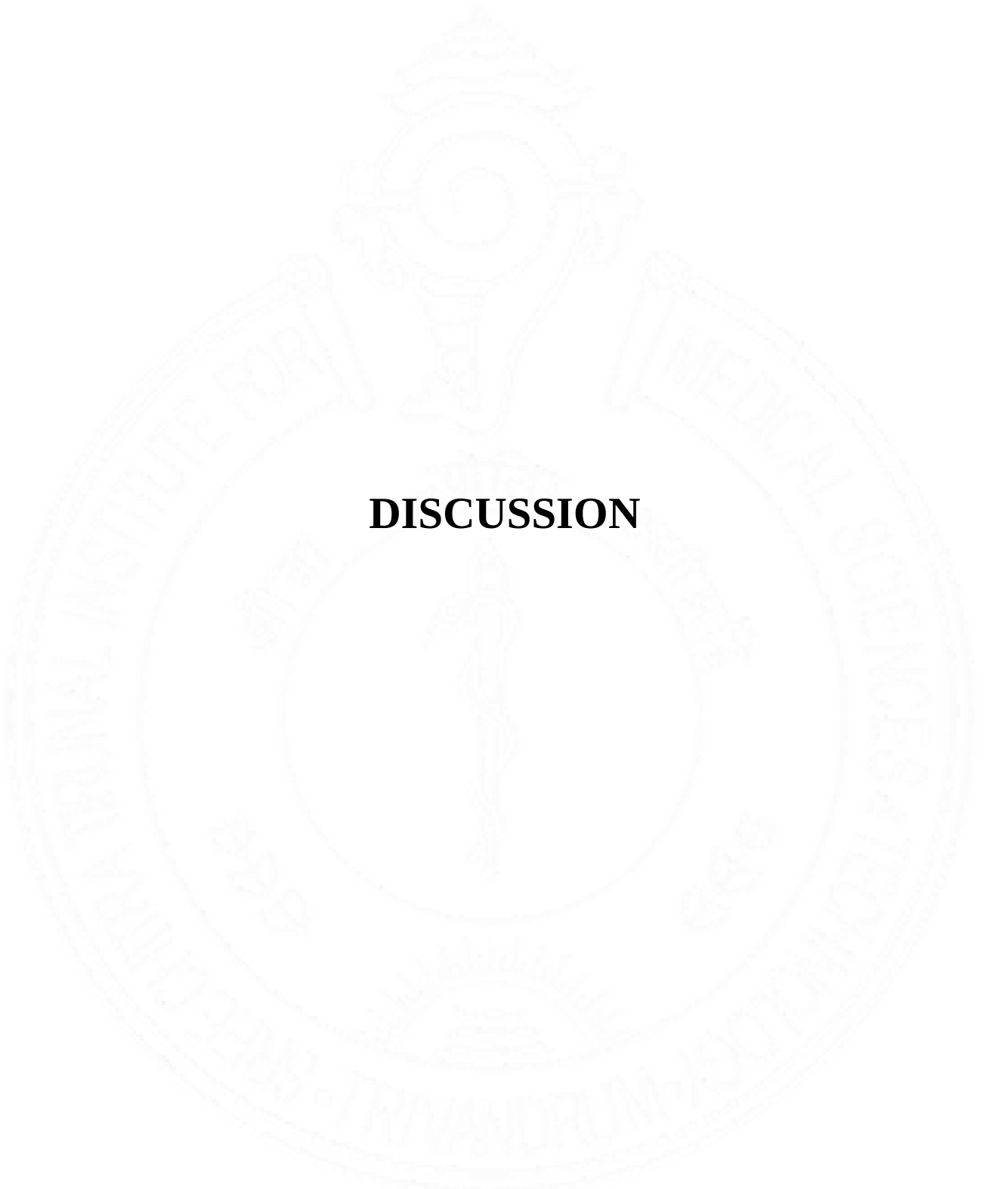
The primary endpoint of perioperative cerebral ischemic events was noted in 6.1% patients, with minor strokes and TIA in 2.1%, and major strokes in 4% patients. Post procedural acute coronary syndromes were noted in 15 (4.7%) patients. A composite endpoint of periprocedural stroke, death or cardiac event was noted in 31 patients (9.7%). There were 2 patients who had perioperative mortality, one of whom had a preoperative renal failure and succumbed to an acute coronary syndrome post procedure. The other patient had a major ipsilateral stroke. Other complications like transient cranial neuropathy, wound hematoma and hyperperfusion syndrome occurred in 7.8%, 3.1% and 0.9% of patients respectively. The baseline vascular risk factors or the type of the initial vascular event (TIA or stroke) did not influence the risk of post-operative ischemic events as detailed in Table 2. However,

there was a trend for a higher incidence of post-operative stroke or TIA among those who underwent the procedure within 2 weeks, although not statistically significant ($P=0.068$). The presence of co-existing significant tandem intracranial atherosclerosis did not predict the risk of periprocedural cerebral ischemic events ($P=0.691$). No patient with a contralateral ICA occlusion had an adverse event($P=0.398$).

Table 2. Factors associated with perioperative ischemic events

Variable	Total (N=319)	Patients with ischemic events, n(%)	P value
Study population	319	20(6.3)	
Age			0.278
<65 years	149	7(4.7)	
≥65 years	170	13(7.7)	
Sex			0.969
Male	247	15(6.1)	
Female	72	5(6.9)	
Hypertension			0.376
No	50	5(10)	
Yes	269	15(5.6)	
Diabetes mellitus			0.844
No	121	8(6.6)	
Yes	198	12(6.1)	
Smoking			0.267
No	248	18(7.3)	
Yes	71	2(2.8)	
Coronary artery disease			0.288
No	249	18(7.2)	
Yes	70	2(2.9)	
Peripheral arterial disease			0.728
No	286	19(6.6)	
Yes	33	1(3.8)	
Dyslipidemia			0.163
No	220	11(5)	
Yes	99	9(9.1)	
Serum creatinine			0.801
≤1.3mg/dL	268	16(5.9)	
>1.3mg/dL	51	4(7.8)	
Timing of CEA			0.068
≤14 days	26	4(15.4)	
>14 days	293	16(5.5)	

Type of initial ischemic event			
Retinal TIA	13	0(0)	>0.999
Hemispheric TIA	99	6(6.1)	
Stroke	207	14(6.8)	
Symptomatic extracranial stenosis			>0.999
<70% stenosis	49	3(6.1)	
≥70% stenosis	270	17(6.3)	
Ulcerated plaque			0.715
No	256	15(5.9)	
Yes	63	5(7.9)	
Ipsilateral intracranial stenosis			0.691
<50% stenosis	242	14(5.8)	
≥50% stenosis	77	6(7.8)	
Contralateral carotid occlusion			0.398
No	295	20(6.8)	
Yes	24	0(0)	
Pattern of infarcts			0.707
Embolitic			
No	108	6(5.6)	
Yes	211	14(6.6)	0.189
Hemodynamic			
No	124	5(4.8)	
Yes	195	15(7.7)	



DISCUSSION

DISCUSSION

The major findings in our study was that a large proportion of our patients for carotid endarterectomy presented late after the ischemic event, mostly after a stroke rather than TIA, and had high grade stenosis of the symptomatic carotid. None of the clinical or imaging features including co-existent tandem significant intracranial atherosclerotic disease or a contralateral carotid occlusion predicted perioperative cerebral ischemic events.

Our patients were predominantly elderly males, that is similar to the existing literature.

Similar to the data from large registries there was no difference in the perioperative outcomes with respect to gender[15,16]. Only 23% of our patients were females, and this may be attributed to the prevailing gender and cultural bias, the perception that women are at higher risk for periprocedural events and the lesser benefit in women referred late for surgery.

Our study provides real world data on the timing of CEA which does not reflect the guideline recommended timing of less than 2 weeks and instead emphasizes the delay. Compared to the western data of about 39-72% of patients undergoing early CEA[8–10], only 8% in our cohort underwent CEA within 2 weeks. On the contrary we found a trend for a higher incidence of perioperative events in those who underwent the procedure within 2 weeks of onset of symptoms, without statistical significance($P=0.068$). The reason for this is less clear, although except for one patient, all had high grade stenosis of the ipsilateral carotid, 3 of them had ulcerated plaques, features that are deemed to have higher perioperative risks. As the number of patients with an adverse perioperative event in those who had early CEA were small ($n=4$), further statistical analysis on predictors could not be done.

About two-thirds of our patients presented after a stroke, despite 40% of them having preceding TIAs. Since patients recover completely after a TIA, they may not appreciate the gravity of the situation and often ignore it until they have a stroke. An Indian study had

previously reported that the lack of recognition of stroke symptoms by the patients, delay in seeking medical care and referral to a stroke neurologist or vascular surgeon, delay in decision making for the procedure, getting a second opinion from another specialist and financial constraints were factors contributing to delay in endarterectomy[17]. A study from Pakistan reported that 15% of patients were not aware of a surgical option for carotid stenosis[18]. Our results were similar to that of few other studies in Asian countries, where the predominant presentation was with a stroke[12–14,19]. This is in contrast to the western world wherein more than 50% of patients undergo CEA after a hemispheric or a retinal TIA [8–11].

The Asian population is known to have a higher prevalence of intracranial atherosclerosis as compared to the western world with about 18-48% of patients having co-existent significant intracranial and extracranial atherosclerotic disease[20,21]. Our findings replicated the same with about one-fourth of our cohort having significant co-existent tandem intracranial atherosclerosis. An analysis from the NASCET cohort reported that the benefit of CEA was less certain in those with severe intracranial atherosclerosis in view of smaller numbers[22]. Our results were similar to a large single center Italian study that reported no difference in the occurrence of perioperative events among those with and without co-existent tandem intracranial atherosclerosis, who underwent CEA[11]. The presence of a proximal lesion may overestimate a distal lesion due to reduced flow. The fact that tandem intracranial lesion did not influence the outcomes in our study may suggest that there might be overestimation of the percentage of intracranial stenosis atleast in some of them.

In the absence of a randomized controlled trials, there is still a debate on the choice of carotid revascularization in patients with contralateral carotid occlusion (CCO) with some studies favouring CEA[23,24] and others favouring carotid artery stenting (CAS)[25,26]. The western world recommends CAS over CEA in such patient groups as reflected by the policies

of Medicare and Medicaid services in the United States. However, none of our patients with a contralateral carotid occlusion had an adverse periprocedural event. This finding is reassuring and suggest that CEA is a safe procedure in these patients.

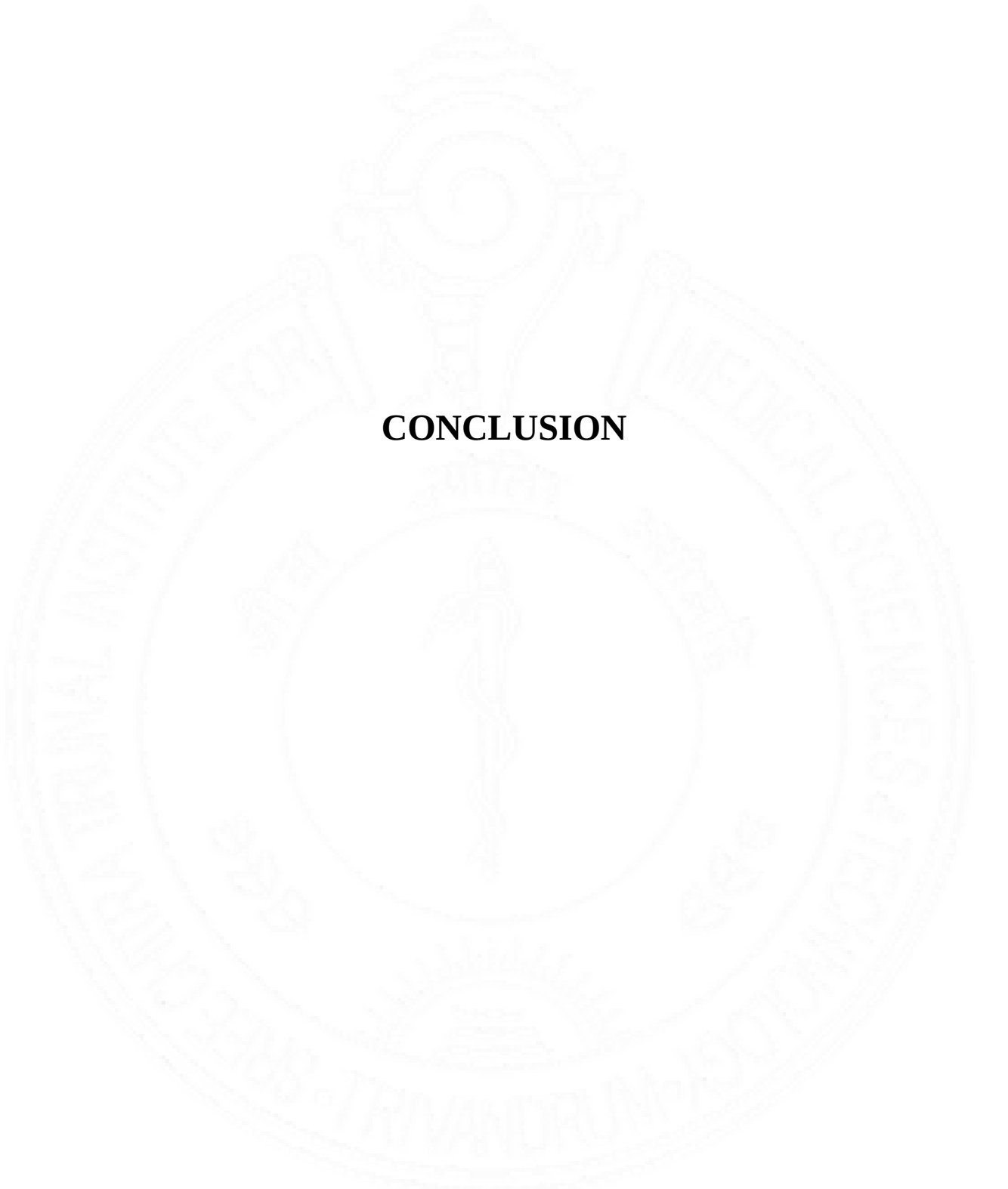
We had a higher postoperative stroke or death rate (6.7%) than the recommended guidelines. This reflects a real-world scenario as opposed to RCT data. However, none of the clinical or imaging factors predicted the occurrence of post-operative cerebral ischemic events (TIA or stroke). About 9.4% of our patients had near occlusion of the symptomatic carotid who were taken up for CEA. Chen et al had performed CEA in 14.7% patients with near occlusion with a periprocedural stroke/death rate of 4.08%[27] while a study from Pakistan reported perioperative stroke rates of 4.8%[28]. It is possible that the higher event rate in our population may be explained by the much higher preprocedural risk factors, although there was no statistically significant association for the same.

About 4.7% of our patients had cardiac events post procedure which is higher than the 3.63% reported by Chen et al[27]. The presence of coronary artery disease was similar between the two cohorts, although we had a higher proportion of patients with peripheral vascular disease (10%) which is a marker for occult cardiovascular disease. All our patients underwent surgery under general anesthesia, which has been reported to have more incidence of cardiac complications[29].

Ours is the largest Indian study and one among the largest single center Asian series [27,30] on the clinic-radiological profile of patients with symptomatic carotid stenosis who underwent carotid endarterectomy, looking at profile of the patients and the perioperative events. Our study highlights the need for public awareness on TIA and stroke, and policies on early referral of patients for CEA. The limitations of our study include retrospective review of data and its potential confounding factors. We did not review the intraoperative characteristics such as cross clamping time, technique of surgery, the histopathology of the

excised plaque and hemodynamic fluctuations during the procedure that could have given us a better insight into the reasons for the perioperative events.

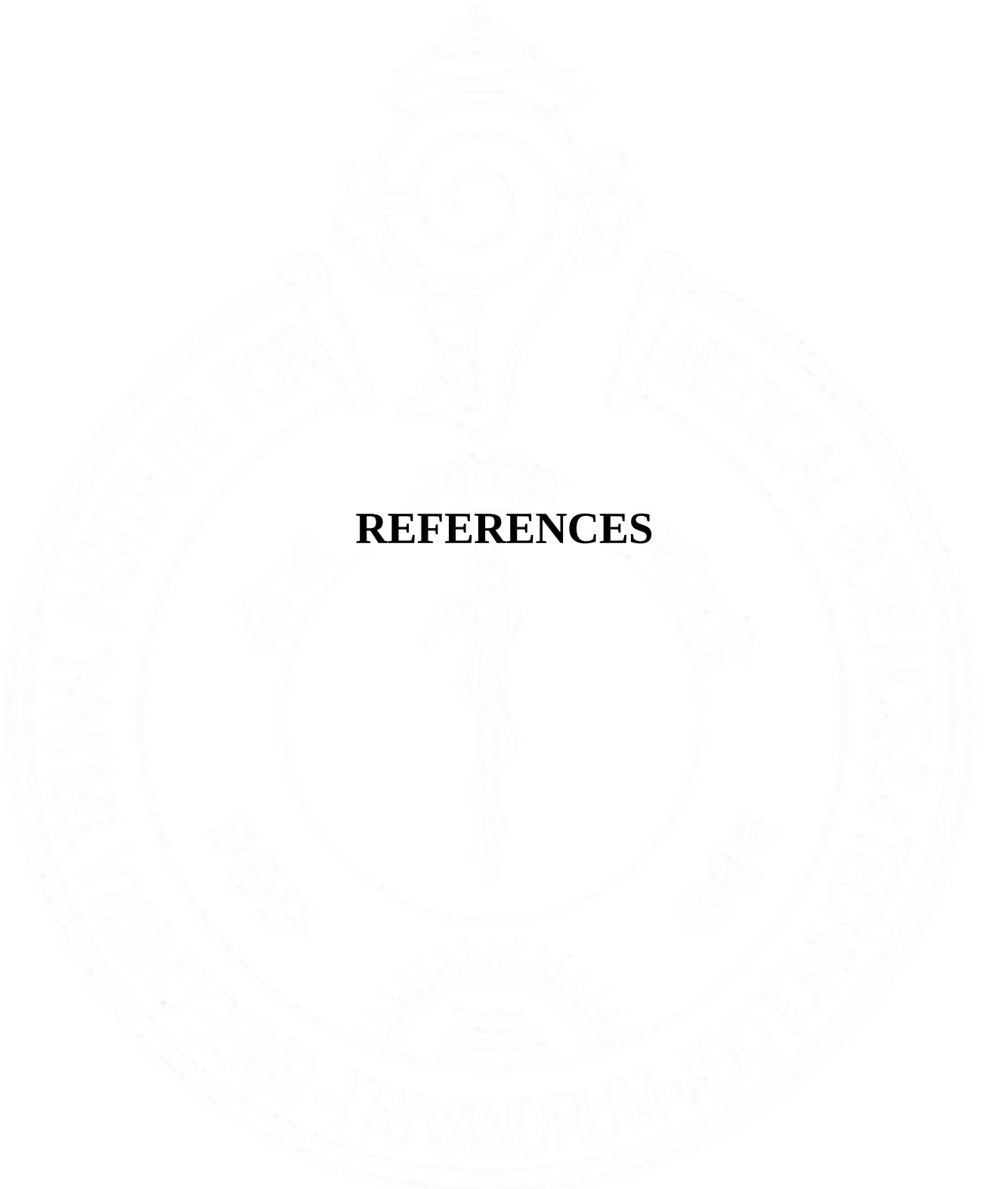




CONCLUSION

CONCLUSION

1. There is a delay in patients undergoing carotid endarterectomy in our country, with majority presenting only after a stroke and high grade stenosis of the symptomatic carotid.
2. CEA can be safely performed in patients with contralateral carotid occlusion and those with co-existent significant tandem intracranial atherosclerotic lesions.



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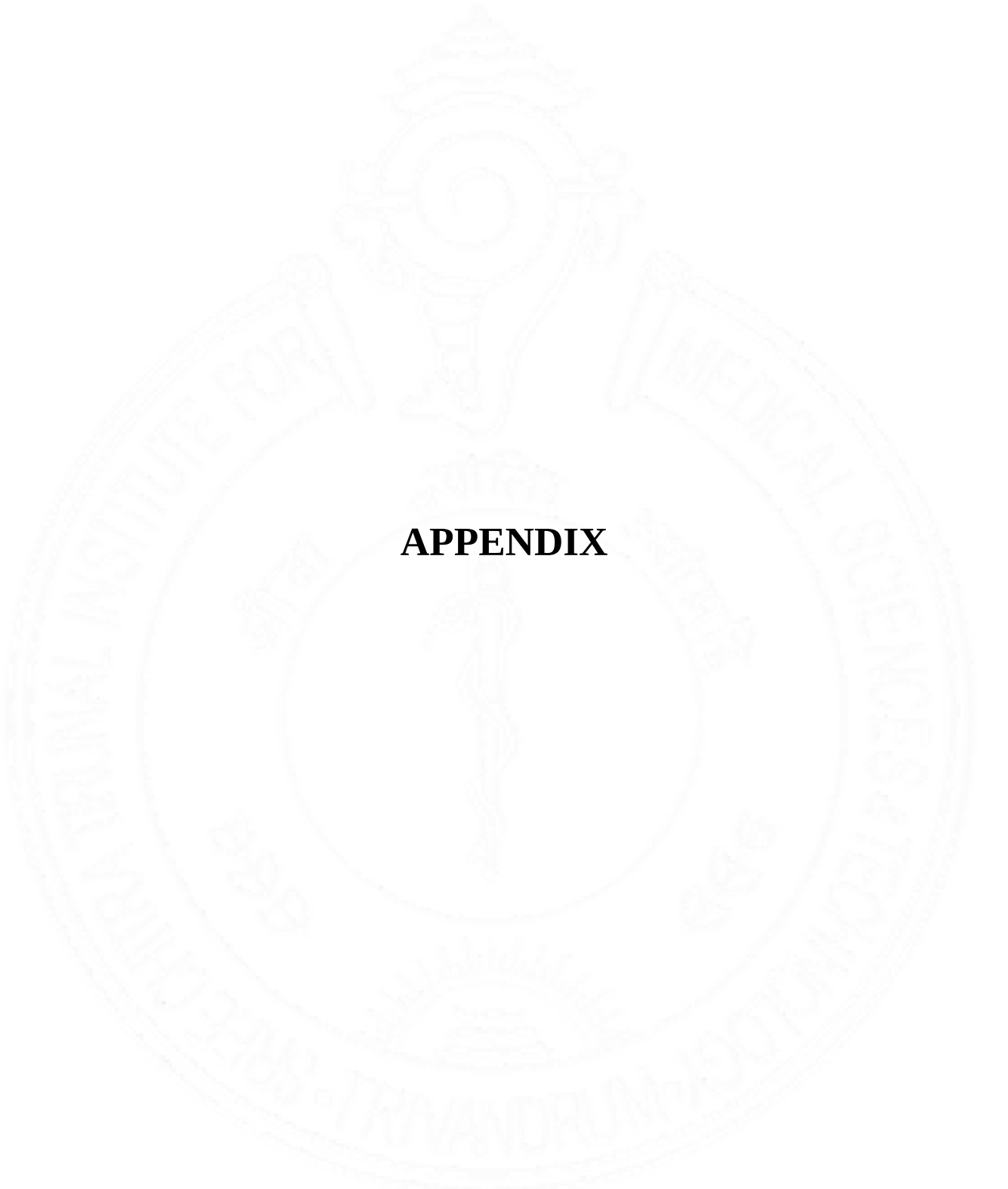
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APPENDIX

PROFORMA FOR CAROTID ENDARTERECTOMY

1. Serial Number

1.1. Age -----

1.2. Sex----- (Male 1, Female-2)

1.3. date of admission----- Date of discharge-----

Risk factors (Yes -1, No -2)

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

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

2.4a. If CABG done-----

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

2.5a. If yes, Specify -----

2.5.b. Prosthetic valve -----

2.6. Congestive heart failure -----

2.7. Peripheral vascular disease.-----

2.8. Hyperlipidaemia.-----

2.9. Atrial fibrillation.-----

2.9.1. If patient on pacemaker -----

3.0. Clinical data

3.1. Type of first event ----- 1. hemispheric TIA 2. Retinal TIA 3. Stroke

3.2. Date of the first event -----

3.3. Number of events (also describe)-----

3.4. Date of last event -----

3.5. Side of the event -----1.Right 2.Left 3.Bilateral

3.6. NIHSS before the procedure-----

3.7. mRS before the procedure -----

4.0. Investigations

4.1. FBS -----

4.2. PPBS ----- 4.2.a.Glycosylated HB -----

4.3. Serum creatinine -----

4.4. Serum cholesterol -----4.4.a.TG -----4.4b.HDL-----4.4c.LDL--

4.5. ECG -----1.Normal 2.Abnormal.Describe -----

4.6. Echo -----1.Normal 2.Abnormal

If abnormal, describe -----

4.7. Holter -----1.Normal 2.Abnormal 3.Not done

4.8. If Holter abnormal ,describe -----

5.0.Neuroimaging (0=No, 1=Yes)

5.1 Imaging modality used.....CT/MRI

5.2 Single infarct.....

5.3 Multiple infarct.....

5.4 Varying ages.....

5.5 Acute-0, Chronic-1, Both-2.....

5.6 Cortical.....

5.7 Embolic infarct.....

5.8 Hand area.....

5.9 Hemodynamic infarct.....

5.10 Fazeka grading for small vessel changes.....

6 VESSEL IMAGING

6.1 Symptomatic Extracranial stenosis(%).....

6.2 Presence of ulcer/thrombus.....

6.3 Asymptomatic Extracranial stenosis(%).....

6.4 Presence of ulcer/thrombus.....

6.5 Symptomatic Intracranial stenosis(%).....

6.6 Asymptomatic Intracranial stenosis(%).....

6.7 Contralateral occlusion.....

6.8 Diffuse atherosclerosis.....

6.9 Modalities available..... (1-DSA,2-CTA,3-CEMRA,4-MRTOF,5-NVD)

6.10 Modality used to assess vessels.....

7.0.PROCEDURE DATE -----

TIMING OF PROCEDURE (number of days after the ictus) -----

PERIPROCEDURAL COMPLICATIONS

TIA -----1.Yes.2.No.If so date of event-----

STROKE -----1.Yes.2.No If so date of event-----

If stroke, NIHSS at stroke onset-----

HYPERPERFUSION SYN -----1.Yes.2.No.If so date of event-----

ACUTE CORONARY EVENT -----1.Yes.2.No.If so date of event-----

POSTPROCEDURAL CT/MRI -----1.Yes2.No

DWI LESIONS ----- 1.Yes 2.No If so , TERRITORY SAME/OTHER(tick as appropriate)

LOCAL COMPLICATIONS

WOUND HEMATOMA-----1.Yes 2.No

CRANIAL NEUROPATHY -----1.Yes2.No

MODIFIED RANKIN SCALE AT DISCHARGE-----



श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेन्द्रम
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Institutional Ethics Committee

(IEC Regn No. ECR/189/Inst/KL/2013/RR-21)

SCT/IEC/1896/AUGUST/2022

17.09.2022

Dr. Naveen Kumar P

Post Doctoral Fellow in Stroke

Department of Neurology

SCTIMST, Thiruvananthapuram

Dear Dr. Naveen Kumar,

The Institutional Ethics Committee held on 6th August, 2022, reviewed and discussed your application to conduct the study titled "CLINICAL PROFILE AND PREDICTORS OF OUTCOMES OF PATIENTS WITH SYMPTOMATIC CAROTID STENOSIS WHO UNDERWENT CAROTID ENDARTERECTOMY" (IEC/1896).

The following members of the Ethics Sub-committee were present at the meeting held on 6th August, 2022.

SL. No.	Member Name	Highest Degree	Gender	Scientific /Non Scientific	Affiliation with Institution(s)
1.	Prof. Kala Kesavan P	MBBS,MD	Female	Basic Medical Scientist	No
2.	Dr. Pradeep S	MBBS, MD	Male	Basic Medical Scientist	No
3.	Smt. Sathi Nair	MA (English Literature)	Female	Lay Person	No
4.	Dr. Christina George	MD Psychiatry	Female	Clinician	No
5.	Adv. N Anand	BAL, L.LB	Male	Legal Expert	No
6.	Dr. Rejnish Kumar	MBBS,MD ,DNB	Male	Clinician	No
7.	Prof. Narayanan Namboodiri. K K	MBBS,MD,DM	Male	Clinician	Yes
8.	Dr. Srinivas G	PhD	Male	Basic Medical Scientist (Member Secretary)	Yes

The following documents were reviewed:

Original submission

1. Checklist Form
2. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 05.05.2022
3. Forwarding letter from HOD dated 05.05.2022
4. IEC Application Form
5. Study Proposal
6. Declaration form
7. CV of PI and Co-PIs
8. Proforma
9. SRC Recommendation letter

Revised submission

1. Covering letter addressed to the Member Secretary, IEC, SCTIMST dated 16.09.2022
2. Checklist Form
3. Covering letter addressed to the Chairperson, IEC, SCTIMST dated 05.05.2022
4. Forwarding letter from HOD dated 05.05.2022
5. IEC Application Form
6. Study Proposal
7. Declaration form
8. CV of PI and Co-PIs
9. Proforma

IEC Decision

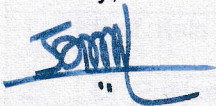
The IEC approved the conduct of the study in the present form.

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.

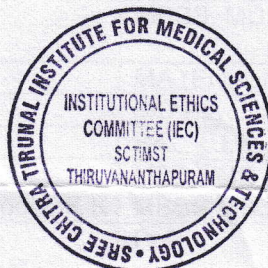
There was no member of the study team who participated in voting / decision making process. The ethics committee is organized and operated according to the requirements of Good Clinical Practice and the requirements of the Indian Council of Medical Research (ICMR).

Sincerely,



Dr. G. Srinivas
Member Secretary, IEC

MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE (IEC)
SCTIMST, THIRUVANANTHAPURAM



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Carotid endarterectomy for symptomatic carotid stenosis: differences in patient profile in a Low-Middle Income Country
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Running title: carotid endarterectomy and periprocedural events

Key words: carotid endarterectomy, symptomatic carotid stenosis, perioperative events

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Abstract:

Introduction: Carotid Endarterectomy (CEA) is the standard treatment for patients with symptomatic carotid stenosis.

Data from Low- and Middle-Income Countries (LMIC) is sparse on CEA and its outcomes. We aimed to describe the profile of our patients, and factors associated with periprocedural cerebral ischemic events in patients with symptomatic carotid stenosis who underwent CEA in our institute. Methods: Retrospective review of patients with symptomatic carotid stenosis (50-99%) who underwent CEA between January 2011 and December 2021 was done. Clinical and imaging parameters and their influence on periprocedural cerebral ischemic events were analysed. Results: Of the 319 patients (77% males) with a mean age of 64 years (SD ± 8.6), 207 (65%) presented only after a stroke. Majority (85%) had high grade stenosis (70%) of the symptomatic carotid. The mean time to CEA was 50 days (SD ± 36), however only 26 patients (8.2%) underwent surgery within 2 weeks. Minor strokes and TIA occurred in 2.2%, while major strokes and death occurred in 4.1% patients. None of the clinical or imaging parameters predicted the periprocedural cerebral ischemic events. The presence of co-existing significant (50%) tandem intracranial atherosclerosis (n=77, 24%) or contralateral occlusion (n=24, 7.5%) did not influence the periprocedural stroke risk. Conclusion: There is a delay in patients undergoing CEA for symptomatic carotid stenosis. Majority have high grade stenosis and present late only after a stroke reflecting a lack of awareness. CEA can be performed safely even in patients with significant intracranial tandem stenosis and contralateral carotid occlusion.

Introduction Large vessel atherosclerotic disease constitutes approximately 20% to 30% of all ischemic strokes [1]. Based on the three major trials (

The North American Symptomatic Carotid Endarterectomy Trial (NASCET), European Carotid Surgery Trial (ECST)

and Veteran Affairs Trial 309) [2–4] and a pooled analysis of the same [5], the current recommendation is to perform carotid endarterectomy (CEA) in patients with symptomatic carotid stenosis (50%) in centers with perioperative morbidity and mortality less than 6% [6]. Recent trials also affirm that CEA is the standard of care with a lower incidence of periprocedural stroke [7]. However, randomized controlled trials (RCTs) include large volume centers with highly specialized surgeons and their results may not be replicable in all patient populations. While the majority of patients in the western world undergo CEA even after a Transient Ischemic Attack (TIA) [8–11], it is the reverse in low and middle income countries (LMIC) where CEA is done most often after a stroke [12–14] and tend to be delayed compared to the guideline recommended timing within 2 weeks. In this background, the application of these guidelines in LMIC requires an understanding of the profile of patients who undergo carotid revascularization. There is lack of data on the clinical profile, imaging characteristics, timing and outcome of CEA in patients who present with symptomatic carotid stenosis from a country like India. We aimed to describe the clinical profile of patients with symptomatic carotid stenosis who underwent CEA in our institute and analysed the factors associated with perioperative vascular events.

Methods:

This study was a retrospective review of prospectively collected data of all patients aged ≥ 18 years with symptomatic carotid artery stenosis (50%) who underwent carotid endarterectomy in the Comprehensive stroke care centre, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology (SCTIMST), Kerala, between 2011 and 2021. The clinical profile of the patients, including the vascular risk factors, clinical characteristics, the admission stroke severity assessed using the National Institute of Health Stroke Scale (NIHSS), disability status assessed using modified Rankin Scale (mRS) were collected. The imaging characteristics such as the pattern of infarcts were assessed by Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) of the brain. The vessels affected both ipsilateral and contralateral, percentage of luminal stenosis both extra and intracranial were assessed through imaging modalities like CT angiography (CTA), MR angiography (MRA), Digital Subtraction Angiography (DSA) or neck vessel doppler. In patients with more than one vascular imaging assessments, DSA was chosen as the modality of review whenever available. When DSA was unavailable, CT angiogram or Contrast enhanced MRA were used with equal weightage given to both. MR TOF angiogram was taken for assessment only when other modalities of vessel assessment were unavailable. The NASCET method for estimating the percentage of stenosis was used in the study. An extracranial carotid stenosis 70% was taken as high grade. Both intracranial and extracranial stenosis as well as the presence or absence of ulcer or thrombus of ipsilateral and contralateral vessels were noted. The presence of intracranial stenosis 50% was considered significant. The patterns of infarcts were classified as embolic or hemodynamic or a combination of both. Territorial infarcts with or without fragmentation, multiple small infarcts in ICA territory were taken as embolic pattern and those infarcts in cortical watershed and internal watershed areas were included under hemodynamic pattern. The timing of CEA from the onset of the symptoms and periprocedural TIA/stroke, cardiac events or any other procedural complications including reperfusion injury, wound hematoma or cranial neuropathy were also collected. Post procedural cardiac events were defined by presence of typical cardiac chest pain, with rise in troponins or dynamic changes in electrocardiogram or new onset regional wall motion abnormalities in echocardiogram. The primary outcome was the occurrence of perioperative cerebral ischemic events that included TIA and stroke. Secondary outcome included a composite of stroke, TIA, cardiac events or death perioperatively. Statistical analysis:

The statistical analysis was performed using Intercooled STATA 14.1 software package (StataCorp, Texas, USA). The timing of CEA was divided into early (14 days) and late (≥ 14 days) after the onset of symptoms, for analysing the relationship to perioperative events. The association of demographic, clinical and radiological characteristics of the patients with perioperative cerebral ischemic events were assessed using Chi-square test or Fisher's exact test as appropriate. A p value ≥ 0.05 was deemed significant.

Results: Between 2011 and 2021, there were 472 patients who were taken up for carotid revascularisation. Of these, 61 underwent carotid stenting while 411 had carotid endarterectomy. Among 411 patients, we excluded those who underwent the procedure for asymptomatic carotid stenosis and those with remote symptomatic carotid stenosis, defined by last symptom onset more than 6 months ago. There were 319 patients of whom 247 (77%) were males. The mean age of the patients was 64 years (SD ± 8.6). The most common presentation was stroke ($n=208, 65\%$). Of those who had presented with stroke, 40% had prior TIAs. The median time to undergo CEA was 39 days (range 4-180), and 26 patients (8.2%) underwent surgery within 2 weeks. Majority of the patients ($n=270, 85\%$) had high grade stenosis (70%) of the symptomatic carotid, while 77 (24%) had co-existent tandem significant ($\geq 50\%$) intracranial stenosis. About 63 patients (19.75%) had an ulcerated plaque in ipsilateral carotid while 24 patients (7.5%) had a contralateral carotid artery occlusion. The demographic, clinical, risk factor profile and imaging patterns of our patients are shown in Table 1. The primary endpoint of perioperative cerebral ischemic events was noted in 6.1% patients, with minor strokes and TIA in 2.1%, and major strokes in 4% patients. Post procedural acute coronary syndromes were noted in 15 (4.7%) patients. A composite endpoint of periprocedural stroke, death or cardiac event was noted in 31 patients (9.7%). There were 2 patients who had perioperative mortality, one of whom had a preoperative renal failure and succumbed to an acute coronary syndrome post procedure. The other patient had a major ipsilateral stroke. Other complications like transient cranial neuropathy, wound hematoma and hyperperfusion syndrome occurred in 7.8%, 3.1% and 0.9% of patients respectively. The baseline vascular risk factors or the type of the initial vascular event (TIA or stroke) did not influence the risk of post-operative ischemic events as detailed in Table 2. However, there was a trend for a higher incidence of post-operative stroke or TIA among those who underwent the procedure within 2 weeks, although not statistically significant ($P=0.068$). The presence of co-existing significant tandem intracranial atherosclerosis did not predict the risk of periprocedural cerebral ischemic events ($P=0.691$). No patient with a contralateral ICA occlusion had an adverse event ($P=0.398$).

Discussion: The major findings in our study was that a large proportion of our patients for carotid endarterectomy presented late after the ischemic event, mostly after a stroke rather than TIA, and had high grade stenosis of the symptomatic carotid. None of the clinical or imaging features including co-existent tandem significant intracranial atherosclerotic disease or a contralateral carotid occlusion predicted perioperative cerebral ischemic events. Our patients were predominantly elderly males, that is similar to the existing literature. Similar to the data from large registries there was no difference in the perioperative outcomes with respect to gender [15,16]. Only 23% of our patients were females, and this may be attributed to the prevailing gender and cultural bias, the perception that women are at higher risk for periprocedural events and the lesser benefit in women referred late for surgery. Our study provides real world data on the timing of CEA which does not reflect the guideline recommended timing of less than 2 weeks and instead emphasizes the delay. Compared to the western data of about 39-72% of patients undergoing early CEA [8–10], only 8% in our cohort underwent CEA within 2 weeks. On the contrary we found a trend for a higher incidence of perioperative events in those who underwent the procedure within 2 weeks of onset of symptoms, without statistical significance ($P=0.068$). The reason for this is less clear, although except for one patient, all had high grade stenosis of the ipsilateral carotid, 3 of them had ulcerated plaques, features that are deemed to have higher perioperative risks. As the number of patients with an adverse perioperative event in those who had early CEA were small ($n=4$), further statistical analysis on predictors could not be done. About two-thirds of our patients presented after a stroke, despite 40% of them having preceding TIAs. Since patients recover completely after a TIA, they may not appreciate the gravity of the situation and often ignore it until they have a stroke. An Indian study had previously reported that the lack of recognition of stroke symptoms by the patients, delay in seeking medical care and referral to a stroke neurologist or vascular surgeon, delay in decision making for the procedure, getting a second opinion from another specialist and financial constraints were factors contributing to delay in endarterectomy [17]. A study from Pakistan reported that 15% of patients were not aware of a surgical option for carotid stenosis [18]. Our results were similar to that of few other studies in Asian countries, where the predominant presentation was with a stroke [12–14,19]. This is in contrast to the western world wherein more than 50% of patients undergo CEA after a hemispheric or a retinal TIA [8–11]. The Asian population is known to have a higher prevalence of intracranial atherosclerosis as compared to the western world with about 18-48% of patients having co-existent significant intracranial and extracranial atherosclerotic disease [20,21]. Our findings replicated the same with about one-fourth of our cohort having significant co-existent tandem intracranial atherosclerosis. An analysis from the NASCET cohort reported that the benefit of CEA was less certain in those with severe intracranial atherosclerosis in view of smaller numbers [22]. Our results were similar to a large single center Italian study that reported no difference in the occurrence of perioperative events among those with and without co-existent tandem intracranial atherosclerosis, who underwent CEA [11]. The presence of a proximal lesion may overestimate a distal lesion due to reduced flow. The fact that tandem intracranial lesion did not influence the outcomes in our study may suggest that there might be overestimation of the percentage of intracranial stenosis atleast in some of them. In the absence of a randomized controlled trials, there is still a debate on the choice of carotid revascularization in patients with contralateral carotid occlusion (CCO) with some studies favouring CEA [23,24] and others favouring carotid artery stenting (CAS) [25,26]. The western world recommends CAS over CEA in such patient groups as reflected by the policies of Medicare and Medicaid services in the United States. However, none of our patients with a contralateral carotid occlusion had an adverse periprocedural event. This finding is reassuring and suggest that CEA is a safe procedure in these patients. We had a higher postoperative stroke or death rate (6.7%) than the recommended guidelines. This reflects a real-world scenario as opposed to RCT data. However, none of the clinical or imaging factors predicted the occurrence of post-operative cerebral ischemic events (TIA or stroke). About 9.4% of our patients had near occlusion of the symptomatic carotid who were taken up for CEA. Chen et al had performed CEA in 14.7% patients with near occlusion with a periprocedural stroke/death rate of 4.08% [27] while a study from Pakistan reported perioperative stroke rates of 4.8% [28]. It is possible that the higher event rate in our population may be explained by the much higher preprocedural risk factors, although there was no statistically significant association for the same. About 4.7% of our patients had cardiac events post procedure which is higher than the 3.63% reported by Chen et al [27]. The presence of coronary artery disease was similar between the two cohorts, although we had a higher proportion of patients with peripheral vascular disease (10%) which is a marker for occult cardiovascular disease. All our patients underwent surgery under general anesthesia, which has been reported to have more incidence of cardiac complications [29]. Ours is the largest Indian study and one among the largest single center Asian series [27,30] on the clinic-radiological profile of patients with symptomatic carotid stenosis who underwent carotid endarterectomy, looking at profile of the patients and the perioperative events. Our study highlights the need for public awareness on TIA and stroke, and policies on early referral of patients for CEA. The limitations of our study include retrospective review of data and its potential confounding factors. We did not review the intraoperative characteristics such as cross clamping time, technique of surgery, the histopathology of the excised plaque and hemodynamic fluctuations during the procedure that could have given us a better insight into the reasons for the perioperative events.

Conclusion: There is a delay in patients undergoing carotid endarterectomy in our country, with majority presenting only after a stroke and high grade stenosis of the symptomatic carotid. CEA can be safely performed in patients with contralateral carotid occlusion and those with co-existent significant tandem intracranial atherosclerotic lesions.

Statement of Ethics: The study protocol was reviewed and approved by the Institutional Ethics Committee, approval number: SCT/IEC/1896/AUGUST/2022. The study was granted an exemption from requiring informed consent by our Institutional Ethics Committee as it was a review of retrospective data.

Conflict of Interest: The authors report no conflict of interest.

Funding sources: There was no funding received for this study.

Author contributions:

Naveen Kumar Paramasivan and PN Sylaja conceived and designed the study and drafted the manuscript; Naveen Kumar Paramasivan collected the data, Jissa VT did the statistical analysis, Naveen Kumar Paramasivan, PN Sylaja, Shivanesan Pitchai, Unnikrishnan Madathipat, Sapna Erat Sreedharan, Sajith Sukumaran critically revised the manuscript.

Data availability statement: All data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

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