ANALYSIS OF CLINICAL AND ANGIOGRAPHIC OUTCOME PREDICTORS IN HIGH RISK CAROTID STENTING

Dr Vikas Chauhan

DM THESIS

2020-2022

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A THESIS SUBMITTED BY

Dr Vikas Chauhan

TO

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

IN PARTIAL FULFILMENT OF THE REQUIREMENTS

FOR THE AWARD OF

DM NEUROIMAGING AND INTERVENTIONAL NEURORADIOLOGY

2020-2022

DECLARATION BY THE STUDENT

CERTIFICATE

I, **DR VIKAS CHAUHAN** hereby certify that I had personally carried out the work depicted in the thesis titled, ***"ANALYSIS OF CLINICAL AND ANGIOGRAPHIC OUTCOME PREDICTORS IN HIGH-RISK CAROTID STENTING."***

No part of this thesis has been submitted for the award of any other degree or diploma prior to this date.

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Date 15 AUG 2022
Trivandrum

(* If external help was sought, declare and acknowledge)

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The thesis entitled, "**Analysis of clinical and angiographic outcome predictors in high-risk carotid stenting**." was carried out under my direct supervision. No part of the thesis was submitted for the award of any degree or diploma prior to this date.

*Clearance was obtained from the Institutional Ethics Committee / Institutional Animal Ethics / Institutional Committee for Stem Cell Research / Other appropriate committees (if any, specify) for carrying out the study.

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APPROVAL OF THE THESIS

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"Analysis of clinical and angiographic outcome predictors in high-risk carotid stenting."

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for the degree of

DM NEUROIMAGING AND INTERVENTIONAL NEURORADIOLOGY

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LIST OF ABBREVIATIONS

S No	Abbreviation	Full Form
1	CAS	Carotid Artery Stenting
2	CEA	Carotid Endartectomy
3	mRS	Modified Rankin Scale
4	NIHSS	National Institutes of Health Stroke Scale
5	CAD	Coronary Artery Disease
6	DSA	Digital Subtraction Angiography
7	CCA	Common Carotid Artery
8	ICA	Internal Carotid Artery
9	MI	Myocardial Infarction
10	HU	Hounsfield Unit
11	ICH	Intracerebral hemorrhage
12	EPD	Embolic Protection Device
13	DAPT	Dual Antiplatelet Therapy

SYNOPSIS

ANALYSIS OF CLINICAL AND ANGIOGRAPHIC OUTCOME PREDICTORS IN HIGH RISK CAROTID STENTING

SYNOPSIS

BY

DR VIKAS CHAUHAN

for

DM NEUROIMAGING AND INTERVENTIONAL NEURORADIOLOGY

of

SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY, TRIVANDRUM

(The typed pages may be stapled and submitted three months prior to the submission of the thesis. When synopsis forms part of the thesis, the cover page need not be included)

SYNOPSIS

Background and purpose: Carotid artery stenting is preferred for patients who need carotid revascularisation but are not surgical candidates due to high risk. The study is aimed at studying the risk predictors for carotid artery stenting (CAS) in the cases of difficult CAS. There are various risk factors like patient's age and coexisting diseases like hypertension, diabetes, difficult aortic arch anatomy, pre-existing atherosclerotic disease of vessels with plaques, etc.

Materials and Methods: 49 cases who underwent carotid artery stenting in the last six years at our institute were studied. We analysed comorbidities, major & minor criteria for high risk, procedure time and fluoroscopic time and their relation to post-procedural adverse events, in-hospital adverse events, and mRS score at 24 hours, 30 days and at three months. Statistics analysis of these parameters were done using Chi-square test and Fisher's exact test.

Results: Coronary artery disease, severe renal disease, and severe cardiac dysfunction on evaluation were significantly related to in-hospital adverse events. ICA – CCA angulation more than 60°, increasing stenosis severity, multiple stent use and presence of tandem lesions were the angiographic factors related to peri-procedural complications or in-hospital adverse events. Type III aortic arch was associated with increased fluoroscopy time. There was a good correlation between the plaque echogenicity on ultrasound and the nature of the plaque on computed tomography.

Conclusion: This study highlights the high-risk clinical and angiography factors for carotid artery stenting and helps us in predicting the prognosis of carotid artery stenting (CAS) treatment based on these high-risk clinical and angiography factors.

1 INTRODUCTION

1.1 General Introduction

Stroke is the second largest cause of mortality and a significant contributor to disability globally. Its prevalence is rising as the average age of the population increases (Jim et al., 2012). Stroke disability and morbidity is also associated with increased economic burden due to treatment and rehabilitation cost (Dumont and Rughani, 2012). Large vessel atherosclerosis especially carotid artery stenosis with subsequent thromboembolic complications accounts for up to 25% of these strokes (Brott et al., 2010). Carotid artery stenosis prevalence increases from the 5th decade of life. Asymptomatic carotid stenosis is more common in patients with vascular illness and several risk factors (like smoking, hyperlipidemia, diabetes, and hypertension). The atherosclerosis of the carotid artery may progress mostly silently and unexpectedly, with the 1 st presentation being a debilitating/fatal stroke. Around 7% of women and over 12% of men over the age of 70 have asymptomatic carotid artery stenosis (Rothwell et al., 1997). Stenosis of more than 50% is considered to be symptomatic stenosis, which raises the risk of stroke (Cheng et al., 2020). Surveys on the natural history of this condition have noted that the incidence of ipsilateral carotid territory ischemic stroke in patients with asymptomatic carotid stenosis ranges from 5 to 17% (Miyake et al., 2022). The BMT (Best Medical Treatment) and carotid revascularization, such as CAS (Carotid Artery Stenting) and CEA (Carotid Endarterectomy), are used to treat this illness. CEA and CAS are suggested for symptomatic individuals with more than 50 per cent stenosis and asymptomatic

patients with greater than 70% stenosis (Schlüter et al., 2007)(Goldstein et al., 2009). Even though CEA is the standard treatment and was revealed to benefit patients who have had symptoms of carotid artery stenosis for a long time (Nevidomskyte et al., 2019), it has several drawbacks due to comorbidities of the patients, surgical difficulties, and unfavourable neck anatomy. However, CAS was designed to boost safety and give a minimally invasive method. However, periprocedural complications of CAS, particularly stroke, provide additional concerns. Various factors are related to the outcome of the CAS procedure. These include patients' age and comorbidities, aortic arch morphology, degree of atherosclerosis of the vessels, plaque morphology (Schmid et al., 2019), and the operator's experience and the workload of the institute performing the CAS. As carotid stenting safety is anticipated to increase with improved patient selection (Carpenter et al., 2018)(Bashar et al., 2014) technological advancements, and more operator experience (Tzoumas et al., 2021) and it may eventually replace endarterectomy as a safe procedure, at least in some patient subgroups, it is vital to study about the high-risk predictors of carotid stenting and the knowledge were beneficial in further refinement of the patient selection protocols. This study aims to study the various factors like plaque morphology, and clinical and angiographic comorbidities as a risk predictor for the outcomes of CAS on mRS and NIHHS scale post-procedure, at 24 hours and 3 months.

2 LITERATURE REVIEW

2.1 Introduction

Extracranial stenosis of the internal carotid artery is an important cause of transient ischemic attacks and ischemic strokes of retinal or cerebral origin. Carotid revascularization is an effective intervention to prevent recurrent stroke or death in both symptomatic and asymptomatic patients with carotid artery stenosis (Jim et al., 2012). Currently available treatments include carotid endarterectomy (CEA), carotid artery stent placement (CAS) and medical therapy. An estimated 151,000 CEAs are performed every year, providing some data regarding the burden of carotid stenosis in the United States. CAS has emerged as an alternative and less invasive treatment for high surgical risk patients and currently 9,000 CAS are performed in the United States annually (Dumont and Rughani, 2012).

After the results of the carotid revascularization endarterectomy versus stenting trial (CREST) (Brott et al., 2010), a large proportion of patients with carotid artery stenosis can be candidates for either CAS or CEA. Better identification of high surgical risk and high stent risk patients is necessary to provide the best treatment option to each patient. Factors characterizing patients at high surgical risk for complications following CEA have been extensively described (Rothwell et al., 1997); however, a comprehensive review of such factors in patients undergoing CAS is not available. We performed a systematic review of clinical, anatomic, and procedure-related factors associated with a higher rate of periprocedural stroke and/or death which is required to identify the high stent risk patients.

2.2 Asymptomatic stenosis

Patients who have got moderate to severe stenosis but are asymptomatic have a lower risk of TIA and strokes, but on following it has been found that this stenosis may progress further and may lead to events later on. So in his paper by Cheng et al concluded that a close follow-up for these patients is needed. (Cheng et al., 2020)

2.3 Low eGFR

Miyake et all studied patients with symptomatic lesions as well as low eGFR (≤49mL/min/1.73m 2) and concluded that symptoms for treatment must be considered strictly. In their study multivariate analysis revealed that staged CAS (odds ratio:38.9, p=0.04) and eGFR ("Estimated Glomerular Filtration Rate") (odds ratio:1.11, p=0.003) were independent predictive variables. The odds ratio, as well as relative risk of mRS deterioration, were 5.2 and 3.74, respectively, when eGFR was below 49mL/min/1.73 m 2 contrasted with when eGFR was higher than 49 mL/min/1.73m. (Miyake et al., 2022).

2.4 Gender and CAS

In a multicenter Italian & German registry, 695 patients (179 women and 516 men) received CAS, and logistic regression analysis demonstrated that gender did no effect on 30-day stroke & mortality rates. (Schlüter et al., 2007) In a single-centre retrospective study done by Goldstein et al on 228 patients (93 women and135 men), undergoing CAS, there was no variation in the 30-day stroke, cardiac event, or death rates between the 2 genders. (Goldstein et al., 2009) Outcomes Assessment Program

registry and Vascular-Interventional Surgical Care from the Washington state hospitals, the composite result of stroke and death after carotid interventions including CEA and CAS from 2010-2015 were found to be similar for men and women. (Nevidomskyte et al., 2019) Gender and CEA—Metanalysis done by Schmid et all of large registries have shown that results of CEA are not influenced by sex(Schmid et al., 2019).

2.5 Previous Neck RT and CAS

It is generally recognized that ionizing radiation increases the likelihood of carotid artery stenosis. There is increasing survival of neck & head oncology patients receiving radiotherapy seen due to advancements in medicine. Increased prevalence of extracranial carotid artery stenosis seen in a patient who is receiving radiation therapy for neck and head malignancies. (Carpenter et al., 2018) There is also increased atherosclerosis seen in these vessels exposed to radiation. (Bashar et al., 2014) CEA is thrice as difficult in these patients due diffuse nature of plaques and adhesion of surrounding tissues predisposing them to the risk of cranial nerve injury. Patients in this study who get CEA treatment had a greater risk of periprocedural CN damage.(Tzoumas et al., 2021) CAS is a better option in the subset of patients having carotid artery stenosis. (Trojanowski et al., 2019)

2.6 Effect of age on CAS

This multicenter registry, by Besma et al, verified the modification impact on the safety and effectiveness of carotid revascularization procedures. The risk-adjusted efficiency of CAS varied according to patient age, while CEA results were rather

consistent across different age groups. In the context of a randomized clinical study, the observed impact was more severe and came a decade sooner than previously documented. (Nejim et al., 2019)

In one study by Wasser et al, the effect of age on cognition after CAS and CEA was studied and the results showed that CEA and CAS had an age-dependent influence on cognitive functions. Individuals under the age of 68 exhibited no significant cognitive changes after either CEA or CAS, however patients ≥ 68 showed a significant reduction in cognition. This reduction was transient after CAS, while it was persistent in patients with CEA. In contrast to the greater clinical complication rates in older patients following CAS, CEA appeared to be related to a higher loss in cognitive performance than CAS in this study. (Wasser et al., 2012)

A recent study also concluded that age is related to an increased risk of post-procedural stroke or mortality following carotid artery stenting in both asymptomatic and symptomatic carotid stenosis. (Schmid et al., 2019)

2.7 Effect of smoking on CAS

It is a known fact that cigarette smoking increases the development of intimal hyperplasia and plays a major role in developing carotid restenosis. (Petrik et al., 1995) It also increases the chances of carotid restenosis after carotid revascularization procedures. (Lal et al., 2012)

2.8 Diabetes and CAS

Diabetes mellitus (DM) causes increased vascular disease and including carotid artery disease. DM has also been related to a greater risk of poor results after carotid stenting or endarterectomy. Furthermore, DM is a well-known risk factor for contrast-induced acute kidney injury.(Katsiki and Mikhailidis, 2020) Patients with diabetes are at a higher risk of perioperative stroke, long-term mortality, and death than nondiabetic patients who have carotid artery endarterectomy or stenting, confirmed the study by Hussain et al.(Hussain et al., 2016) Contrary to this a recent metanalysis by Chu et al concluded, compared to non-diabetic patients, diabetes did not increase the incidence of perioperative stroke, mortality, MI, TIA, as well as a composite of death or stroke in patients undergoing CAS. (Chu et al., 2021)

2.9 Hypertension and CAS

High blood pressure (>130mmHg) within 24 hours after a CAS greatly increases the risk of secondary cerebral haemorrhage, unsatisfactory discharge, and mortality in the hospital. This paper by Zheng et al concluded that BP must be maintained below 130mmHg in the first 24 hours after CAS. (Zheng et al., 2020) At the 1-year follow-up, CAS may also have a BP-lowering impact for individuals with symptomatic carotid artery stenosis, particularly in hypertensive patients. (Chung et al., 2014) In recent research done by Arhuidese et al, it was found that periprocedural hypertension is related to a four times higher risk of immediate peri-procedural stroke. (Arhuidese et al., 2020)

2.10 CAD and CAS

Coronary and carotid artery stenosis often co-exist as a part of systemic atherosclerotic disease. A study done by Waigand et al suggested that CAS in individuals with concurrent severe coronary artery disease is possible, safe, and could be an alternative to combined coronary and carotid surgery. (Waigand et al., 1998) Volkers et al concluded that concomitant CHD does not change the death risk or procedural stroke of CAS in comparison with CEA. In patients with CHD aged <75 years, CAS is as safe as CEA, however in those without a CHD history, the risk following CAS compared to CEA was only equivalent in those aged <70 years. (Volkers et al., 2019) Yoon et al also showed that CAS is possible, safe, and produces positive follow-up results in patients with concurrent coronary and carotid artery disease. (Yoon et al., 2000)

2.11 Hypercholesterolemia and CAS

A recognized risk factor for carotid artery stenosis and stroke is hypercholesterolemia. (Paraskevas et al., 2020) Carotid artery stenosis or atherosclerosis is commonly seen at the carotid bifurcation or proximal internal carotid artery, accounting for approximately 20 per cent of all ischemic strokes. Low-density lipoprotein cholesterol and high blood total cholesterol levels both increase the risk of atherosclerotic lesions developing and progressing. A high triglyceride level is also linked to an increased risk of developing atherosclerosis. Most thromboembolic ischemic events are caused by the "vulnerable plaque", which has a big lipid core, a thin fibrous cap, and intra-plaque bleeding. Statins are known to reduce serum

cholesterol levels and to promote plaque stabilization through various pleiotropic impacts like leukocyte intra-plaque infiltration, endothelial activation, decreasing subclinical systemic inflammation, as well as rising intimal smooth muscle cell migration. (Miura and Suzuki, 2019) However recent research on the influence of statin pretreatment on the problems of carotid stenting in asymptomatic patients, observational research by Jang et al concluded that Statin pre-treatment before CAS illustrated neither absolute nor dose-dependent influences against periprocedural problems in asymptomatic patients receiving CAS. (Jang et al., 2021)

2.12 Renal disease and CAS

According to a study by Yuo et al., CEA is not recommended for asymptomatic individuals with stage 5 CKD/end-stage renal disease. (Yuo et al., 2015) Dialysis patients were identified to have a 30-day death rate that was near 10% and a 3-year survival rate that was close to 43percent in their cohort. Their argument was based on the very high postoperative death reported in this category of patients, with the assumption that they cannot survive long enough to take advantage of the benefits of the CAS or CEA's stroke prevention. In the research by Klarin et al., the survival results of asymptomatic individuals with severe CKD were investigated, and those patients fared noticeably better. Their 5-year survival rate was >70%, indicating that the majority of these patients survive long enough to experience the benefits of the intervention. Additionally, their postoperative results were acceptable and low in terms of death and stroke rates. (Klarin et al., 2016) In another study by Adil et al, both CEA and CAS were related to 4-fold increased risks of in-hospital death in ESRD patients

and such explanations have questioned the advantage of carotid revascularization in these patients. (Adil et al., 2016)

2.13 Contralateral ICA occlusion and CAS

The study by Oka et al noted hemodynamic variations after CAS for serious ICA stenosis in patients with contralateral ICA occlusion. In the immediate post-procedure period, CBF did not alter substantially in both hyperperfusion and hemispheres or hemodynamic ischemia did not occur. Long-term improvements in cerebral hemodynamics were observed on both the treated side as well as the side of the ICA occlusion. CAS was thus efficient in avoiding ischemic attacks in both hemispheres from a hemodynamic perspective. (Oka et al., 2013) In a study done by Bracale et al, the occlusion time of ICA was 27.9±2 min in CEA, and 5±1 s in balloon inflation during CAS ($P<0.001$). The perioperative rate of stroke/TIA was not substantially greater in patients with contralateral ICA blockage after both CAS (1.85percent versus 1.04 per cent) and CEA (3.22percent versus 1.20percent). Additionally, there were no significant differences (CEA: 6.45percent versus 1.60percent; CAS: 3.70 per cent versus 1.56 per cent) in the prevalence of 30-day total stroke/ mortality. They concluded that CAS is an effective and safe option for treating carotid artery stenosis in individuals with contralateral occlusion. The CAS avoided general anaesthesia and had a substantially reduced time of ICA blockage during balloon inflation, which may result in a 1.7-fold lower risk following CAS. (Bracale et al., 2012)

2.14 Aortic arch type and CAS

The kind of aortic arch has a significant impact on CAS. More challenges and problems are linked to type III arches. (Shen et al., 2019) In CAS processes, adverse aortic arch anatomies are commonly seen and are linked to prolonged treatment times. The likelihood of a negative result rises when the catheter is handled for a longer period. Their data recommend that careful process planning intended at minimizing catheter manipulation time is crucial for enhancing the safety of CAS processes.(Burzotta et al., 2015) A study by Madhwal et al confirmed that anatomical aspects of the aortic arch have a significant role in determining the technical complexity of CAS. They proposed that the distance between the stenosis to be treated to the starting of the descending aorta as well as tortuosity predicted extended CAS times and subsequent risk of thromboembolism. (Surabhi Madhwal, 2008)

2.15 Circumferential calcification

The study by Tsutsumi et al. found no problems in any of the fifty-one lesions treated with CAS with EPDs, even though highly calcified lesions are a contraindication for CAS due to poor stent expansion and substantial procedural risks(Choi et al., 2004). Despite the residual stenosis being proportional to the plaque calcification's arc, they could achieve good dilation of all the lesions treated, regardless of the level of plaque calcification. According to their findings, CAS with EPDs is a secure and efficient way to treat lesions, including those that have almost complete circumferential plaque calcification. (Tsutsumi et al., 2008) However recent research by Lv et al concluded that the circumferential level of carotid calcification was related

to novel ischemic brain lesions after CAS and CAS must be prevented if feasible for carotid stenosis with huge circumferential calcified plaques. (Lv et al., 2021)

2.16 Use of multiple stents

The lesion features such as length, numerous stenoses, etc have a vital role in eventual CAS results, and a substantial and independent correlation also exists between the number of stents utilized and procedural CAS risk. This study by Lal et al. strongly recommends careful angiographic viewing of both lesions ends with suitable stent size and length selection, followed by precise insertion of the stent without delivery system movement during deployment. The usage of multiple stents is a surrogate indicator of the stent operator's technical competence and a possibly adjustable procedure-related risk factor for stroke in CAS. (Lal et al., 2019)

2.17 Nature of the Plaque

Risk factors for embolization and subsequent infarction following CAS include plaques with uneven surfaces or ulceration, plaques with a peripheral site of calcification, and enhancement of carotid plaque. CTA is a key method for assessing vascular stenosis and plaque features before receiving treatment. These plaque characteristics should be considered when choosing the optimal treatment for patients. (Qu et al., 2020) In a study by Tanemura et al, the 3-dimensional sequence of T1GRE was capable of identifying vulnerable plaques with increased risk for cerebral embolism during CAS. Greater signal intensity ratio and plaque volume studied with three-dimensional T1GRE images associated substantially with the presence of restricted diffusion foci in the brain post-CAS. They suggested that new risk factors

for cerebral embolism linked to CAS must be identified, including greater T1 intensity and bigger plaque volume on 3-dimensional T1GRE images. (Tanemura et al., 2013)

2.18 Complications seen with CAS

Apart from the local complications at the puncture site and systemic complications, there is the possibility of cerebral ischemic complication, cerebral haemorrhage due to hyperperfusion syndrome, complications at the site of stent insertion, and embolic protection device-related complications.

2.18.1Embolic stroke

After carotid artery stenting, there is micro embolisation seen in almost all of the cases, which has been seen by researchers using trans thoracic Doppler. Also on diffusion-weighted imaging up to 50% of these cases show foci of restricted diffusion. But most of the cases are clinically silent with patients not developing any symptoms.

2.18.2Hyperperfusion syndrome

Once the stenosed carotid artery is dilated after stent placement, the brain immediately receives high blood flow and the brain gets no time to adapt to this increased pressure of blood. However, the majority of the patients can constrict their blood vessels to correct this increased perfusion pressure after a few minutes of CAS. This is due to auto-regulation in the brain. Few patients suffer from the lack of this capability of auto-regulation as they have been chronically exposed to low blood flow in the brain, thereby having hyperperfusion syndrome due to continued elevated perfusion pressure. (Kim et al., 2013) The hyperperfusion increases the intracranial

pressure thereby leading to headache, vomiting, seizures or reduced consciousness, and sometimes fatal cerebral haemorrhage too. It takes a few days generally for the hyperperfusion syndrome symptoms to manifest after stenting, but in a few cases, the symptoms are seen just after the procedure. The SBP should ideally be maintained on the lower side of 140 mmHg during and post-procedure.

2.18.3Cerebral haemorrhage

After CAS, in about 0.7% of cases, intracerebral haemorrhage can happen. It is the most dreaded complication and is generally forewarned by the symptoms of hyperperfusion. (Ogasawara et al., 2007) The bleeding into the parenchyma usually happens if there is failure to control the BP, inappropriate anticoagulation, excessive guide wire manipulation, presence of an aneurysm in intracranial circulation, following reperfusion of an infarcted territory. So these condition needs extra vigilance on the part of caregivers. Cerebral haemorrhage after CAS mostly happens just after some hours post-procedure and often leads to fatality. In case of deterioration of consciousness post development of unbearable headache, ICH should be ruled out by NCCT. After confirming the bleed by CT scan of the head, the coagulation profile of the patient may be corrected by giving IV protamine sulfate. Anticoagulants and antiplatelet agents should be withheld for 3 days at least but at the increased risk of in-stent thrombosis.

2.18.4Spasm and dissection of the carotid artery

Conditions usually associated with spasm of the ICA after CAS are tortuosity of the artery, use of an EPD, and inappropriate manipulation of the wire. If a spasm is

detected during the procedure the guidewire is to be removed immediately and infusion of nimodipine or nitroglycerin done locally into the carotid artery.

Although rare, dissection of the carotid artery is one of the major complications which can occur during CAS in cases where the carotid artery is tortuous or due to inappropriate manipulation of hardware. Also, dissection is seen after ballooning of the stent distal part, post-stenting of the and excessive pushing of the guiding catheter. Small non-flow limiting dissection can be managed conservatively and heal spontaneously in due course of treatment. But if the dissection extends distally or leads to drop ion distal perfusion another stent placement is needed to repair the dissected artery.

2.18.5Stent thrombosis

Stent thrombosis although a rare complication can happen if antiplatelet agents are not used optimally or if, the stent sizing is inaccurate. It is also noted after the use of balloon dilatation in case of inadequate stent opening. Aspirin and clopidogrel, which form the part of most common DAPTs should be started at least 5 days before the planned procedure. In case of emergent procedures to make up for the desired anticoagulation status, an appropriate loading regimen is to be used before the procedure. Post-procedure the DAPTs need to be given for at least 4 weeks and Aspirin to be continued life-long thereafter. Patients with radiation-induced stenosis are prone to develop late in-stent thrombosis and thus require a prolonged duration of antiplatelet treatment.

2.19 Reason for stenting – which are the main risk factors

Carotid artery stenting is mainly done for patients who are not candidates for general anaesthesia which is required in CEA. In cases where there is damage to the contralateral little vocal cord due to previous CEA or neck surgery can also be undertaken for CAS. In previous neck surgery cases, CAS is preferred. Patients with cancers of the head and neck region with irradiation of the neck are also good candidates for CAS. In cases where restenosis has occurred after CEA can also be safely undertaken for CAS.

CAS is generally reserved for high-risk patients for CEA, like patients with pulmonary diseases, a history of recent MI or congestive heart failure, and patients with unstable angina pectoralis. The patient who had undergone radiation therapy in the head and neck region for a prior malignancy has fibrosis of tissues and is difficult to operate upon. Other indications are in the patients with contralateral vocal cord palsy; tracheostomised patients, the presence of contralateral CCA/ ICA occlusion; and cases with recurrent stenosis after carotid endarterectomy (1).

The transfemoral approach is contraindicated in patients with prohibitive aortic arches, like an aortic arch with heavy calcification or a type III aortic arch. Patients allergic to intravenous contrast medium pose a moderate threat to CAS procedure and are a relative contraindication.

2.20 EPD usage

Embolic protection devices are used distally in the internal carotid artery to catch the microemboli shower and have specially designed pores of 100–150 μm. FilterWire

EZ Embolic Protection System from Boston Scientific, Angioguard and Guardwire from Cordis Endovascular, Emboshield NAV6 from Abbott Vascular, and the Spider FX from Covidien are the available devices currently on market. These devices maintain the blood flow to the cerebrum during the procedure, which reduces the risk of ischemia. They also allow the use of contrast for positioning the stent correctly. These devices permit the use of a sheath of 6–7 Fr lumen. The drawback of these EPDs is that these devices must pass across the lesion to be placed distally before they can provide any embolic protection. As these devices are inflexible and relatively bulky, it is not possible to pass the stenosis with less than a 0.014-inch guide wire. They provide only limited protection in case the anatomy of the distal ICA is tortuous. They are not capable of capturing microemboli less than the pore size and there is a risk of them getting entrapped in a stent while extracting them once the procedure is completed.

3 MATERIALS AND METHODS

3.1 Introduction

Primarily this is a data analytical study. This study has a retrospective and a prospective arm (01 Jan 2015 to the date of IEC approval are included in the retrospective arm and from the date of IEC approval till 31 May 2022 in the prospective arm). Patients with Carotid artery stenosis coming to Sree Chitra hospital in neurosurgery, neurology or interventional radiology clinics by referrals from outside hospitals or via consultations from other departments were taken up for the study. From this patients with high-risk carotid stenting were included in the study. These patients underwent carotid artery stenting and the various patients' high-risk parameters and their relationship to the outcome as per the study protocol were studied.

Radiological and Clinical data of the patients were analysed. For this purpose patients, files were taken out from MRD / details stored in the computer archive of the hospital was used. Angiograms were analysed from the hospital computer archive in the picture archiving and communicating system (PACS). After the collection of data statistical analyses were done to generate the inferences.

Retrospective analysis of data was studied from the patient electronic records and archived Digital Subtraction Angiography (DSA) images of patients undergone CAS since 2015. Patients with Carotid artery stenosis coming to Sree Chitra hospital in neurosurgery, neurology or interventional radiology clinics by referrals from outside hospitals or via consultations from other departments were taken up for the study. The patients who will undergo CAS as per the present protocol were included in the study. Consent was obtained from patient bystanders. Patients unable to give informed

consent, normal/healthy volunteers, Prisoners, and students/staff of the institute were not included in the study.

All patients with carotid artery stenosis who underwent CAS from 01 Jan 2015 to the date of IEC approval were included in the retrospective arm and patients presenting with carotid artery stenosis and undergoing CAS from the date of IEC approval till 31 May 2022 in the prospective arm.

3.2 Key Inclusion Criteria

3.2.1 General criteria

Age should be more than 18 years.

Symptomatic with a stenosis > 50% {North American Symptomatic Carotid Endarterectomy Trial (NASCET) criteria (*Stroke*, 1991)}

Asymptomatic with a stenosis > 70% by CT angiography.

3.2.2 Major criteria for high risk

3.2.2.1 Need one or more of for including in to the study.

(i) Severe cardiac dysfunction on evaluation {Left ventricular ejection fraction less than 30% or New York Heart Association (NYHA) class III}

(ii) Dialysis-dependent renal failure

(iii) Restenosis after previous CEA

(iv) High internal carotid artery (ICA) or common carotid artery (CCA) lesions below clavicle

(v) Prior radiation to neck

(vi) Prior radical neck surgery

(vii) Spinal immobility

(viii) Tracheostomy stoma

(ix) Contralateral laryngeal nerve paralysis

3.2.2.2 Or need two or more of the following for entry:

(i) Need open heart surgery within 30 days

(ii) Two or more diseased coronary arteries with 70% stenosis

(iii) Contralateral ICA occlusion

(iv) Unstable angina

(v) Myocardial Infarction (MI) within 30 d and need carotid revascularization

3.3 Key exclusion criteria

(i) Patient has an evolving stroke

(ii) Patient has a history of major ipsilateral stroke

(iii) Patient has a neurologic deficit not due to stroke that would confound the neurologic assessment

(iv) Patient has had a recent (< 7 days) stroke

(v) Patient had hemorrhagic transformation of an ischemic stroke within the past 60 days

(vi) Known cardiac sources of emboli

3.4 Preparation of the patient

All patients were pre-treated with dual antiplatelets (Tab Aspirin 150mg once a day (OD) and Tab Clopidogrel 75mg OD) at least 7 days before the treatment.

One bilateral neck vessel Doppler study, CT angiogram and relevant lab investigations were done before the carotid stenting procedure. No extra/additional tests/procedures were done exclusively for the study. All the above-mentioned tests are part of the routine evaluation of each carotid stenting patient.

Stenting procedures were conducted in GE Innova 3100 biplane neurovascular catheterization lab.

All stenting procedures were planned under local anaesthesia, and general anaesthesia was considered only in cases where prolonged supine positioning is difficult, especially in severely obese and extreme tortuous vascular anatomy.

Preferred vascular access: right common femoral artery and right brachial access were considered only in case of extreme tortuosity of the left common carotid artery.

Systemic heparinization protocol: was followed with 80 IU/Kg body weight as a bolus and 1000 IU every hour keeping Activated Clotting Time (ACT) two times above the baseline value.

3.5 Stenting procedure

7F Guiding catheter/long sheath was placed into the ipsilateral common carotid artery after a baseline four-vessel angiogram using a 5F vertebral glide catheter.

Through the guiding system, the lesion was crossed using a 0.014-inch neuro guide wire, and embolic protection devices were deployed. If needed, pre dilatation of the carotid stenosis was done using a 3x15mms monorail coronary angioplasty monorail balloon. Carotid stenting was performed after the removal of the angioplasty balloon. Nitinol stents were deployed across the lesion ensuring the complete coverage of the carotid plaque. The embolic protection device and guide wire were removed after the deployment of the stent. Post-procedure ipsilateral Intra cranial angiograms were carried out to check for any vessel dropout and in-stent thrombosis. Femoral arterial and venous sheath were removed once the ACT value comes below 150 seconds. Patients were transferred to the stroke intensive care unit and were observed for any neurological deficits and puncture site hematoma.

3.6 Post-procedure evaluation and follow-up

Neurologic examination was done by a neurologist who was not a part of the study using the National Institutes of Health Stroke Scale and modified Rankin Scale at 24 hours, 30 days, and 3 months.

Transient ischemic attack/stroke questionnaire at 30 days and 3 months and carotid duplex ultrasonography at 30 days were done.

The primary study endpoint was a combined data of all deaths, strokes, and nonfatal MIs within 30 days of the procedure plus ipsilateral strokes between days 30 and 90.

3.7 Following data were collected for analysis

Patient's data: Age, sex, comorbidities like systemic hypertension, diabetes mellitus, dyslipidemia, smoking, severe renal disease, cardiac disease.

Access related: Type II or III arch, calcification of arch, Tandem lesions in innominate artery of CCA, angulation between ICA- CCA ≥60°

Lesion related: Stenosis severity, lesion ulceration, circumferential calcification, lesion at ostial of ICA with maximal stenosis, Long lesion of length >10–15 mm, use of more than one stent, hypoechoic plaques on ultrasound and presence sequential lesions.

Distal ICA: Diffuse atherosclerosis, excessive tortuosity, tandem lesion, presence of fresh thrombus or reduced calibre.

3.8 Statistical Analysis

The data collected was analysed using IBM SPSS Statistics for Windows, Version 23.0. (Armonk, NY: IBM Corp). Frequency analysis and percentage analysis were used for categorical variables and the mean & standard deviation were used for continuous variables. Unpaired sample t-test was used for finding a significant difference between the bivariate samples in the independent groups. The Chi-Square test was used to find the significance of categorical data. The probability value </=0.05 was considered significant.

No specific gender, class, caste, ethnicity or race bias is intended in the study.

4 RESULTS

A total of 49 study subjects were imaged as a part of the study. One of the cases included carotid stenting as a part of the mechanical thrombectomy due to occlusion by the thrombus. Rest 48 cases were due to carotid artery stenosis.

4.1 Demographics

82% of the patients were male. The minimum age in this study was 49 years and the eldest patient was of age 82 years. The median age of 66 years in this study. There were 29% smokers, 67% had diabetes mellitus, 86% were hypertensive, 43% had coronary artery disease, 31% had dyslipidaemia, 12% had severe renal disease and 27% had cardiac disease in this study.

4.2 Sex distribution

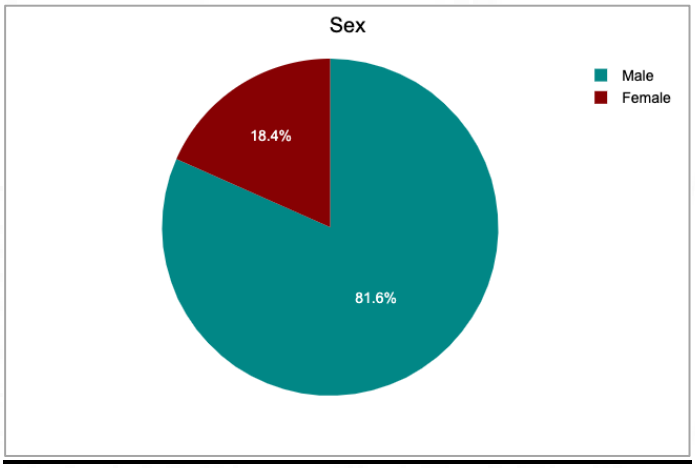

Fig. 1. Frequency distribution of sex in the study population

4.3 Age distribution

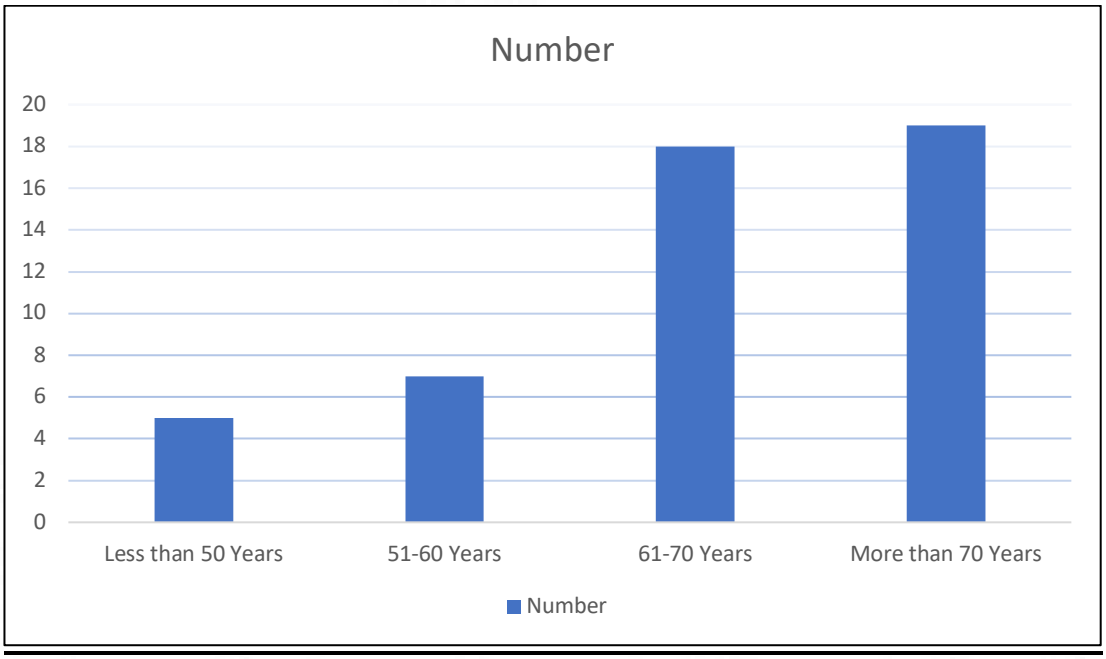

Fig. 2. Age distribution in the study population

4.4 Comorbidities/ risk factors in study population

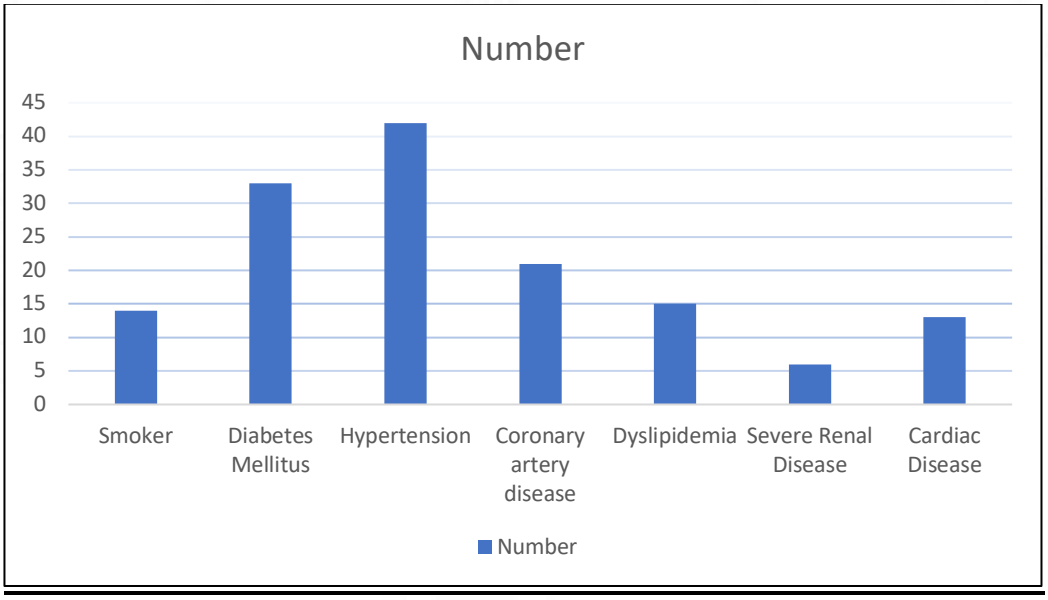

Fig. 3. Comorbidities/ risk factors in study population

4.5 Major criteria for high risk in study population

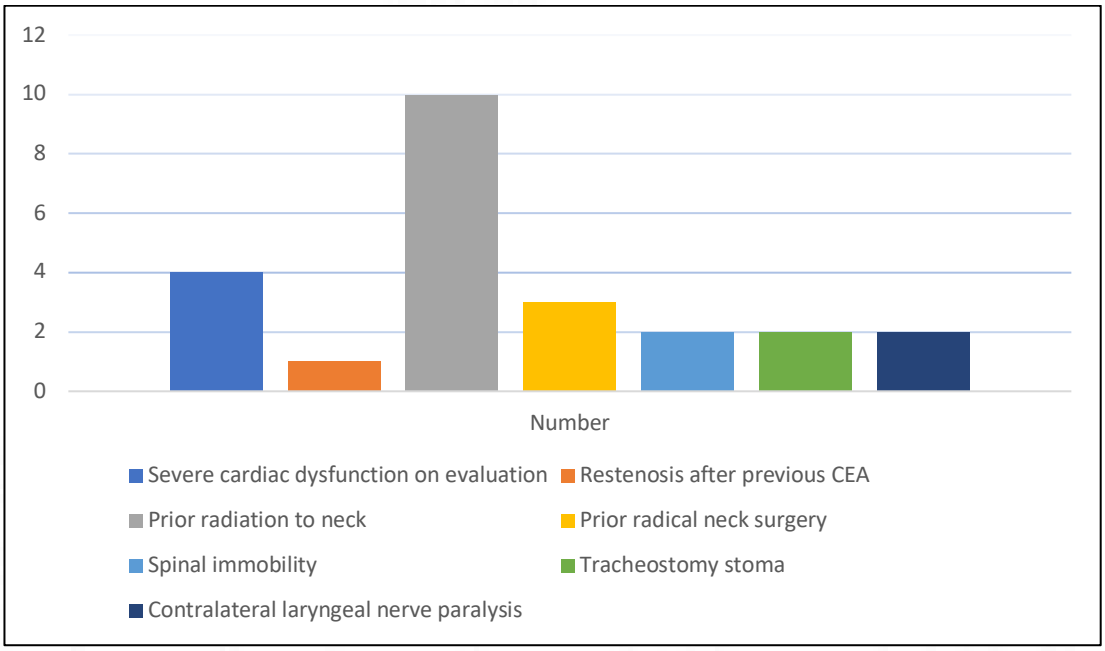

Fig. 4. Major criteria for high risk in study population

4.6 Minor criteria for high risk in study population

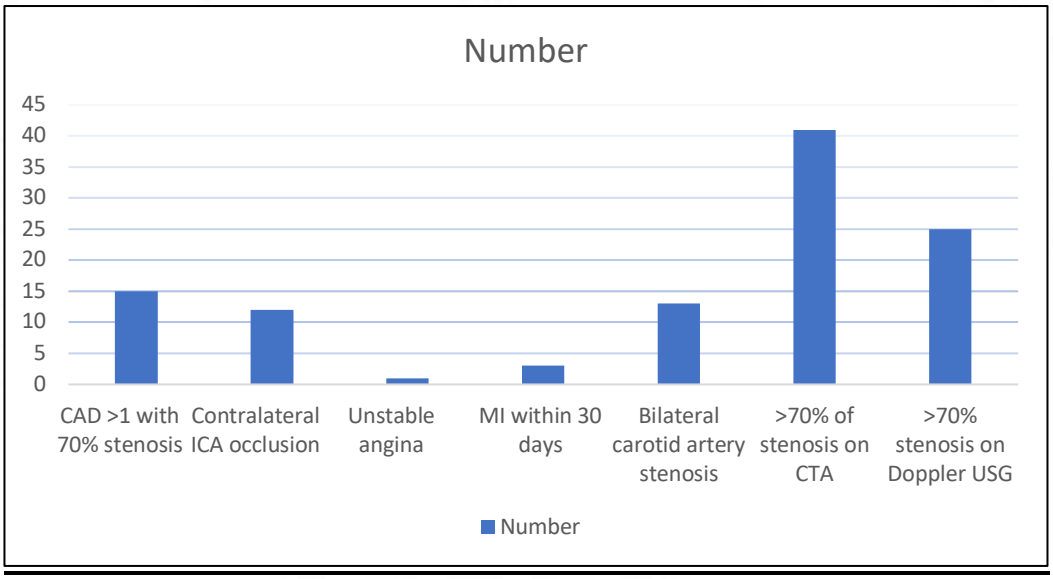

Fig. 5. Minor criteria for high risk in study population

4.7 Coronary artery disease and In hospital adverse events.

Table 1. Coronary artery disease and in hospital adverse events

		In hospital adverse events NCP		
		No	Yes	Total
Coronary Artery Disease	No	28	0	28
	Yes	16	5	21
	Total	44	5	49

Chi-Square Test

Chi^2	7.42
df	1
p	.006

A Chi^2 test was performed between Coronary Artery Disease and In hospital adverse events NCP. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi^2 test were not met. There was a statistically significant relationship between Coronary Artery Disease and In hospital adverse events NCP, $\chi^2(1) = 7.42$, $p = .006$, Cramér's $V = 0.39$

This results in a p-value of .006 which is lower the defined significance level of 5%. The Chi^2 test is therefore significant and the null hypothesis is rejected.

In our study we found that coronary artery disease in patients undergoing carotid artery stenting is related to in hospital adverse events.

4.8 Severe renal disease and In hospital adverse events.

Table 2. Severe renal disease and in hospital adverse events

		In hospital adverse events NCP		
		No	Yes	Total
Severe Renal Disease	No	40	3	43
	Yes	4	2	6
	Total	44	5	49

Chi-Square Test

Chi^2	3.99
df	1
p	.046

A Chi^2 test was performed between Severe Renal Disease and In hospital adverse events NCP. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi^2 test were not met. There was a statistically significant relationship between Severe Renal Disease and In hospital adverse events NCP, $\chi^2(1) = 3.99$, $p = .046$, Cramér's $V = 0.29$

This results in a p-value of .046 which is lower the defined significance level of 5%. The Chi^2 test is therefore significant and the null hypothesis is rejected.

In our study we found that severe renal disease in patients undergoing carotid artery stenting is related to in hospital adverse events.

4.9 Severe cardiac dysfunction on evaluation and In hospital adverse events.

Table 3. Severe cardiac dysfunction and in hospital adverse events

		In hospital adverse events NCP		
		No	Yes	Total
Severe cardiac dysfunction on evaluation	No	42	3	45
	Yes	2	2	4
	Total	44	5	49

Chi-Square Test

Chi^2	7.53
df	1
p	.006

Fishers Exact Test

	p
Left-sided	.998
Two-sided	.047
Right-sided	.047

A Chi^2 test was performed between Severe cardiac dysfunction on evaluation and In hospital adverse events NCP. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi^2 test were not met. There was a statistically significant relationship between Severe cardiac dysfunction on evaluation and In hospital adverse events NCP, $\chi^2(1) = 7.53$, $p = .006$, Cramér's $V = 0.39$

A Fisher exact test was performed between Severe cardiac dysfunction on evaluation and In hospital adverse events NCP. There was a statistically significant relationship between Severe cardiac dysfunction on evaluation and In hospital adverse events NCP, $p = .047$

This results in a p-value of .006 which is lower the defined significance level of 5%. The Chi^2 test is therefore significant and the null hypothesis is rejected.

In our study we found that severe cardiac dysfunction on evaluation in patients undergoing carotid artery stenting is related to in hospital adverse events.

4.10 ICA-CCA angulation ≥60° and In hospital adverse events.

Table 4. ICA-CCA angulation ≥60° and in hospital adverse events

		In hospital adverse events NCP		
		No	Yes	Total
ICA-CCA angulation ≥60°	<30°	30	0	30
	30°-59°	11	3	14
	>60°	3	2	5
	Total	44	5	49

Chi-Square Test

Chi^2	10.18
df	2
p	.006

A Chi2 test was performed between ICA-CCA angulation ≥60° and In hospital adverse events NCP. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi2 test were not met. There was a statistically significant relationship between ICA-CCA angulation ≥60° and In hospital adverse events NCP, $\chi^2(2) = 10.18$, p = .006, Cramér's V = 0.46

This results in a p-value of .006 which is lower the defined significance level of 5%. The Chi2 test is therefore significant and the null hypothesis is rejected.

In our study we found that ICA-CCA angulation ≥60° in patients undergoing carotid artery stenting is related to in hospital adverse events.

4.11 Increasing stenosis severity and Procedure related complications.

Table 5. Increasing stenosis severity and procedure related complications

		Procedure related complications		
		No	Yes	Total
Increasing stenosis severity	50-69%	6	0	6
	70-99%	39	3	42
	100%	0	1	1
	Total	45	4	49

Chi-Square Test

Chi^2	11.84
df	2
p	.003

A Chi2 test was performed between Increasing stenosis severity and Procedure related complications. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi2 test were not met. There was a statistically significant relationship between Increasing stenosis severity and Procedure related complications, $\chi^2(2) = 11.84$, $p = .003$, Cramér's $V = 0.49$

This results in a p-value of .003 which is lower the defined significance level of 5%. The Chi2 test is therefore significant and the null hypothesis is rejected .

In our study we found that increasing stenosis severity has increased procedure related complications.

4.12 Multiple stent use and Procedure related complications.

Table 6. Multiple stent use and procedure related complications

		Procedure related complications		
		No	Yes	Total
Multiple stent use	Single stent	45	3	48
	Two stents	0	1	1
	Total	45	4	49

Chi-Square Test

Chi^2	11.48
df	1
p	.001

A Chi2 test was performed between Multiple stent use and Procedure related complications. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi2 test were not met. There was a statistically significant relationship between Multiple stent use and Procedure related complications, $\chi^2(1) = 11.48$, $p = .001$, Cramér's $V = 0.48$

This results in a p-value of .001 which is lower the defined significance level of 5%. The Chi2 test is therefore significant and the null hypothesis is rejected.

In our study we found that multiple stent use is related to procedure related complications.

4.12 Tandem lesion in CCA/ innominate & 30 Day MI/ Stroke.

Table 7. Tandem lesion in CCA or innominate and 30 Day MI/ Stroke

		30 Day MI/ Stroke		
		No	Yes	Total
Tandem lesion in CCA or innominate	No	38	1	39
	Yes	8	2	10
	Total	46	3	49

Chi-Square Test

Chi^2	4.21
df	1
p	.04

A Chi2 test was performed between Tandem lesion in CCA or innominate and 30 Day MI/ Stroke. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi2 test were not met. There was a statistically significant relationship between Tandem lesion in CCA or innominate and 30 Day MI/ Stroke, $\chi^2(1) = 4.21$, $p = .04$, Cramér's $V = 0.29$

This results in a p-value of .04 which is lower the defined significance level of 5%. The Chi2 test is therefore significant and the null hypothesis is rejected.

In our study we found that tandem lesion in CCA or innominate had more number of 30 Day MI/ Stroke events.

4.13 Nature/ HU of Plaque and Plaque echogenicity

Table 8. Nature/ HU of plaque and plaque echogenicity

		Plaque echogenicity					
		Echolucent	Isoechoic	Echogenic	Calcified	NA	Total
Nature/ HU of Plaque	Calcium (>130 HU)	0	0	0	1	0	1
	Fibrous tissue (60 to 130 HU)	1	1	1	0	6	9
	Lipid tissues (<60 HU)	5	2	2	0	15	24
	NA	2	0	3	0	10	15
	Total	8	3	6	1	31	49

Chi-Square Test

Chi^2	52.08
df	12
p	<.001

A Chi2 test was performed between Nature/ HU of Plaque and Plaque echogenicity. At least one of the expected cell frequencies were less than 5. Therefore, the assumptions for the Chi2 test were not met. There was a statistically significant relationship between Nature/ HU of Plaque and Plaque echogenicity, $\chi^2(12) = 52.08$, p = <.001, Cramér's V = 0.6

This results in a p-value of <.001 which is lower the defined significance level of 5%. The Chi2 test is therefore significant and the null hypothesis is rejected.

In our study we did ultrasound of the carotids and characterised the echogenicity of the plaque into echolucent with increased fatty content or lipid rich necrotic core, isoechoic, echogenic with increased fibrous tissue and calcified. Similarly on CT the Hounsfield units of the plaque was measured and labelled as calcified (>130 HU), fibrous tissue (60 to 130 HU) or lipid tissues (<60 HU). The relationship was significant with p value of 0.001 and helps in determining the nature of the plaque and the risk associated with it by using any of the modalities available.

4.14 Aortic arch type and Total Fluoroscopic time

Table 9. Aortic arch type and total fluoroscopic time

Groups	N	Mean Rank
Type 3	13	31.96
Type 2	22	19.09
Type 1	13	27.92
NA	1	26.5
Total	49	

Statistics

	Values
Chi^2	9.76
df	3
p	.021

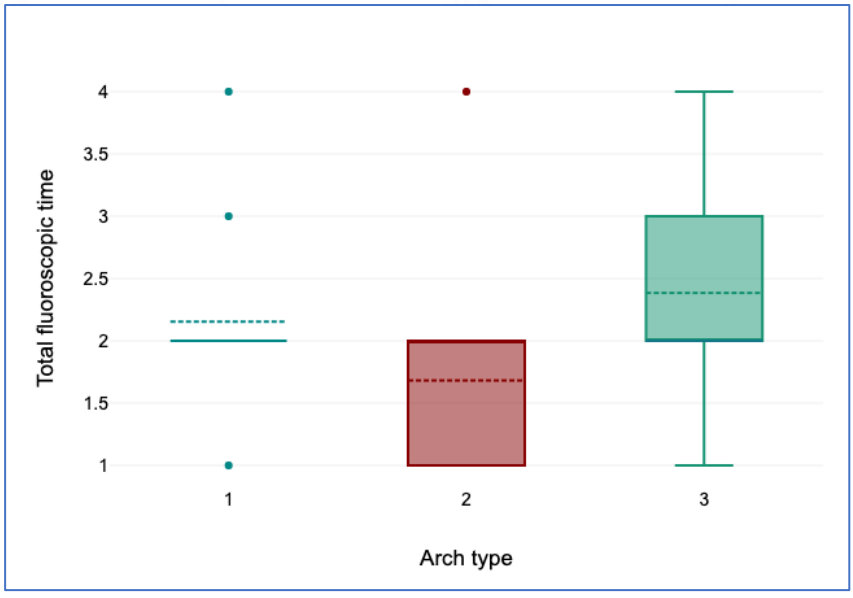

Fig. 6. Box plot between total fluoroscopic time and aortic arch type

Kruskal-Wallis Test

A Kruskal-Wallis test showed that there is a significant difference between the categories of the independent variable with respect to the dependent variable Total fluoroscopic time, p=.021. Thus, with the available data, the null hypothesis is rejected.

Our study also found that the difficult type of aortic arch was associated with increased fluoroscopic time during the procedure of carotid artery stenting and Kruskal-Wallis test showed significant p value of 0.021.

5 DISCUSSION

Carotid artery stenosis is a cause of ischaemic stroke in about 15% of the cases(Flaherty et al., 2013). The incidence of stroke in India ranged from 108 to 172/per 100,000 people per year (Jones et al., 2022) during the past two decades in different parts of the country. Atherosclerosis of the carotid artery is a significant cause of stroke, accounting for 30% of all ischemic strokes. This study was performed to analyse the clinical and angiographic outcome predictors in high-risk carotid stenting in our population. These are the cases which are not generally suitable for carotid endarterectomy. A total of 49 patients underwent carotid artery stenting over the last 6 years. Only limited studies analysing these outcome predictors were available on literature search internationally, with none from India published show for so far.

5.1 Demographics

The majority (75%) of the study subject were in the age group more than 60 years. This was similar to the data on the incidence of stroke in the Trivandrum stroke registry in which the median age was similar approximately 67 years (Sridharan et al., 2009). Our study population ranged from 49 years to 82 years with a median age of 66 years. The male to female ratio of the subjects was 4.4:1, which indicated that relatively more males underwent carotid artery stenting secondary to symptomatic carotid artery stenosis.

5.2 Comorbidities/ risk factors in the study population

The clinical risk factors which were seen in our study were: smoking 29%, diabetes mellitus 67%, hypertension 86%, coronary artery disease 43%, dyslipidaemia 31%, severe renal disease 12% and cardiac disease 27%. This was similar to the risk factor in the population with stroke incidence. We had a relatively higher percentage of cases of coronary artery disease and renal disease. This is attributed to the fact that patients who had coronary artery disease / renal disease had a higher risk for surgical morbidity/mortality and hence were not taken up carotid endarterectomy, instead underwent carotid artery stenting.

5.3 Coronary artery disease and In-hospital adverse events.

In our study, we found that coronary artery disease in patients undergoing carotid artery stenting is related to in-hospital adverse events. However, a study by Volkers et al (Volkers et al., 2019) stated that CAD does not modify the procedural stroke or death risk of CAS compared with CEA. CAS might be as safe as CEA in patients with a history of CAD aged <75 years, whereas, for patients without a history of CAD, risk after CAS compared with CEA was only equal in those aged <70 years. We had nine patients having adverse events.

Patient 2 presented with altered behaviour on day 2. Patient 3 had an acute infarct in the left ACA-MCA watershed territory post-procedure day.

Patient 7 had acute pulmonary oedema on post-procedure day 3. Patient 8 presented with malignant hypertension in the evening of the day procedure was done.

Patient 12 had worsening upper limb drift and ataxia on post-procedure day 11 and a repeat CT brain done showed no acute infarcts. The next day patient sustained NSTEMI with pulmonary oedema and hypotension which was managed with Lasix, inotropes and intravenous heparin. His hospital course was complicated by lower respiratory infection evident by increased infiltrates on chest Xray and increased total counts, managed with parenteral antibiotics.

Patient 29 developed anaemia postoperatively with a haemoglobin value of 6.5 Gm%, which was corrected with 2 units of packed cell transfusion.

Patient 32 had sudden onset tachypnoea on post-procedure day 2 with ECG showing poor R wave progression and elevated Trop T (>2000 ng/l). A cardiology review was sought and he was diagnosed to have NSTEMI. He was managed by Inj. LMWH and dual antiplatelets were continued. He was confused for one day, repeat CT brain did not show any new infarct or bleeds.

Patient 34 was detected to have a haematoma in the right groin above the puncture site and an interventional radiology opinion was sought. Ultrasound revealed right groin puncture site pseudoaneurysm which was obliterated by compression under USG guidance and advice to continue further conservative management.

Patient 47 had post-procedure blood pressure fluctuations. Post-procedure he also had new onset dysarthria along with unsteadiness on standing. His repeat MRI brain showed acute infarcts involving the right parieto-occipital region (MCA-PCA watershed), and right cerebellar hemisphere (PICA and SCA territory).

5.4 Severe renal disease and In-hospital adverse events.

In our study, we found that severe renal disease in patients undergoing carotid artery stenting is related to in-hospital adverse events. Chronic kidney disease (CKD) was seen as an independent predictor of CAS periprocedural complications and long-term disability in the study by various studies (Saw et al., 2004)(Wimmer et al., 2012)(Dinculescu et al., 2015). On the other hand, a care registry analysis by Gruberg et al contradicted our results and showed that severe renal disease was not an independent predictor of the early outcome (Gruberg et al., 2014). We had two patients having adverse events.

Patient 12 had worsening upper limb drift and ataxia on post-procedure day 11 and a repeat CT brain done showed no acute infarcts. The next day patient sustained NSTEMI with pulmonary oedema and hypotension which was managed with Lasix, inotropes and intravenous heparin. His hospital course was complicated by lower respiratory infection evident by increased infiltrates on chest Xray and increased total counts, managed with parenteral antibiotics.

Patient 32 had sudden onset tachypnoea on post-procedure day 2 with ECG showing poor R wave progression and elevated Trop T (>2000 ng/l). A cardiology review was sought and he was diagnosed to have NSTEMI. He was managed by Inj. LMWH and dual antiplatelets were continued. He was confused for one day, repeat CT brain did not show any new infarct or bleeds.

5.5 Severe cardiac dysfunction on evaluation and In-hospital adverse events.

In our study, we found that severe cardiac dysfunction on evaluation in patients undergoing carotid artery stenting is related to in-hospital adverse events. However, a study by Wimmer et al found no significant association between severe cardiac dysfunction on evaluation and in-hospital adverse events (Wimmer et al., 2012). We had two patients having adverse events.

Patient 4 had an acute infarct in the left ACA-MCA watershed territory on the post-procedure day. Patient 34 was detected to have a haematoma in the right groin above the puncture site and an interventional radiology opinion was sought. Ultrasound revealed right groin puncture site pseudoaneurysm which was obliterated by compression under USG guidance and advice to continue further conservative management.

5.6 ICA-CCA angulation ≥60° and In-hospital adverse events.

In our study, we found that ICA-CCA angulation ≥60° in patients undergoing carotid artery stenting is related to in-hospital adverse events. A study by Myouchin et al found that placement of the Carotid Wallstent is difficult in increased ICA-CCA angulation (Myouchin et al., 2013). Similarly, Werner et al in their single centre experience of 833 consecutive cases concluded that anatomic variables like ICA-CCA angulation ≥60° contributed to a higher periprocedural incidence of stroke and TIA in carotid artery stenting (Werner et al., 2012). We had four patients having adverse events.

Patient 12 had worsening upper limb drift and ataxia on post-procedure day 11 and a repeat CT brain done showed no acute infarcts. The next day patient sustained NSTEMI with pulmonary oedema and hypotension which was managed with Lasix, inotropes and intravenous heparin. His hospital course was complicated by lower respiratory infection evident by increased infiltrates on chest Xray and increased total counts, managed with parenteral antibiotics.

Patient 36 developed hypotension after the procedure which lasted for 24 hours treated with inotropes after ICA stenting. Cardiac re-evaluation was normal.

Patient 43 was detected to have anaemia which was corrected with a packed red cell transfusion. She had a febrile non-haemolytic reaction during the transfusion of packed red cells.

Patient 47 had post-procedure blood pressure fluctuations. Post-procedure he also had new onset dysarthria along with unsteadiness on standing. His repeat MRI brain showed acute infarcts involving the right parieto-occipital region (MCA-PCA watershed), and right cerebellar hemisphere (PICA and SCA territory).

5.7 Increasing stenosis severity and Procedure-related complications.

In our study, we found that increasing stenosis severity has increased procedure-related complications and the results were statically significant with a p-value of 0.003. The cases with 50-69% stenosis had no procedure-related complications but cases having 70-99% or 100% stenosis had 4 cases of procedure-related complications.

Patient 7 had a complication at the right CFA puncture site due to mal deployment of the Vascular closure device and the patient was shifted for emergent

vascular surgical repair. Patient 19 had an area cut off in the right mid part of the angular branch of the MCA.

Patient 21 had mild distal migration of the stent and another Protege bare metal stent (8 x 40 mm) was deployed across the stenosis (with overlap with the previously deployed stent). Patient 45 had transient bradycardia and hypotension after deployment of the stent.

5.8 Multiple stent use and Procedure-related complications.

In our study, we found that multiple stent use is related to procedure-related complications and the results were statically significant with a p-value of 0.001. A study by Lal et al observed that in carotid stenting, a significant and independent relationship existed between the number of stents used and the procedural risk of CAS (Lal et al., 2019). They postulated that this was an indicator of the operator's inexperience with the procedure. Additionally, the study by et al showed in their results that the isolated endovascular group with tandem lesions had a 30-day death/stroke rate of 1.5% (Robertson et al., 2020).

Patient 2 had stent buckling with 60% stent stenosis proximally. Patient 21 had mild distal migration of the stent with stasis of flow and therefore another Protege bare metal stent (8 x 40 mm) was deployed across the stenosis (with overlap with the previously deployed stent).

5.9 Tandem lesion in CCA/innominate and 30 Day MI/Stroke.

In our study, we found that tandem lesions in CCA or innominate had more number of 30 Day MI/ Stroke events and the results were statically significant with a p-value of 0.04. Similarly, long-term data in a study by et al showed a relatively high number of adverse events with carotid tandem lesions in symptomatic patients (Meershoek et al., 2019). Additionally, a study by et al showed that patients with tandem lesions had a 30-day death/stroke rate of 1.5% (Robertson et al., 2020).

5.10 Nature/ HU of Plaque and Plaque echogenicity

In our study, we did an ultrasound of the carotids and characterised the echogenicity of the plaque into echolucent with increased fatty content or lipid-rich necrotic core, isoechoic, echogenic with increased fibrous tissue and calcified. Similarly, on CT the Hounsfield units of the plaque were measured and labelled as calcified (>130 HU), fibrous tissue (60 to 130 HU) or lipid tissues (<60 HU). The relationship was significant with a p-value of 0.001 and helps in determining the nature of the plaque and the risk associated with it by using any of the modalities available. By applying these thresholds, Ajduk et al concluded that it is possible to identify the plaques with a lipid-rich necrotic core from others (Ajduk et al., 2009). Based on this analysis, calcified plaques were found to be 21 times less likely to be symptomatic than noncalcified plaques, whereas fatty plaques were associated with an increased risk of rupture (Nandalur et al., 2007).

5.11 Aortic arch type and Total Fluoroscopic time

Our study also found that the difficult type of aortic arch was associated with increased fluoroscopic time during the procedure of carotid artery stenting and the Kruskal-Wallis test showed a significant p-value of 0.021. Our results were in line with the data generated by the study of Shen et al where the fluoroscopy time was significantly longer in patients with Type III than in Type I and II arches (Shen et al., 2019). However in an earlier study by Madhwal et al, the presence of a Type 3 arch and angulated takeoff showed a trend towards increased time, but it was not statistically significant. As this study has limited power due to the small number of patients and may have failed to detect a small, but significant, difference between the two groups (Surabhi Madhwal, 2008).

5.12 Limitations

A small sample size walls limitation in this study which affected the power of the study. This is because only high-risk carotid artery stenting is performed in our institute. Another limitation was that carotid ultrasound was not available for all the retrospective patients. This could affect the results of the correlation between the ultrasound and CT findings on the nature of plaque. Future studies with a larger proportion of prospective patients and evaluations with much larger samples may be important in validating the findings of our study and proving its utility.

6 SUMMARY AND CONCLUSION

The study of clinical and angiographic outcome predictors in high risks carotid stenting was done on 49 patients which included both prospective and retrospective cases from a single institute in South India. Technical success was achieved in 100% of the cases. We found out that the clinical factors which were significantly related to in-hospital adverse events were coronary artery disease, severe renal disease, and severe cardiac dysfunction on evaluation. The angiographic outcome predictors which were related to procedure-related complications or in-hospital adverse events were ICA - CC angulation at more than 60°, increasing stenosis severity, multiple stent use and presence of tandem lesions. We also found a good correlation between the type of aortic arch and the total fluoroscopic time taken, with type III aortic arch associated with increased fluoroscopy time. There was also a good correlation between the plaque echogenicity on ultrasound and the nature of the plaque on computed tomography. Although the sample size of the study was small the results which we got are in line with the other studies which are available in the current literature on this topic.

In conclusion, carotid artery stenting is indicated in cases which on not fit for carotid endarterectomy due to high surgical risk. The awareness of the clinical and angiographic outcome predictors will help in doing the procedure of carotid artery stenting with greater safety and thus avoiding the procedural risk, in-hospital adverse events and 30-day myocardial infarction or stroke and leading to a good mRS score in the patients on follow up.

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ANNEXURES

List of publications from Thesis

Curriculum Vitae – Dr Vikas Chauhan

<table>
<tr><td>Chauhan</td><td>Vikas</td><td></td></tr>
<tr><td>Last Name</td><td>First Name</td><td>Middle Name</td></tr>
<tr><td colspan="2">Date of Birth (dd/mm/yy): 29/11/1980</td><td>Sex: Male</td></tr>
<tr><td colspan="3">Study Site Affiliation (e.g. Principal Investigator, Co-Investigator, Coordinator)
Principal Investigator</td></tr>
<tr><td colspan="2">Professional Mailing Address
(Include Institution name)</td><td>Study Site Address
(Include Institution name)</td></tr>
<tr><td colspan="2">Senior Resident, Department of IS&IR,
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Kerala -695011</td><td>Senior Resident, Department of IS&IR,
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<tr><td colspan="2">Telephone (Office): 04712524304</td><td>Mobile Number: 8500030572</td></tr>
<tr><td colspan="2">Telephone (Residence): 8369253985</td><td>Email: drvikaschauhan@gmail.com</td></tr>
<tr><td colspan="3">Academic Qualifications (Most recent qualification first)</td></tr>
<tr><td colspan="2">Degree/Certificate</td><td>Institution, Country</td></tr>
<tr><td colspan="2">MD Radiodiagnosis</td><td>INHS Asvini, Mumbai, India</td></tr>
<tr><td colspan="2">MBBS</td><td>AFMC, Pune, India</td></tr>
<tr><td colspan="3">Details of professional registration: (MCI/State Registration/Bar Council/DCI/etc including Registration Number and Year of Registration: Maharashtra Medical Council; Registration Number: 2005/01/0371; Year of Registration: 2005 (Applied for TCMC Registration)</td></tr>
<tr><td colspan="3">Current and previous positions (most recent position first)</td></tr>
<tr><td>Month and Year</td><td>Title</td><td>Institution/Company, Country</td></tr>
<tr><td>Feb 17 to Dec 19</td><td>Asst Prof Radiology</td><td>INHS Asvini, Mumbai</td></tr>
<tr><td>Feb 16 to Feb 17</td><td>Senior Resident Radiology</td><td>INHS Asvini, Mumbai</td></tr>
<tr><td>Jun 12 to Feb 16</td><td>Radiologist</td><td>INHS Kalyani, Visakhapatnam</td></tr>
<tr><td colspan="3">Brief summary of relevant research experience:
Done thesis in “Antenatal Ultrasound Evaluation of Congenital Fetal Anomalies”.</td></tr>
<tr><td colspan="3">Current project/s at hand:
1. Role of Zero Time of Echo (ZTE) magnetic resonance imaging (MRI) in analysis of the bone lesions of the skull base and calvarium in comparison to the Computed Tomography (CT) scan modality.
2. Imaging and Intervention outcomes of various treatment modalities in direct carotid cavernous fistula (CCF).
3. Preoperative evaluation of Pituitary macroadenomas using MRI modalities of DTI and ASL for predicting the consistency and vascularity.</td></tr>
<tr><td colspan="2">Signature:  </td><td>Date: 14 Aug 2022
Place: Trivandrum</td></tr>
</table>

Appendices

APPENDIX A – ETHICS COMMITTEE APPROVAL

श्री चित्रा तिरुनाल आयुर्विज्ञान और प्रौद्योगिकी संस्थान, त्रिवेंद्रम - 695 011, केरल, भारत
SREE CHITRA TIRUNAL INSTITUTE FOR MEDICAL SCIENCES AND TECHNOLOGY
TRIVANDRUM - 695 011, KERALA, INDIA
(एक राष्ट्रीय महत्व का संस्थान, विज्ञान एवं प्रौद्योगिकी विभाग, भारत सरकार)
(An Institution of National Importance, Department of Science and Technology, Government of India)
टेलीफॉन न./Telephone No.: 0471-2443152 फैक्स/Fax: 0471-2446433, 2550728
ई-मेल/E-mail: sct@sctimst.ac.in वेबसाइट/Website: www.sctimst.ac.in

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

SCT/IEC/1602 /NOVEMBER-2020 30.11.2020

Dr. Vikas Chauhan
Senior Resident
Department of Department of IS & IR,
SCTIMST, Thiruvananthapuram

Dear Dr.Vikas Chauhan,

Thank you for submitting documents related to your proposal titled "**ANALYSIS OF CLINICAL AND ANGIOGRAPHIC OUTCOME PREDICTORS IN HIGH RISK CAROTID STENTING** (IEC/1602)" to the IEC for review.

List of documents:

1. Covering letter addressed to the IEC, SCTIMST dated 22.10.2020 by the PI forwarded by HOD
2. Check list Form
3. TAC Approval Letter
4. IEC Application Form
5. Project Proposal
6. Proforma
7. Consent Form in English
8. Consent Form in Malayalam
9. Patient Information Sheet in English
10. Patient Information Sheet in Malayalam
11. CV of Dr Vikas Chauhan with MMC number
12. CV of Dr Jayadevan ER TCMC number
13. CV of Dr Santhosh Kumar K with TCMC number
14. CV of Dr PN Sylaja with TCMC number
15. CV of Dr P Shivanesan with TNMC number

IEC Recommendations

1. The study includes a prospective arm and a retrospective arm. If the required data will be available in the medical records, then the information about case availability in the medical records can be used to ensure that a one year follow up is available till August 2021. In that case, the study will be eligible for consent waiver and the required information can be collected from the medical records.
2. In case the PI wishes to include a prospective arm, the additional information that will be collected, which is not avialable in the medical records needs to be made clear.
3. If there is going to be a prospective arm, the contact mail id for the Member Secretary should be included.

One set of all the documents including those revised may be submitted as a single pdf to iec.mem.sec@sctimst.ac.in. The covering letter should indicate the revisions made with page numbers.

Sincerely,

Mala Ramanathan
Member Secretary, IEC

APPENDIX B – SUPPLEMENTARY TABLES

Table 10. Comorbidities/ Risk Factors

Comorbidities/ Risk Factors		n	%
Smoker	Absent	35	71%
	Present	14	29%
Diabetes Mellitus	Absent	16	33%
	Present	33	67%
Hypertension	Absent	7	14%
	Present	42	86%
Coronary Artery Disease	Absent	28	57%
	Present	21	43%
Dyslipidemia	Absent	34	69%
	Present	15	31%
Severe Renal Disease	Absent	43	88%
	Present	6	12%
Cardiac Disease	Absent	36	73%
	Present	13	27%

Table 11. Major Criteria for high risk

Major Criteria for high risk		n	%
Severe cardiac dysfunction on evaluation	Absent	45	92%
	Present	4	8%
Dialysis-dependent renal failure	Absent	49	100%
	Present	0	0%
Restenosis after previous CEA	Absent	47	96%
	Present	1	2%
	NA	1	2%
High ICA or CCA lesions below clavicle	Absent	48	98%
	Present	0	0%
	NA	1	2%
Prior radiation to neck	Absent	39	80%
	Present	10	20%
Prior radical neck surgery	Absent	46	94%
	Present	3	6%
Spinal immobility	Absent	47	96%
	Present	2	4%

Tracheostomy stoma	Absent	46	94%
	Present	2	4%
	NA	1	2%
Contralateral laryngeal nerve paralysis	Absent	47	96%
	Present	2	4%

Table 12. Minor Criteria for high risk

Minor criteria for high risk		n	%
Need open heart surgery within 30 days	Absent	49	100%
	Present	0	0%
CAD >1 with 70% stenosis	Absent	34	69%
	Present	15	31%
Contralateral ICA occlusion	Absent	37	76%
	Present	12	24%
Unstable angina	Absent	48	98%
	Present	1	2%
MI within 30 days	Absent	45	92%
	Present	3	6%

	NA	1	2%
Carotid artery stenosis	Right	12	24%
	Left	24	49%
	Bilateral	13	27%
Degree of stenosis on CTA	50-69%	2	4%
	70-99%	41	84%
	Dissection	1	2%
	NA	5	10%
Degree of stenosis on Doppler USG	50-69%	3	6%
	70-99%	25	51%
	NA	21	43%

Table 13. Access related anatomical factors

Access related		n	%
Arch calcification	No	22	45%
	Mild	26	53%
	Moderate	0	0%
	Severe	0	0%

	NA	1	2%
Arch type	Type 1	14	29%
	Type 2	21	43%
	Type 3	13	27%
	NA	1	2%
Tandem lesion in CCA or innominate	No	39	80%
	Yes	10	20%
ICA-CCA angulation	<30°	30	61%
	30°-59°	14	29%
	>59°	5	10%

Table 14. Lesion related factors

Lesion related		n	%
Increasing stenosis severity	50-69%	6	12%
	70-99%	42	86%
	100%	1	2%
Circumferential calcification	No	29	59%
	<50%	13	27%

	>50%	7	14%
Ulcerated lesion	No	37	76%
	Yes	12	24%
Ostial lesion	No	10	20%
	Yes	38	78%
	NA	1	2%
Lesion length >10–15 mm	<10 mm	21	43%
	10-20 mm	19	39%
	20-30 mm	4	8%
	30-40 mm	4	8%
	NA	1	2%
No. of stents used	One	48	98%
	Two	1	2%
Sequential lesions	No	48	98%
	Yes	1	2%
Nature/ HU of Plaque	Calcium	1	2%
	Fibrous Tissue	9	18%
	Lipid Tissue	24	49%

	NA	15	31%
Plaque echogenicity	Echo lucent	8	16%
	Isoechoic	3	6%
	Echogenic	6	12%
	Calcified	1	2%
	NA	31	63%

Table 15. Factors related to the anatomy of distal ICA

Distal ICA		**n**	**%**
Tortousity	No	22	45%
	Yes	27	55%
Diffuse atherosclerosis	No	44	90%
	Yes	5	10%
Tandem lesion	No	45	92%
	Yes	3	6%
	NA	1	2%
Thrombus	No	49	100%
	Yes	0	0%

Small caliber	>3 mm	42	86%
	2-3 mm	7	14%

Table 16. Other factors related to the outcome

		n	%
Total procedure time	<60 Minutes	1	2%
	60-120 Minutes	36	73%
	>120 Minutes	9	18%
	NA	3	6%
Total fluoroscopic time	<20 Minutes	11	22%
	20-29 Minutes	30	61%
	>29 Minutes	5	10%
	NA	3	6%
24 hour NIHSS	0	30	61%
	1	7	14%
	2	4	8%
	3	4	8%
	4	1	2%

	5	1	2%
	6	1	2%
	7	1	2%
24 hour mRS	0	27	55%
	1	10	20%
	2	8	16%
	3	3	6%
	4	1	2%
30 days mRS score	0	35	71%
	1	5	10%
	2	4	8%
	3	4	8%
	4	1	2%
3 months mRS score	0	34	69%
	1	5	10%
	2	4	8%
	3	4	8%
	4	2	4%

EPD usage	1	5	10%
	2	44	90%
In hospital adverse events NCP	1	44	90%
	2	5	10%
30 Day MI/ Stroke	1	46	94%
	2	3	6%
Procedure related complications	1	45	92%
	2	4	8%
Stent Opening	>90%	4	8%
	70-89%	11	22%
	50-69%	30	61%
	<50%	2	4%
	NA	2	4%
Residual stenosis scale	<30%	15	31%
	30-50%	30	61%
	>50%	2	4%
	NA	2	4%
Corrected Osteal lesion	1	9	18%

	2	39	80%
	NA	1	2%

APPENDIX C – PLAGIARISM CHECK REPORT

Ouriginal by Turnitin

Document Information

Analyzed document	Thesis Dr Vikas.docx (D142906386)
Submitted	2022-08-14 19:12:00
Submitted by	Jayadevan
Submitter email	drjayadevan@sctimst.ac.in
Similarity	2%
Analysis address	drjayadevan.sctims@analysis.urkund.com

Sources included in the report

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Entire Document

ANALYSIS OF CLINICAL AND ANGIOGRAPHIC OUTCOME PREDICTORS IN HIGH RISK CAROTID STENTING
Dr Vikas Chauhan
DM THESIS
2020-2022

100% **MATCHING BLOCK 1/15** W

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Dept. of Science and Technology, Govt. of India www.sctimst.ac.in
ANALYSIS OF CLINICAL AND ANGIOGRAPHIC OUTCOME PREDICTORS IN HIGH RISK CAROTID STENTING
A THESIS SUBMITTED BY
Dr Vikas Chauhan
TO