

# Comparison of Best Medical Management with Carotid Intervention Procedures in the Prevention of Stroke Recurrence in Patients with Symptomatic Internal Carotid Artery Stenosis

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## Abstract

**Background:** As per the current recommendations, carotid interventional procedures (carotid endarterectomy/carotid artery stenting) are considered superior to medical management in reducing the stroke recurrence in patients with symptomatic extracranial internal carotid artery (ICA) stenosis. **Objective:** The objective of this study is to compare the best medical management with carotid interventional procedures in the prevention of stroke recurrence in the patients with symptomatic extracranial ICA stenosis. **Materials and Methods:** This was a parallel, prospective, two-arm, open-label, observational study. Participants were selected consecutively and prospectively among patients from Outpatient and Inpatient Departments of Neurology at Nizam's Institute of Medical Sciences, Hyderabad, Telangana, India. The study period was from January 2012 to December 2017. **Results:** Of 150 patients with symptomatic extracranial ICA stenosis of  $\geq 50\%$ , 100 preferred best medical management ( $m = 75$ ,  $f = 25$ ) and 50 ( $m = 37$ ,  $f = 13$ ) opted for carotid intervention. The mean age of the patient cohort was  $59.8 \pm 12.7$ . Follow-up was done at regular intervals from 3 months to 1 year. In the medical group, the recurrence occurred in 10 patients; 4 (40%) within 6 months, 5 (50%) within 6–12 months, and 1 (10%) after 1 year. In the intervention group, the recurrence occurred in 6 patients; 5 (83%) within the first 6 months and 1 (17%) within 6–12 months. **Conclusions:** Overall, there was no statistically significant difference in the rate of recurrence between the best medical management and the carotid interventional procedures.

**Keywords:** Best medical management, carotid artery stenosis, carotid intervention, Hyderabad, India

## INTRODUCTION

Stroke is the second common cause of death<sup>[1]</sup> and a leading cause of disability worldwide.<sup>[2]</sup> Approximately 7% to 18% of all first strokes have been shown to be associated with stenosis of the extracranial part of internal carotid artery (ICA), across various studies.<sup>[3-5]</sup> The risk for recurrent strokes among survivors is 4% to 15% within a year after the initial stroke and 25% by 5 years.<sup>[6]</sup> As per the current guidelines,<sup>[7]</sup> patients who experience nondisabling ischemic stroke or transient cerebral ischemic symptoms, including hemispheric events or amaurosis fugax due to ipsilateral ICA stenosis  $>50\%$ , should undergo carotid intervention in the form of a revascularization procedure such as carotid endarterectomy (CEA) or carotid artery stenting (CAS), within 6 months of the event. However, these guidelines are based on the results of several randomized controlled trials, conducted in the late 1980s and mid-1990s,

such as the European Carotid Surgery Trial (ECST)<sup>[8]</sup> and North American Symptomatic Carotid Endarterectomy Trial (NASCET).<sup>[9]</sup> Best medical therapy during this period was scant by modern standards. In NASCET study, only 70% of patients were placed on antihypertensive drugs and an even smaller proportion were given lipid-lowering agents and ACE Inhibitors. Hence, there is a need to reexamine the best medical management versus interventional treatment (CEA or CAS) in preventing the recurrence of stroke in patients

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**How to cite this article:** Deepa Rani BV, Gampa S, Sirineni D, Harshavardhana KR, Krishna SR, Kaul S. Comparison of best medical management with carotid intervention procedures in the prevention of stroke recurrence in patients with symptomatic internal carotid artery stenosis. *Ann Indian Acad Neurol* 2018;21:179-83.

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10.4103/aian.AIAN\_124\_18

with symptomatic extracranial ICA stenosis. Best medical management includes aggressive risk factor modification and medical therapy with dual antiplatelet agents for 3 months followed by single antiplatelet agent, statins, and effective antihypertensive medications.<sup>[10]</sup>

### Aim of the study

This study was aimed to compare best medical management with carotid interventional procedure (CEA or CAS) in preventing stroke recurrence in the patients with symptomatic extracranial ICA stenosis.

## MATERIALS AND METHODS

This was a parallel, prospective, two-arm, open-label, observational study. Participants were enrolled prospectively from the Outpatient and Inpatient Departments of Neurology at Nizam's Institute of Medical Sciences, Hyderabad, which is a major university hospital and referral center in the South Indian state of Telangana. The study period was from January 2012 to December 2017. The inclusion criteria comprised symptomatic patients in the age group between 18 and 80 years and having >50% diameter stenosis in the extracranial ICA. Symptomatic patients were defined as those having experienced TIA or stroke in the appropriate ICA territory within preceding 6 months. The exclusion criteria were patients having disabling strokes (modified Rankin scale [mRS]  $\geq 3$ ), total carotid artery occlusion, organ failure (kidney, liver, and heart), myocardial infarction (MI) within previous 30 days, chronic atrial fibrillation, and unstable angina. All participants underwent a detailed neurological evaluation including the use of the mRS.<sup>[11]</sup> Electrocardiography and two-dimensional echo were performed in all patients before inclusion in the study to exclude probable cardiac sources of emboli (e.g., floating thrombus in the left ventricle, vegetations in the infective endocarditis, and others) by a standard protocol. The detailed carotid duplex evaluation was performed on high-resolution duplex ultrasound system (CX50, Philips Scanner) with a 7–10-MHz transducer probe. The study was performed, as far as possible, by a single, experienced sonologist to minimize interobserver variability. Longitudinal and transverse views of common carotid and ICAs were performed. Parameters studied included intima-media thickness, plaque thickness, plaque character (homogeneous or heterogeneous, hypoechoic, or hyperechoic), and percentage diameter stenosis. In Doppler study, peak systolic velocity in excess of 200 cm/s was required to indicate stenosis of 50% or more. ICA stenosis was diagnosed based on duplex ultrasonography and/or computerized tomographic angiography (CTA). In case of discrepancies, preference was given to CTA or digital subtraction angiography. Patients with ICA diameter stenosis of >50% were explained the superiority of carotid intervention (CEA/CAS) over medical management as per existing guidelines. The choice of interventional procedure (CEA vs. CAS) was given to the patient. Patients were subjected to aggressive medical management if they did not agree for the intervention. Best or aggressive medical

management<sup>[12,13]</sup> included aspirin at a dose of 325 mg/day and clopidogrel at a dose of 75 mg/day for 90 days after the event followed by aspirin 325 mg/day; atorvastatin 80 mg daily was also given. Primary risk factors such as hypertension (HTN), diabetes, and hyperhomocysteinemia were tightly controlled. Patients who opted for carotid intervention were subjected to CAS/CEA by interventional cardiologist/neurosurgeon at our center while continuing the best medical management. Patients who underwent carotid intervention were assessed immediately in postoperative period for the development of fresh neurological deficit and any postoperative complications. All vascular events including TIA, stroke, or MI within 30 days of surgery were treated as postoperative complications.<sup>[14]</sup> After discharge, patients were followed by phone and in outpatient department (OPD). Patients from both, the medical and the intervention groups were followed in OPD at 1 month, 3 months, 6 months and every 6 months thereafter. During these visits, patients were also subjected to carotid duplex study, and any increase or decrease in the degree of carotid stenosis was noted. The primary outcome was recurrent stroke in corresponding vascular territory and death during follow-up. The secondary outcome included death from any cause and stroke.

### Statistical analysis

The medical and interventional groups were assessed for risk factors and the symptoms of recurrence during follow-up. The recurrence rates in both the groups were compared for any statistical significance using Fisher's exact test.

## RESULTS

A total of 150 patients with symptomatic extracranial ICA diameter stenosis of  $\geq 50\%$  were evaluated prospectively. Of these, 100 patients preferred medical management (male = 75, female = 25) and 50 (male = 37, female = 13) opted for carotid intervention (CAS in 44; CEA in 6). The mean age of the patient cohort was  $59.8 \pm 12.7$  years. The risk factors were equally balanced between medical and intervention group except for the higher frequency of hyperlipidemia in the latter group ( $P = 0.019$ ). The patients with severe degree of ICA stenosis constituted 37 (74%) in intervention group and 56 (56%) in the medical group ( $P = 0.032$ ) [Table 1]. Recurrence in the culprit artery was noted in 10/100 patients (10%) in medical group and 6/50 (12%) patients in intervention group with no statistically significant difference. There was recurrence in different artery (vertebrobasilar territory) in 1 patient in the intervention group. All patients were followed up at regular intervals at 1, 3, and 6 months and later every 6 months till 5 years. The minimum follow-up was 3 months (3 months, 2 patients; 3–6 months, 6 patients; 6 months to 1 year, 38 patients; and >1 year, 104 patients). Recurrence in only one patient each in the medical and the interventional group occurred in association with poor compliance to drugs. One patient in interventional group continued to have limb-shaking TIA after stenting for 6 months. Follow-up carotid duplex study

was done in all patients as per the schedule. Stent patency was maintained in all patients, but there was restenosis in one patient of CEA. Among the medical group, eight patients showed increase in stenosis up to 15%, while 10 patients showed decrease in stenosis up to 10% and rest had more or less same degree of stenosis. Notably, 6 out of 8 patients who showed increased stenosis also had recurrence of symptoms. None of the recurrent strokes were disabling. Comparing the degree of stenosis with recurrence of stroke/TIA from both the groups [Table 2], 7 (5 – medical arm and 2 – intervention arm) had moderate carotid artery stenosis and 9 (5 – medical arm and 4 – intervention arm) had severe carotid artery stenosis with no statistically significant difference ( $P = 0.45$ ) among both the groups. There was no statistical difference in recurrence rate among genders in both the groups, but there was higher overall recurrence in women undergoing intervention in comparison to medical treatment (30.7% vs. 8%). Regarding the time frame of recurrence in the 10 patients in medical group, the recurrence in 2 (20%) patients occurred between 1 and 3 months, 2 (20%) patients between 3 and 6 months, 5 patients (50%) between 6 and 12 months, and in 1 (10%) after 1 year. In the intervention group, the recurrence occurred in 6 patients out of whom 2 patients (33%) within 1 month, 2 (33%) patients between 1 and 3 months, 1 (17%) patient between 3 and 6 months, and 1 (17%) occurred with in 6 and 12 months.

**Table 1: Comparison of various risk factors between both the groups**

Variable	Medical (n=100), n (%)	Surgical (n=50), n (%)	P
Age (years)	60.26-12.654	59.06-12.999	0.594
Men	75 (75)	37 (74)	0.895
HTN	62 (62)	36 (72)	0.228
DM	40 (40)	19 (38)	0.815
Smoking	31 (31)	15 (30)	0.901
Hyperhomocysteinemia	16 (16)	9 (18)	0.759
Hyperlipidemia	34 (34)	27 (54)	0.019 ( $P < 0.05$ )
Severe ICA stenosis (70%-99%)	56 (56)	37 (74)	0.032 ( $P < 0.05$ )

HTN=Hypertension, DM=Diabetes mellitus, ICA=Internal carotid artery

## DISCUSSION

This observational study was aimed to study the recurrence rate of stroke among patients with symptomatic extracranial ICA diameter stenosis ( $\geq 50\%$ ) who underwent carotid intervention (CEA or CAS) in comparison with best medical management alone. In our cohort of 150 patients with symptomatic extracranial ICA stenosis, 100 patients preferred best medical management alone, whereas fifty patients opted for carotid intervention procedure (44 – CAS and 6 – CEA) in combination with best medical management. It was interesting to observe that two-thirds of patients in our study opted against interventional treatment option, even when explained its superiority. Only in the severe stenosis group, more patients opted for intervention. Again, within the intervention group, there was a clear preference for CAS rather CEA, probably due to fear of complications.<sup>[15]</sup> The fear is not entirely unfounded. Major neurological complications associated with CEA, though rare, are both ischemic and hemorrhagic stroke. Ischemic strokes can occur due to local occlusion of the operative site, distal thromboembolism, or hypoperfusion due to cross-clamping of ICA.<sup>[16]</sup> The major systemic complication seen in the CEA arm of carotid revascularization endarterectomy versus stenting trial (CREST) was MI (2.3%). Other local complications usually seen with CEA were neck hematoma, cranial nerve palsy (4.7% CEA vs. 0.3% CAS in CREST), and operative site infections.<sup>[17]</sup> Stenting can be associated with groin hematoma, dissection, hypotension, and bradycardia which can be seen postprocedure due to baroreceptor stimulation. It can persist up to 48 h and may result in adverse outcome.<sup>[18]</sup> Another rare, serious complication with either procedure is hyperperfusion syndrome, especially seen in hypertensive patients with poor collaterals.<sup>[19,20]</sup> The economic costs of the increased hospitalizations arising from inadequate vascular access and perioperative mortality and morbidity (stroke and MI) are considerable. It should be noted that the landmark trials which showed the value of CEA were designed and carried out in the prestatin era. As a result, data from the first-generation CEA trials, namely, ECST<sup>[8]</sup> and NASCET<sup>[9]</sup> are somewhat outdated. Modern medical treatment has improved dramatically since the design of the first-generation

**Table 2: Comparing recurrence rates in both the groups**

Recurrence	Medical group (n=100), n (%)	Intervention group (n=50), n (%)	P
Overall recurrence	10 (10)	6 (12)	0.45
Males (n=112)		2 (5.4) (total male=37)	0.29
Females (n=38)	2 (8) (total female=25)	4 (30.7) (total female=13)	0.08
Moderate stenosis (50%-60%)	5 (11.3) (total number=44)	2 (15.3) (total number=13)	0.5
Severe stenosis (70%-99%)	5 (8.9) (total number=56)	4 (10.8) (total number=37)	0.5
Timing of recurrence <1 month	0	2 (33)	0.12
1-3 months	2 (20)	2 (33)	0.48
3-6 months	2 (20)	1 (17)	0.69
6 months-1 year	5 (50)	1 (17)	0.21
>1 year	1 (10)	0	0.62

CEA trials in the late 1980s. This raises the issue of whether clinicians should continue to make decisions based on data which is 20–25 years old. Best medical management at present for large artery stenosis is focused on treatment and reduction of both risk factors and thrombotic state. Risk factor reduction includes behavioral modifications such as smoking cessation,<sup>[12]</sup> weight control,<sup>[21]</sup> and aggressive control of cardiovascular risk factors such as HTN (goal <140/90),<sup>[22]</sup> glycemic control (hemoglobin A1c level <6.5%),<sup>[23]</sup> moderate exercise, and reduction in hypercholesterolemia (<100 mg/dl).<sup>[24]</sup> The use of statin and antiplatelet therapy has resulted in a significant decline in the incidence of stroke and overall cardiovascular diseases in recent times.<sup>[10,25,26]</sup> With the results of SAMMIPRIS trial<sup>[10]</sup> establishing aggressive medical management superior to stenting in intracranial stenosis, the role of aggressive medical therapy in the management of symptomatic carotid artery stenosis needs serious consideration. A SAMMIPRIS study randomized the patients with severe (70%–99%) intracranial stenosis to optimal medical treatment (OMT) plus stenting versus OMT alone. OMT included aggressive control of blood pressure, dual antiplatelet therapy (aspirin 325 mg/day plus clopidogrel 75 mg/day) for 90 days followed by aspirin (325 mg/day) monotherapy, aggressive use of high-potency statins with a target low-density lipoprotein of <70 mg/day, and lifestyle modification. The study was halted early due to the superiority of OMT alone compared to OMT plus intracranial stenting. Another recently published trial, the Vitesse Intracranial Stent Study for Ischemic Stroke, comparing OMT with intracranial stenting versus OMT, also found a higher number of adverse events in the intervention arm as compared to the medical arm alone and was stopped prematurely.<sup>[27]</sup> Similar trends have been noted in the management of extracranial carotid disease. Mervick *et al.* analyzed rate of stroke in patients with or without statin pretreatment from >2000 TIA patients; 387 of which had significant carotid disease. These authors found that the rate of stroke was 3.8% in the statin-treated group as compared to 13.2% in the nontreatment group.<sup>[28]</sup> A study from Denmark analyzed the patients referred to vascular surgery clinic either after stroke or after TIA for possible CEA. Patients while awaiting CEA were treated with multimodal approach consisting of a dual antiplatelet therapy and high-dose statins. Results showed a remarkable decrease in the recurrence of neurological outcome in only 2.5% of participants as compared to the recurrence rate of 29% before this approach.<sup>[13]</sup>

The present study has clearly shown that there is no difference in the outcome after best medical management versus intervention in patients with symptomatic ICA with >50% diameter stenosis. Both the groups had equally balanced risk factors except hyperlipidemia and higher frequency of patients with severe stenosis in the intervention group. In our cohort of symptomatic patients, the recurrence rate in medical group was 10%, and in intervention group, it was 12% with no statistically significant difference ( $P = 0.45$ ). However,

the overall recurrence was higher in females (15.7%) than males (8.9%), and this was driven mainly by the high rate of recurrence among females in the intervention group (30.7%) compared to males (5.4%) in the intervention group [Table 2]. This is in agreement with few previous studies, demonstrating that female patients benefit less from carotid intervention.<sup>[29]</sup> No significant perioperative complications occurred in our cohort. One patient in intervention arm had cerebellar ischemic stroke in vertebrobasilar artery territory in the 2<sup>nd</sup> month after CAS. Similar strokes also occurred in CREST trial,<sup>[30]</sup> where not all strokes that recurred were related to the initially culprit artery. Strokes that were posterior, contralateral, or multiterritory occurred in both the CAS and CEA arms but quantitatively more commonly with CAS. It is straightforward to envision catheter-related disruption of the aortic arch plaque causing posterior, contralateral, or multiterritory anterior circulation strokes. It is less clear how this occurs with CEA; metachronous atherosclerotic plaque instability in the aortic arch, contralateral carotid artery, intracranial circulation, and an alternate cardioembolic source are possible explanations.<sup>[31]</sup>

Among the medical group, almost half of the recurrences occurred in the first 6 months and other half occurred in the next 6 months while only 1 recurrence occurred at the 13<sup>th</sup> month. In the intervention group, almost all the recurrences occurred within the first 3 months and one occurred at 10 months. Although not randomized, to our knowledge, this is the first study in India, comparing both modalities of treatment for symptomatic carotid artery stenosis.

### Limitations

This is a nonrandomized observational study as randomization is not possible due to the existing evidence-based guidelines where a patient has to be given the option of endovascular intervention. Due to this, the frequency of patients with severe stenosis is higher in the intervention group, which we believe represents the real world situation. Second, there are more patients in medical group, causing the data to be skewed toward medical side.

### CONCLUSIONS

This study has demonstrated that best medical treatment alone as compared with carotid intervention is equally efficacious in prevention of recurrence of stroke or TIA among patients with symptomatic extracranial ICA stenosis. Most patients preferred medical management to carotid intervention. Recurrence was more common during the first 6 months after carotid stroke. This paves the way for future larger randomized trials for comparing both modalities of treatment.

### Financial support and sponsorship

Nil.

### Conflicts of interest

There are no conflicts of interest.



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