










■ Original Article

## Procedural and mid-term outcomes of carotid artery stenting and carotid endarterectomy in asymptomatic patients: A single center experience

### *Asemptomatik hastalarda karotis arter stentleme ve karotis endarterektominin prosedürel ve orta dönem sonuçları: Tek merkez deneyimi*

Ali Baran BUDAK<sup>1</sup> , Husniye SARIYILDIZ<sup>2</sup> , Orhan Eren GUNERTEM<sup>3</sup> , Emre KULAHCIOGLU<sup>2</sup> ,  
Gurdal ORHAN<sup>4</sup> , Naim Boran TUMER<sup>2</sup> , Atike Tekeli KUNT<sup>5</sup> , Kanat OZISIK<sup>2</sup> , Serdar GUNAYDIN<sup>2</sup> 

<sup>1</sup>Başkent University School of Medicine, Alanya Practice and Research Center, Department of Cardiovascular Surgery, Antalya/TURKEY

<sup>2</sup>University of Health Sciences, Ankara City Hospital, Department of Cardiovascular Surgery, Ankara/TURKEY

<sup>3</sup>Başkent University School of Medicine, Ankara Hospital, Department of Cardiovascular Surgery, Ankara/TURKEY

<sup>4</sup>University of Health Sciences, Ankara City Hospital, Department of Neurology, Ankara/TURKEY

<sup>5</sup>Kırıkkale University School of Medicine, Department of Cardiovascular Surgery, Kırıkkale/TURKEY

### Abstract

**Aim:** Atherosclerotic carotid artery stenosis (CS) is responsible for ~20% of strokes. The management of CS in an asymptomatic patient has been less clear. In situations where carotid endarterectomy (CEA) is thought to be more risky, surgeons must also have enough experience and capability to perform carotid artery stenting (CAS) to provide suitable, patient-tailored treatment. In this study, the same investigator performed all interventions (CAS and CEA), and one type of stenting device and EPD was used. In addition, periprocedural monitoring was carried out for at least 24 h. The objective of this study was to compare procedural results and 12-month follow-up outcomes of patients who were treated by the same operator- either CAS or CEA- in one year.

**Material and Methods:** A retrospective single-center review involving asymptomatic patients with severe stenosis of the ICA caused by atherosclerotic disease who was treated with either stenting with embolic protection (Group 1, n=17) or carotid endarterectomy (group 2, n=18) according to their clinical and anatomical risk profile between 1 January 2018 and 31 December 2018 at Numune Research and Training Hospital, Department of Cardiovascular Surgery, Ankara-Turkey was conducted. A duplex ultrasound (DUS) and neurological assessment was obtained prior to hospital discharge as a baseline, 30-days, 6 months, and 1 year thereafter. Patients' demographic and clinical characteristics, angiographic variables, primary endpoints including the composite of death, stroke and myocardial infarction during the 30 days after the procedure or ipsilateral stroke during the 365 days after the procedure was compared. Primary endpoints also including primary technical success, periprocedural clinical success, primary patency, clinical failure, periprocedural adjunctive maneuvers and secondary endpoints including complications, freedom from clinically driven target-lesion revascularization at 12 months, freedom from death, freedom from all stroke and freedom from restenosis rates were assessed and compared between the groups.

Corresponding Author\*: Ali Baran Budak, Başkent University School of Medicine, Alanya Practice and Research Center, Department of Cardiovascular Surgery, Antalya/TURKEY

Email: drbaranbudak@gmail.com

ORCID: 0000-0002-9772-1765

Received: 02.03.2020 accepted: 16.05.2020

Doi: 10.18663/tjcl.739395

**Results:** High-risk anatomical criteria were present in 8 (47.0%) patients, high-risk clinical criteria were present in 11 (64.7%) patients. Group 2 patients were older ( $67.7 \pm 7.4$  vs  $71.2 \pm 6.9$ ,  $p < 0.05$ ), but hyperlipidemia (58.8% vs 44.4%,  $p < 0.05$ ), chronic renal insufficiency requiring hemodialysis (11.7% vs 0.0%,  $p < 0.05$ ) and left ventricular dysfunction (17.6% vs 0.0%,  $p < 0.05$ ) were significantly more frequent in Group 1. CCDS of group 1 was significantly lower than group 2 ( $4.7 \pm 1.3$  vs  $7.3 \pm 1.2$ ;  $p < 0.05$ , respectively). The lesions of the patients undergoing CEA were significantly longer ( $12.7 \pm 2.6$  vs  $18.5 \pm 4.2$  mm.;  $p < 0.05$ ) and more calcified (11.7% vs 50.0%,  $p < 0.05$ ) than the patients in group 1. Likewise, the degree of stenosis in group 2 was significantly more than that of group 1 ( $81.4 \pm 4.2$  vs  $88.3 \pm 6.4$  %;  $p < 0.05$ , respectively). Primary technical success was 100% for both groups. Periprocedural clinical success was 100% for Group 1, and 94.4% for group 2. Primary patency rates at 1/6/12 months were 100%/ 94.1%/94.1% for group 1, and 100%/100%/94.4% for group 2. Freedom from restenosis and freedom from CD-TLR at 12 months was 94.1% and 94.4% for group 1 and group 2. No death, major strokes, myocardial infarction and systemic complications occurred.

**Conclusion:** This study showed similar short and mid-term results for CEA and CAS in asymptomatic patients with significant carotid disease. Although we have shown good results for both CEA and CAS, CAS should be limited to those cases that are not suitable for open surgery and treatment of asymptomatic carotid artery disease with CEA should be considered for patients with few risk factors and long life expectancy. Both CEA and CAS reduce the long-term stroke risk in asymptomatic patients. The appropriate treatment strategy should be selected according to the patient's individual risk factors and imaging data.

**Keywords:** asymptomatic; carotid artery stenting; carotid endarterectomy

## Öz

**Amaç:** Aterosklerotik Karotid Arter Stenozu (CS) tüm inmelerin %20'sinden sorumludur. Asemptomatik CS yönetimi daha belirsizdir. Hastaya özel tedavi için, Karotis Endarterektomi (KEA) işleminin daha riskli olduğu durumlarda, cerrahlar ayrıca karotis arter stentlemesi (KAS) yapabilecek tecrübe ve kapasitede olmalıdır. Bu çalışmada, tüm işlemleri (KAS ve KEA) aynı cerrah yapmış ve tek tip stent ve emboli koruma aracı kullanılmıştır. Ayrıca, prosedür sırasındaki monitorizasyon 24 saate yayılmıştır. Bu çalışmanın amacı, aynı operatör tarafından 1 yılda KAS veya KEA uygulanan asemptomatik CS hastalarının işlem ve takip sonuçlarını karşılaştırmaktır.

**Gereç ve Yöntemler:** İnternal karotid arter ciddi oklüzyonu nedeniyle klinik ve anatomik risk profillerine göre, Ocak.2018-31.Aralık 2018 tarihleri arasında Ankara Numune Eğitim ve Araştırma Hastanesi Kalp-Damar Cerrahi Kliniğinde KAS (Grup 1, n=17) veya KEA (Grup 2, n=18) uygulanan asemptomatik hastaların retrospektif incelemesi yapıldı. Doppler Ultrason ve nörolojik değerlendirme hastalar işleme alınmadan, taburcu olmadan, prosedür sonrası 30.gün, 6.ay ve 1.yılda yapıldı. Hastaların demografik ve klinik özellikleri, anjiyografik değişkenleri, işlem sonrası 30 gün boyunca ölüm, inme ve miyokard enfarktüsü ve 1 yıllık ipsilateral inme oranları karşılaştırıldı. Teknik başarı, prosedür başarı, birincil açıklık, klinik başarısızlık, işlem sırasında yardımcı manevraları içeren diğer birincil sonlanım noktaları ve komplikasyonlar, 12 ayda klinik olarak yönlendirilen hedef lezyon revaskülarizasyonundan kurtulma, ölümden kurtulma, tüm felçlerden kurtulma ve restenoz oranlarından kurtulma oranlarını içeren ikincil sonlanım noktaları değerlendirildi ve gruplar arasında karşılaştırıldı.

**Bulgular:** Sekiz hastada (47.0%) yüksek riskli anatomik kriter ve 11 hastada (%64.7) yüksek riskli klinik kriterler mevcuttu. Grup 2'deki hastalar daha yaşlı ( $67.7 \pm 7.4$  vs  $71.2 \pm 6.9$ ,  $p < 0.05$ ) idi, ancak hiperlipidemi (58.8% vs 44.4%,  $p < 0.05$ ), hemodiyaliz gerektiren kronik böbrek yetmezliği (11.7% vs 0.0%,  $p < 0.05$ ) ve sol ventrikül disfonksiyonu (17.6% vs 0.0%,  $p < 0.05$ ) sıklığı Grup 1'de fazlaydı. Grup 1'deki hastaların CCDS skoru Grup 2'ye göre düşüktü ( $4.7 \pm 1.3$  vs  $7.3 \pm 1.2$ ;  $p < 0.05$ ). CEA yapılan hastaların lezyonları daha uzun ( $12.7 \pm 2.6$  vs  $18.5 \pm 4.2$  mm.;  $p < 0.05$ ) ve daha kalsifikti (11.7% vs 50.0%,  $p < 0.05$ ). Benzer şekilde, grup 2'de damardaki darlık derecesi grup 1'e göre yüksek bulundu ( $81.4 \pm 4.2$  vs  $88.3 \pm 6.4$  %;  $p < 0.05$ ). Primer teknik başarı her iki grup için de %100 idi. Prosedürel klinik başarı Grup 1 için %100, Grup 2 için %94.4 idi. Primer patens oranları grup 1 için 1/6/12. aylarda 100%/ 94.1%/94.1%, grup 2 için 100%/100%/94.4%. restenozdan ve klinik olarak yönlendirilen hedef lezyon revaskülarizasyondan kurtulma oranları grup 1 için %94.1, grup 2 için %94.4 idi. Hiçbir hastada ölüm, major inme, miyokard infarktüsü ve sistemik komplikasyon gerçekleşmedi.

**Sonuç:** Bu çalışma, önemli karotis hastalığı olan asemptomatik hastalarda KEA ve KAS için benzer kısa ve orta dönem sonuçları göstermiştir. Hem KEA hem de KAS için iyi sonuçlar göstersek de, KAS açık cerrahi için uygun olmayan vakalarla sınırlı olmalı ve az risk faktörü ve uzun yaşam beklentisi olan hastalar için asemptomatik karotid arter hastalığının KEA ile tedavisi düşünülmelidir. Hem KEA hem de KAS asemptomatik hastalarda uzun süreli inme riskini azaltır. Uygun tedavi stratejisi, hastanın bireysel risk faktörlerine ve görüntüleme verilerine göre seçilmelidir.

**Anahtar Kelimeler:** asemptomatik; karotis arter stentleme; karotis endarterektomi



## Introduction

Approximately 6.5 million strokes occur per year.[1] Stroke is the second leading cause of death and is the leading cause of premature mortality and morbidity for both men and women.[2,3] Atherosclerotic carotid artery stenosis (CS) is responsible for ~20% of strokes.[4,5] Patients with vascular disease and risk factors such as diabetes mellitus (DM), hypertension, hyperlipidemia, and smoking are at significantly higher risk of developing carotid artery atherosclerosis. Not all patients with carotid atherosclerosis are at increased risk of stroke; however, a strong association between the severity of stenosis and stroke risk still exists. The prevalence of severe asymptomatic CS is as high as 3.1%.[6]

CS refers to a >50% stenosis of the extracranial internal carotid artery (ICA), with stenosis severity estimated using the North American Symptomatic Carotid Endarterectomy Trial (NASCET) method.[7] Of all strokes, 10–15% occurs due to thromboembolism that stems from a 50–99% ICA stenosis.[8] CS is defined as 'symptomatic' if associated with symptoms in the preceding 6 months and 'asymptomatic' if no prior symptoms can be identified, or when symptoms occurred beyond 6 months. Unfortunately, carotid atherosclerosis is often asymptomatic until a disabling or fatal stroke occurs. Even when asymptomatic, stenosis of the carotid artery has been reported to place an individual at more than a 3% increased risk of having a stroke in the following year (greater than 50% increased relative risk).[9]

CS often is treated with aggressive medical therapy (statins, antiplatelet and antihypertensive agents), smoking cessation, treatment of comorbidities, and surgical intervention—either carotid artery stenting (CAS) or carotid endarterectomy (CEA)—and CS revascularization has conventionally been performed by CEA. CAS was developed as an alternative to CEA, and in the current era, it is a widely used procedure for carotid artery occlusive disease, especially in patients at high risk for CEA.[10]

There are subtle differences in recommendations regarding CAS in symptomatic patients. Guidelines stipulate that CEA should be preferred over CAS in symptomatic patients with 70–99% CS as class Ia recommendation and with 50–69% CS as class IIa recommendation [11, 12]—especially if >70 years old [13]—; and CAS as an alternative for patients who present with

adverse anatomical features or medical comorbidities that are considered to make them high risk for CEA.[14] Though the risk of operative stroke/death is higher with CAS, major randomized clinical trials (RCTs) report event rates under the recommended 6% cut-off value for both treatment modalities. But as a general recognition, guidelines recommend that CEA be performed as early as possible after the neurologic symptom seen in patients with symptomatic carotid stenosis ( $\geq 50\%$ ).

On the other hand, the management of CS in an asymptomatic patient has been less clear, and there is also an ongoing debate. Since the reduction in the incidence of stroke among asymptomatic patients with established severe CS has not been shown in prospective studies with BMT, uncertainty remains regarding the optimal technique for long-term prevention of vascular events. It is clear that both CEA and CAS reduce long-term stroke risk in asymptomatic patients. With regard to perioperative outcomes of RCTs, most recent ESVS guidelines recommend patients with an "average surgical risk", and asymptomatic CS of 60–99% should be considered for CEA and suggest CAS in asymptomatic patients who have been deemed "high risk for CEA and who have an asymptomatic 60–99% stenosis in the presence of clinical and/or imaging characteristics that may be associated with an increased risk of late ipsilateral stroke, documented perioperative stroke/death rates are <3%, and if the patient's life expectancy is >5 years as class IIa recommendation.[8] Factors that are classified as a high risk for CEA include age >80 years, clinically significant cardiac disease, severe pulmonary disease, contralateral ICA occlusion, contralateral recurrent laryngeal nerve injury, previous radical neck surgery or radiotherapy, in situ tracheotomy, severe cervical spine arthritis, surgically inaccessible carotid stenosis.[15] A relative contraindication to CAS is octogenarians, where high complication rates have been reported from several trials.[16] Potential advantages include avoidance of general anesthesia, avoidance of an incision in the neck with the risk of cranial and cutaneous nerve damage, and a reduction in the rate of general complications of the surgery, for example, myocardial infarction. However, CAS does not remove the atherosclerotic lesion and may dislodge emboli during catheterization, causing the perioperative stroke. We know that the risk of the permanent

neurological deficit because of diagnostic cerebral angiography alone is considerable and estimated to be about 1%.[17] Percutaneous transluminal angioplasty (PTA) is a critical component of CAS procedures and carries significant embolic risk.[18] Its use before or after stent deployment is being scrutinized. Concern regarding the risk of distal embolization of debris being dislodged from the atheromatous plaque during stent deployment and resulting in neurological deficit has led to the introduction and increasing use of cerebral embolic protection devices (EPD), but evidence on protection devices used during CAS is scarce since a small amount of randomized evidence comparing the different cerebral protection systems exists.[1] However, ESVS guidelines' class of recommendation for the use of EPDs in patients undergoing CAS is defined as class IIa.[8]

The local anatomic and lesion factors increase the fluoroscopy time and risks associated with CAS [19] whereas systemic factors and comorbidities increase the risks associated with CEA.

The main aim of treating CS is the prevention of stroke in the long term. CEA is effective at preventing ipsilateral stroke over long-term follow-up periods of 10 years or longer.[20] To provide an alternative, CAS needs to have similar long-term effectiveness, but in situations where CEA is thought to be more risky, surgeons must also have enough experience and capability to perform CAS to provide suitable, patient-tailored treatment, should not choose the one which the operator is experienced. Better selection of high-risk surgical patients or high-risk CAS patients is critical in providing the best therapy for each individual patient. In this study, the same operator performed all interventions (CAS and CEA), and one type of stenting device and EPD was used. In addition, periprocedural monitoring was carried out for at least 24 h. The objective of this study was to compare procedural results and 12-month follow-up outcomes of asymptomatic patients who were treated by the same operator- either CAS or CEA- in one year.

## Material and Methods

### *Study Design and Patient Population*

A retrospective single-center review involving asymptomatic patients with severe stenosis of the ICA caused by atheroscle-

rotic disease who was treated with either stenting with embolic protection (Group 1, n=17) or carotid endarterectomy (group 2, n=18) between 1 January 2018 and 31 December 2018 at Numune Research and Training Hospital, Department of Cardiovascular Surgery, Ankara-Turkey was conducted. The study was approved by the regional ethics committee at Başkent University. Procedural data were prospectively recorded; data on complications were retrospectively recorded from the computerized chart. Informed consent was obtained from all the patients participating in the study.

Patients were recruited in clinical practices and referred for possible revascularization of known or suspected CS; they were then screened for eligibility on the basis of findings from duplex ultrasonography. Before enrollment, a neurologist confirmed each patient's asymptomatic status (defined as having been free, in the ipsilateral hemisphere, from stroke, transient ischemic attack, and amaurosis fugax for 180 days before enrollment).

### *Planning*

In order to compliment treatment strategy towards individual patients, primary interest has been developed in identifying whether any carotid lesion characteristics place a patient at high risk for operative stroke with CAS or CEA. Various lesion-related and procedure-related risk factors have been described, which may increase the CAS-related risk of operative stroke and high surgical risk for CEA, many of which have been identified on secondary analyses of major RCTs. The formal decision for the type of treatment was taken by the surgeon. Only patients with an asymptomatic 60-99% stenosis according to NASCET criteria, which may be associated with an increased risk of late ipsilateral stroke, were recruited in the study. Those patients who were eligible and carried high surgical risk for CEA [8] was operated via CAS (Group 1), whereas patients who had "average surgical risk" and criteria associated with increased difficulty for CAS was operated by CEA. The criteria were previously described and were similar to the criteria for other registries and ESVS guidelines.[8, 21-24] Enrollment criteria were shown in table 1.

Furthermore, operator characteristics which had reported to in-



**Table 1:** Inclusion criteria of groups

CAS (Group 1; n=17)	CEA (Group 2; n=18)
<p><b>1. Eligibility Criteria</b></p> <ul style="list-style-type: none"> <li>• Target vessel diameter 4.5–9.5 mm for Protege Stent</li> <li>• Internal carotid artery diameter 3–7 mm for SpideFX device</li> <li>• Age &lt;70 y</li> <li>• Tolerate aspirin, clopidogrel and heparin</li> <li>• Must meet high-risk criteria for high-risk patients</li> <li>• Must comply with follow-up and provide informed consent</li> </ul> <p><b>2. Patients High-Risk for CEA</b></p> <p><b>Anatomical High Risk</b></p> <ul style="list-style-type: none"> <li>• Contralateral carotid artery occlusion</li> <li>• Tandem stenoses &gt;70%</li> <li>• Surgically inaccessible lesions: High cervical (above C2) or infraclavicular</li> <li>• Bilateral carotid artery stenosis requiring treatment</li> <li>• Hostile neck*</li> </ul> <p><b>Clinical High Risk</b></p> <ul style="list-style-type: none"> <li>• Two or more diseased coronary arteries with &gt;70% stenosis</li> <li>• Unstable angina (CCS class III or IV)</li> <li>• Congestive Heart Failure (NYHA class III/IV) congestive heart failure class 3–4</li> <li>• Left ventricular ejection fraction &lt;30%</li> <li>• Recent myocardial infarction (&gt;24 hours and &lt;4 weeks)</li> <li>• MI within 30 days and need carotid revascularization</li> <li>• Need open heart surgery within 30 days</li> <li>• Severe pulmonary disease**</li> <li>• Chronic Renal Insufficiency ***</li> <li>• Permanent contralateral cranial nerve injury</li> </ul>	<p><b>1. Average surgical risk</b></p> <p><b>2. Inability to obtain femoral artery access</b></p> <p><b>3. Increased risk of Stroke for CAS (particularly Age&gt;70)</b></p> <p><b>Access related</b></p> <ul style="list-style-type: none"> <li>• Aortic arch/supra-aortic vessel calcification</li> <li>• Aortic arch elongation (type II/III arch)</li> <li>• Tandem lesion in CCA or innominate</li> <li>• ICA-CCA angulation <math>\geq 60^\circ</math></li> </ul> <p><b>Lesion related</b></p> <ul style="list-style-type: none"> <li>• Severe stenosis &gt;85%</li> <li>• Circumferential calcification</li> <li>• Ulcerated lesion</li> <li>• Ostial lesion</li> <li>• Lesion length &gt;10–15 mm</li> <li>• Lesions which will require multiple stent use</li> <li>• Sequential lesions</li> <li>• Echolucent plaque (on ultrasound)</li> </ul> <p><b>Distal ICA</b></p> <ul style="list-style-type: none"> <li>• Tortuosity</li> <li>• Diffuse atherosclerosis</li> <li>• Tandem lesion</li> <li>• Thrombus</li> <li>• Small caliber</li> </ul>
<p>CEA: Carotis endarterectomy, CAS: Carotid Artery Stenting, CCS: Canadian Cardiovascular Society, NYHA: New York Heart Association</p> <p>*Defined as prior neck irradiation, radical neck dissection, cervical spine immobility, tracheostomy</p> <p>** Defined as the need for home oxygen, pO<sub>2</sub> &lt;60 mmHg on room air, or FEV1.0 &lt;50% predicted</p> <p>*** Serum creatinine &gt; 3.0 mg/dl or currently on dialysis</p>	<p>CEA: Carotis endarterectomy, CAS: Carotid Artery Stenting, ICA: internal carotid artery</p>
<p><sup>a</sup> Based on conditions that were used to determine patients at high risk for carotid endarterectomy in carotid stenting trials and registries, such as ARCHER, CABERNET, CREATE, SAPPHIRE, and BEACH.</p>	

crease the risk of stroke with CAS such as, inexperience, aortic arch injection, failure to use EPD, predilatation prior to EPD was prohibited.

For CAS, operator experience is critically important. A pooled analysis of early carotid stent trials for symptomatic carotid stenosis showed that operators with low (mean  $\leq 3.2$  procedures per year) or intermediate (mean 3.2–5.6 procedures per

year) in-trial case volume had 10.1% and 8.4% risk of operative stroke/death, respectively. High-volume operators (>5.6 procedures per year) like in our study, had the lowest operative stroke/death rate at 5.1%.[25]

Exclusion criteria are listed in table 2 and previously described [21-23, 26]

**Table 2:** Exclusion criteria

Clinical criteria	Angiographic criteria
<ul style="list-style-type: none"> <li>• Atrial fibrillation (chronic or paroxysmal) not treated by coumadin</li> <li>• Bleeding requiring blood transfusion within 1 month CABG or vascular surgery within 30 days (before or after intervention)</li> <li>• Life expectancy &lt;12 months</li> <li>• Intolerance to heparin, or aspirin, or clopidogrel.</li> <li>• No femoral arterial access</li> <li>• MI within 72 hours</li> <li>• Prior stent of target carotid artery</li> <li>• Symptoms within 6 months</li> <li>• CVA or retinal embolus within 1 month, with any major neurological deficit</li> <li>• Allergy to nickel or titanium</li> <li>• Allergy to radiographic contrast that cannot be pretreated.</li> <li>• WBC &lt;3000/mm<sup>3</sup>, PLT &lt;50,000/mm<sup>3</sup> or &gt;700,000/mm<sup>3</sup></li> <li>• Any intracranial tumor</li> </ul>	<ul style="list-style-type: none"> <li>• Target vessel is occluded</li> <li>• Critical (99+%) stenoses (“string sign”)</li> <li>• Ostium of common carotid artery requires treatment</li> <li>• Tandem lesions that cannot be covered by 1 stent</li> <li>• Ipsilateral intracranial stenosis requires treatment</li> <li>• Any AVM or aneurysm requiring treatment</li> </ul>

## Procedures

### CAS

Before the procedure, all patients received aspirin (100 mg/d) and clopidogrel (75 mg/d) for at least 2 days plus a loading dose of clopidogrel (300 mg) if they had not previously been on clopidogrel. The patients still received their regular antihypertensive medications, with the exception of beta-blockers, on the morning of the procedure.

Patients are placed in a supine position; both groins are prepared routinely. The head is placed in a cradle and gently secured to decrease patient motion during critical portions of the procedure. The procedure is performed with the patient awake under local anesthesia, although minimal sedation is acceptable in particularly anxious subjects. After retrograde femoral access with a 5F sheath under US control, 1 mg/kg unfractionated heparin was administered to maintain activated clotting time >250 sec throughout the procedure. Continuous arterial pressure and electrocardiographic monitoring were performed during the procedure.

Diagnostic angiography was performed using a diagnostic catheter (5-Fr Omni Flush; Cordis, Fremont, CA, USA) including arch angiography to opacify the aortic arch and supra-aortic vessels in order to evaluate the anatomic characteristics such as lesion location, the severity of the stenosis, tortuosity of the target vessels, distance from the origin of the treated artery to the beginning of the descending aorta, the vertical distance from the top of the arch to the origin of the target vessel, angulated takeoff of the vessel ( $\leq 30$  degrees between the aortic arch and the innominate artery [for right-sided lesions] or left CCA [for left-sided lesions]), index lesion calcification, ulceration, and eccentricity.

Following selective catheterization of the ipsilateral mid-distal common carotid artery (CCA) (typically with a Simmons II catheter), a selective arteriogram of the carotid bifurcation is performed, paying careful attention to choose a view that provides minimal overlap of the ICA and external carotid arteries (ECA) and provides maximum visualization of the target lesion. A complete cerebral arteriogram, if not performed previously, is performed as a baseline and to identify intracranial pathologies, such as aneurysms and arteriovenous communications, and to determine the patency and completeness of the circle of Willis. After selective catheterization, the diagnostic catheter and 5F sheath were removed (while maintaining constant visualization of the guidewire in the ECA during this process) and a long (70 to 90 cm, depending on patient body habitus) 6F sheath was advanced with its dilator, into the CCA. If a difficulty occurs in advancing the long-sheath into CCA, as an alternative, the long sheath can be advanced into the transverse

arch over a guidewire, the dilator is removed, and an appropriate selective diagnostic catheter is advanced into the CCA. A stiff guidewire was then advanced into the ECA, then using the wire and catheter for support the sheath was advanced into the CCA. In the alternative method, care must be taken to minimize the probability of dissection or distal embolization from the junction of the aortic arch and the innominate or left CCA, because you could not use the protection of the sheath dilator. Following maintenance of the sheath access to distal CCA, the dilator and the 0.035-inch guidewire were removed and ultimately exchanged for a 0.014-inch wire. We prefer to attach the sheath sidearm to a slow, continuous infusion of the heparin-saline solution to avoid stagnation of blood in the sheath. We performed a selective angiogram of the carotid bifurcation again, for demonstrating the area of maximal stenosis, the extent of the lesion, and normal ICA and CCA above and below the lesion, and road-mapping.

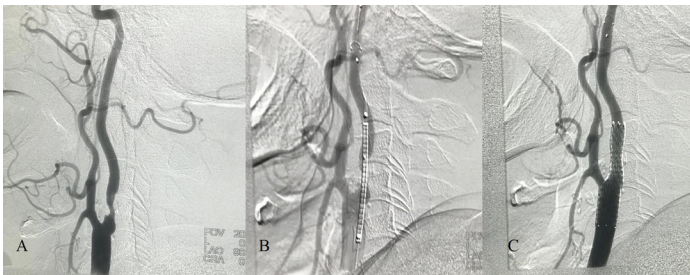
The SpiderFX Embolic Protection Device (Medtronic, MN-USA) (Figure 1) was advanced across the lesion, with the aid of road-mapping and deployed into the distal extracranial ICA, just prior to the horizontal petrous segment. The capture wire in the Spider system was not used to cross the target lesion in any procedure.



**Figure 1.** The SpiderFX Embolic Protection Device (Medtronic, MN-USA)

We never perform predilatation before EPD deployment. Atropine (0.5 to 1.0 mg intravenously) was administered as prophylaxis against bradycardia during balloon inflation in the carotid bulb. If hypotension occurred, the patients received 2 to 3 mg dopamine and rapid administration of additional fluids. The lesion was predilated with a 3- to 5-mm angioplasty balloon (Armada, Abbott, Cal-USA). After the predilation, the balloon was removed, another bifurcation angiogram was performed through the sheath. After proper road-mapping, The Protege RX Carotid Stent System (Medtronic, MN-USA) via a 6F-delivery system compatible with 0.014" guidewire was deployed. Although the stent was reported to have a specific release technology (EX.P.R.T.TM) essentially eliminating premature deployment or jumping, two or three stent rings were exposed and waited for 5 to 7 seconds, allowing the distal stent to become fully expanded, well-opposed, and fixed to the ICA

above the lesion for safety. Subsequently, the remainder of the stent can be deployed more rapidly with little worry that it will migrate. If necessary, the lesion was post dilated with a 5-mm balloon; larger balloons are rarely necessary. No specific balloons were used for calcific lesions. Residual stenosis of 10% or so was completely acceptable; the goal was protection from embolic stroke, not necessarily a perfect angiographic result. After CAS was completed, the delivery catheter was reversed, so the opposite end was used to capture and retrieve the filter, followed by completion angiography of the carotid bulb/bifurcation and distal extracranial ICA to assure that a dissection or occlusion did not occur.(Figure 2)



**Figure 2.** Procedural Images. (A) Lesion (B)Measurements (C)Postprocedural angiography.

### **CEA**

Traditional endarterectomy was performed under general anesthesia with patch closure (prosthetic). As a clinic routine, we prefer standard arteriotomy and plaque elevation. We never mobilize the carotid bifurcation until the carotid arteries have been clamped to avoid the potential of embolization of atherosclerotic plaque or thrombus in the area of the critical stenosis. As carotid clamping reduces cerebral perfusion, which may cause hemodynamic brain injury, we prevented this by routinely using a temporary shunt.

### **Postoperative Care**

A duplex ultrasound (DUS) was obtained prior to hospital discharge as a baseline index. Subsequent DUS examinations are performed at 30-days, 6 months, and 1 year thereafter. DUS, [27] was undertaken with a standardized protocol that stipulated 16 doppler waveform samples at every examination (eight samples were taken from each side of the neck: six at 1–2 cm intervals along with the CCA and ICA, one from the ECA, and one from the vertebral artery). Waveform samples were to be obtained at a 60-degree angle between the ultrasound beam and the long axis of the vessel. The highest systolic velocity measurement from each treated carotid pathway was used to identify restenosis.

The immediate neurologic assessment of the patient upon completion of the procedures was performed by the opera-

tor, secondary and follow-up neurologic assessments were performed within 24 hours and in doppler follow-up days by a neurologist. Patients in group 1 continued with dual antiplatelet therapy (a daily combination of aspirin (75-100 mg) and clopidogrel (75 mg) for 1 month, then only aspirin indefinitely. Patients in group 2, received single antiplatelet therapy with either aspirin or clopidogrel (class 1A).[8]

### **Definitions and Study Endpoints**

**Asymptomatic:** Patients with no neurologic symptoms referable to the cerebral hemisphere ipsilateral to the carotid stenosis or a history of previous neurologic events without subsequent event within 180 days. Patients with prior symptoms referable only to the hemisphere contralateral to the target vessel or symptoms in either hemisphere occurring 180 days or longer prior to the initial evaluation were also considered asymptomatic.

Measurements of angiographic carotid stenosis (percentage by diameter) in CTA or DSA images were standardized by NAS-CET methodology as recommended.[28]

**Cumulative Carotid Disease Severity Score (CCDS)** [29]: a global disease severity score for the carotid lesions which categorize the grades of severity of carotid artery disease prior to CEA or CAS, including a 0 to 3 scale corresponding to absent, mild, moderate, and severe that can be obtained for each of the risk factors.

Specific anatomical factors that may affect perioperative CAS outcomes were reported, including lesion length, lesion location, severity, calcification were recorded. Lesion length was defined using the American Heart Association/American College of Cardiology classification for coronary lesions as modified by Ellis et al,(30) in which the distance from the distinct proximal to the distal shoulder of the lesion is assessed in the projection that best elongates the portion of stenosis that is >50%. Lesion location was defined at the distal common carotid artery or proximal ICA, including the bulb, or a combination of the common distal carotid and ICA (bifurcation lesion). Target site calcification was defined as no or mild calcification vs heavily calcified lesions (>50% circumferential calcification), which was based primarily on computed tomography angiography or ultrasound imaging, or both.

### **Primary Endpoints**

The primary endpoint was the composite of death, stroke (ipsilateral or contralateral, major or minor) and myocardial infarction during the 30 days after the procedure or ipsilateral stroke during the 365 days after the procedure. Stroke or cerebrovascular accident is defined as a cerebral infarction that manifests as a sudden onset of focal neurological deficits that persist for more than 24 hours.[31] The National Institutes of

Health Stroke Scale (NIHSS), which is a serial measure of the neurologic deficit on a 42-point scale across 11 categories, including paralysis, speech difficulty, and sensory and visual loss, was used to report stroke severity.[31] A minor stroke is a new neurologic event that persists for more than 24 hours but completely resolves or returns to baseline within 30 days and changes the NIHSS by 2 to 3 points. A major stroke is a new neurologic event that persists after 3 days and changes the NIHSS by at least 4 points. An ipsilateral stroke is a stroke affecting the cerebral hemisphere supplied by the treated carotid artery. TIA is defined as a temporary focal neurologic deficit that changes the NIHSS by one or more points or retinal deficits that persists for <24 hours with a return to baseline or complete resolution of the event.[32] The periprocedural occurrence of MI in 30 days of the procedure was also reported. Accepted confirmatory evidence of an MI includes the combination of either chest pain or equivalent symptoms consistent with myocardial ischemia or electrocardiographic evidence of ischemia, including new ST-segment depression or elevation >1 mm in two or more contiguous leads, plus a significant elevation of cardiac enzymes (creatinine kinase-MB or troponin) to a value 2 or more times the individual clinical center's laboratory upper limit of normal.[33,34]

The other primary endpoints were primary technical success, periprocedural clinical success, primary patency at 1st-6th, and 12th months, clinical failure rates. For CEA, primary technical success is defined as the successful exclusion of the carotid plaque and closure of the artery with patch and less than a 30% residual stenosis. For CAS, primary technical success defines successful access to the carotid arterial system using a remote site; successful deployment and placement of the EPD and the carotid stent excluding the entire length of the carotid lesion; patent carotid stent with normal flow and without a significant twist, kinks, or obstruction (>30% luminal stenosis or a pressure gradient >10 mm Hg) by intraoperative measurements; and successful removal of the EPD without evidence of EPD-related vascular injuries.

**Periprocedural clinical success:** Vascular closure or deployment of the carotid stent. The definition of clinical success for both carotid interventions includes the absence of periprocedural stroke, death and MI and ipsilateral stroke as the result of carotid stenosis-related treatment, patch or stent infection or thrombosis, failure of device integrity, including stent fracture or pseudoaneurysm formation.

**Primary patency** refers to patency that is obtained without the need for an additional or secondary surgical or endovascular procedure.

**Clinical failure** includes a failure to complete a CEA or deploy

the stent at the intended location, carotid or stent thrombosis or infection, restenosis, conversion to open or endovascular repair, or death as a result of carotid stenosis or carotid artery-related treatment.

**Periprocedural adjunctive maneuvers** were classified as planned procedures or unplanned procedures. *Planned procedures* comprise techniques that are part of a preformulated procedural strategy, and *unplanned procedures* are necessary for the management of unintended complications or an otherwise unsatisfactory outcome.

### **Secondary Endpoints**

The secondary endpoints included complications, freedom from clinically driven target-lesion revascularization at 12 months, freedom from death, freedom from all stroke and freedom from restenosis rates.

**Target lesion revascularization (TLR):** any surgical or percutaneous revascularization procedure involving the original target lesion site, including repeat balloon angioplasty, stenting, endarterectomy, or any other open vascular reconstruction of the treated lesion.

**Restenosis:** restenosis, defined as 70% or more diameter-reducing stenosis, or target-artery occlusion occurring at the ultrasound scans at 1, 6 or 12 months. The <70% threshold to define high-grade restenosis is the most accepted threshold and has been used in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS), the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) trial, and the Endarterectomy versus Angioplasty in Patients with Severe Symptomatic Carotid Stenosis (EVA-3S) trial.[35-37] Assessment of restenosis was done when the peak systolic velocity at any location within the treated internal or common carotid artery reached or exceeded 3.0 m/s. The decision to use 3.0 m/s as the definition for restenosis was also made before unblinding of the restenosis data. Several single-institution reports [38-41] support the use of 3.0 m/s or more as an appropriate threshold to identify high-grade restenosis

**Complications** were categorized as procedure related and systemic. All complications graded as moderate (2) or severe (3) are considered *major complications*, and those graded as mild (1) can be considered *minor complications*.

### **Statistical Analysis**

Baseline variables are summarized with the use of descriptive statistics. Continuous variables were expressed as mean, median and  $\pm$  standard deviation. Categorical variables are summarized as counts, percentages (%). Categorical values between technical success, complication and revascularization rates will be evaluated by Chi-Square analysis. For time-





to-event variables, Kaplan–Meier estimates were used. The power of the study calculated in this way was calculated as 0.82 in the G-Power 3.1.9 package program and the sufficient sample width was determined as 17. All statistical evaluations will be made using SPSS 25.0 software (SPSS, Chicago, Illinois) and  $p < 0.05$  will be considered statistically significant.

## Results

### Patient Characteristics and High-Risk Inclusion Criteria

Baseline demographics and the lesion characteristics of the study group are shown in Table 3 and high-risk inclusion criteria characteristics is shown in Table 4. High-risk anatomical criteria were present in 8 (47.0%) patients, high-risk clinical criteria were present in 11 (64.7%) patients. Group 2 patients were older ( $67.7 \pm 7.4$  vs  $71.2 \pm 6.9$ ,  $p < 0.05$ ). Among the demographic risk factors, hyperlipidemia (58.8% vs 44.4%,  $p < 0.05$ ), chronic renal insufficiency requiring hemodialysis (11.7% vs 0.0%,  $p < 0.05$ ) and left ventricular dysfunction (17.6% vs 0.0%,  $p < 0.05$ ) were significantly more frequent in Group 1.

**Table 3:** Baseline demographics and lesion characteristics of the patients

Parameter	Group 1 (CAS, n=17)	Group 2 (CEA, n=18)
<b>Patient demographic and clinical characteristics</b>		
Age (SD)*	67.7±7.4	71.2± 6.9
Men (%)	12 (70.6%)	13 (72.2%)
Smoking (%)	7 (41.1%)	8 (44.4%)
Hypertension (%)	14 (82.3%)	15 (83.3%)
Diabetes Mellitus (%)	7 (41.1%)	7 (38.8%)
Hyperlipidemia (%)*	10 (58.8%)	8 (44.4%)
COPD (%)	2 (11.7%)	2 (11.1%)
Chronic Renal Insufficiency req HD(%)*	2 (11.7%)	0 (0.0%)
Left ventricular dysfunction(%)*	3 (17.6%)	0 (0.0%)
Prior MI (%)	5 (29.4%)	6 (33.3%)
Prior PCI/CABG	8 (47.0%)	8 (44.4%)
<b>Lesion/procedure characteristics</b>		
Left Lesion Side	9 (52.9%)	10 (55.5%)
Stenosis (%vessel of diameter)*	81.4±4.2	88.3±6.4
Cumulative Carotid Disease Score*	4.7 ± 1.3	7.3 ± 1.2
Lesion Length (mm)*	12.7 ± 2.6	18.5 ± 4.2
<b>Lesion Location</b>		
Proximal Internal Carotid Artery	14 (82.4%)	14 (77.8%)
Bifurcational*	0	4 (22.2%)
High Cervical*	3 (17.6%)	0 (0.0%)
Target site calcification (heavy calcified)*	2 (11.7%)	9 (50.0%)
Ulcerated lesion	2 (11.7%)	3 (16.6%)

Taking lesion characteristics into consideration, CCDS of group 1 was significantly lower than group 2 ( $4.7 \pm 1.3$  vs  $7.3 \pm 1.2$ ;  $p < 0.05$ , respectively). The lesions of the patients undergoing

CEA were significantly longer ( $12.7 \pm 2.6$  vs  $18.5 \pm 4.2$  mm.;  $p < 0.05$ ) and more calcified (11.7% vs 50.0%,  $p < 0.05$ ) than the patients in group 1. Likewise, the degree of stenosis in group 2 was significantly more than that of group 1 ( $81.4 \pm 4.2$  vs  $88.3 \pm 6.4$  %;  $p < 0.05$ , respectively).

**Table 4:** High Risk Inclusion Criteria for group 1

Anatomic criteria	N (%)
• Contralateral carotid occlusion	2
• High cervical or intrathoracic stenosis	3
• Cervical spine immobility, tracheostomy	1
• Hostile neck (previous neck surgery)	1
• Post-radiation therapy	1
<b>Clinical criteria</b>	
• Ejection fraction <30%	3
• 2-vessel disease and history of angina	3
• Severe pulmonary disease	1
• MI within 30 days	1
• Chronic Renal Insufficiency	2
• Unstable angina (CCS class III or IV)	1
<b>Other</b>	
• Patients' preference	2

### Procedural

Primary technical success was 100% for both groups. All procedures were completed without a clinical failure.

Among group 1, 15/17 (88.2%) procedures were performed as preformulated. Planned periprocedural adjunctive maneuvers were required in two patients: in one patient (69 y, CHF req dialysis, prior CABG, CCDS=4 and contralateral carotid occlusion) management of concomittant common iliac artery critical stenosis was treated with stent placement and in the other patient (64 y, prior MI and PCI, CCDS=5, LVEF<30%, with history of previous neck surgery), during the balloon dilatation, we had to administer dopamine infusion (because of bradycardia and hypotension despite administration of atropine) for 4 hours. No unplanned procedure was performed as an periprocedural adjunctive maneuver. Grossly visible debris was observed in the SpiderFX filter in 7 (41.1%) patients, as in one of them we had difficulty recovering the filter. The mean fluoroscopy time for group 1 was  $13.2 \pm 5.1$  minutes and mean contrast dose used was  $84.6 \pm 12.5$  mL.

Taking group 2 into consideration, no blood transfusion required and all operations were performed without hemodynamic instability. In one patient (with a high calcified bifurcation lesion) surgical dissection was difficult and we had to mobilize the bifurcation before clamping. Mean duration of the operation for CEA was  $62.3 \pm 12.1$  minutes.

All patients stayed in intensive care unit for 24 hours under

continuous monitorization. No patients experienced, major stroke, myocardial infarction, or death. In one patient in group 2 (the same patient whose dissection was difficult), facial numbness due to frontal lobe minor stroke was seen. It did not cause any neurological disability and resolved after 2 months. As a result, periprocedural clinical success was 100% for Group 1, and 94.4% for group 2 ( $p > 0.05$ ).

Other non-neurological events included vasovagal reactions in 5 patients (Group 1: two patients (11.7%) vs Group 2: three patients (16.6%);  $p > 0.05$ ), all treated successfully by administration of intravenous fluids and atropine, and in one patient dopamine.

**Follow-up**

In-stent restenosis was diagnosed in two patients as one of them from group 1 at 6th month control follow-up, and the other patient from group 2 at 12th month control follow-up, both treated successfully by balloon angioplasty. Primary patency rates at 1/6/12 months were 100%/ 94.1%/94.1% for group 1, and 100%/100%/94.4% for group 2. Both patients were female with DM and hyperlipidemia. Freedom from restenosis and freedom from CD-TLR at 12 months was 94.1% and 94.4% for group 1 and group 2. No death and major strokes and systemic complications occurred. Complications are listed in table.6.

**Table 6: Complications**

Complication	Group 1	Group 2
Bradycardia/hypotension	1= temporary, hospital stay not prolonged. (minor)	0
Distal microembolization detected as new small infarctions in brain imaging studies	0	1= frontal lobe minor stroke- facial numbness. No neurological disability-resolved in 2 months (minor)
Cranial Nerve palsy	0	0

**Discussion**

Our study shows that it is possible to achieve acceptable results with CAS at a single centre among the asymptomatic group. For an asymptomatic patient with severe CS, the most important question is how to prevent an ischemic stroke. We showed in our study that, for those patients not suitable for standard open repair, a CAS procedure could be an alternative in selected cases.

We selected the asymptomatic group to study and compare, because there is still an ongoing debate about how best to

treat the asymptomatic patient. Furthermore, trials and ESVS guidelines target symptomatic patients generally favor CEA over CAS.[8, 42-44]

In symptomatic carotid stenosis  $>70%$ , the ipsilateral stroke risk is about 13%/year with the best medical treatment and it is reduced to 4.5% by CEA.[28] Looking at randomised trials comparing CAS with CEA for symptomatic patients, the international carotid stenting study (ICSS) is the largest RCT comparing CAS with CEA in patients with symptomatic CS and reported an 8.0% frequency of any stroke/death at 120 days after CAS.[45] Furthermore, SPACE trial reported a frequency of 7.7% of any stroke or death at 30 days after CAS [36] and the EVA 3S trial reported exceptionally high rates of periprocedural stroke/ death with CAS (9.6%) led to the trial being stopped prematurely.[37] The CREST Trial was a large multicentre RCT, including 1321 symptomatic and 1181 asymptomatic patients. The most important result they found the overall periprocedural incidence of stroke or death was statistically significantly higher after CAS than CEA in symptomatic patients ( $p = 0.02$ ), this was not statistically significant for asymptomatic patients. They reported a 4.4% periprocedural stroke or death frequency in total, among symptomatic patients 6.0% and for the asymptomatic 2.5% .[34]

Since carotid artery revascularization is most often recommended to prevent stroke in asymptomatic patients, the risk of neurological complications after CAS is particularly important. The RCTs carried out comparing CEA with CAS in asymptomatic population have produced unreliable results due to heterogeneous patient populations with different endpoints being used, use of a variety of endovascular devices, varying EPDs between studies. The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial compared CAS with CEA in 334 patients at high operative risk [46], and reported that CAS was associated with a 56% reduction in perioperative death, stroke, and MI compared to CEA, a 39% reduction in death and ipsilateral stroke at 1 year, and similar cardiac and stroke reduction. This difference was explained by the SAPPHIRE population having greater co-morbidities (75.5% of patients undergoing CEA had coronary artery disease), leading to a significantly higher rate of MI in the CEA compared to the CAS group. The Asymptomatic Carotid Trial-1 (ACT-1) reported that CAS was non-inferior to CEA with regard to the composite endpoint of death, stroke or MI within 30 days of the procedure in 1453 asymptomatic patients with severe CS.[47] In CREST, which included symptomatic and as-



ymptomatic patients who were deemed to be at average risk, the estimated 10-year rate of ipsilateral stroke (excluding the perioperative period) was 6.9% after stenting (i.e., 0.7% per year) and 5.6% (0.6% per year) after endarterectomy.[34] The ACST2 trial report a 1% rate of periprocedural disabling stroke, fatal MI and death in all included participants.[48]

The most widely used estimator of long-term stroke risk in asymptomatic patients is severity of stenosis.[49,50] The ACSRS study (Asymptomatic Carotid Stenosis and Risk of Stroke) determined predictors of ipsilateral TIA/stroke in asymptomatic patients on medical therapy, incorporating plaque morphology characteristics from ultrasound.[51] It was previously claimed that the addition of clinical and ultrasound-detected plaque features to stenosis severity improved the ability to predict stroke. Furthermore, Mathur et al [52] showed that CAS performed for lesions with >90% stenosis was associated with a higher 30-day stroke rate of 14.9%, compared with 3.5% in patients with lesion severity of <90%. But as another conflict, neither the ACAS nor ACST trials found any evidence that stenosis severity or contralateral occlusion increased late stroke risk.[20,53,54] Ulcerated plaque morphology was detected in 11.7% of patients in group 1, and 16.6% of the patients in group 2. The lesions in group 2 was more stenotic and the CCDS was increased. But the number of patients included in our trial was too small to permit conclusions with regard to the relative benefit of each technique or prediction of stroke, however in 12-months, a minor stroke was diagnosed in one patient in the CEA group after the procedure. Accordingly, there have been increasing calls to lower the acceptable stroke/death thresholds set by many guidelines as <3% for asymptomatic group. In CREST and ACT1, which mandated EPD use, 30-day stroke/death rates of 2.5% and 2.9% were reported, respectively [47,55], and are acceptable based on current guidelines. Our major stroke rate was 0%, minor stroke rate was 2.85%. in this study no strokes occurred in 12-month follow up . This might be due to the combination of our small sample size, the wide use of statins (100%), and a strict protocol for patient selection.

As an other conflict, Mukherjee D. and Roffi M claimed that randomized trials did not demonstrate a significant difference between CAS and CEA in terms of procedure-related major strokes, and the statistical difference was actually related to the high association of CAS with minor strokes.[56] Likewise, a 2017 review of 6526 patients from five RCTs and a mean follow-up of 5.3 years demonstrated a higher risk of periprocedural stroke plus nonperiprocedural ipsilateral stroke with CAS (OR 1.50;

95% CI 1.22-1.84), primarily due to increased minor stroke rates in the periprocedural period.[4] On the other hand, Hussain et al., reported that over long-term follow-up (up to 13 years), CEA was associated with approximately 55% increased hazard for major adverse events (30- day death, stroke, MI, stroke during 13-year follow-up).[57] Alhaidar et al [58], evaluated a sample of 54640 patients – a database of 705 hospitals-, and finally concluded that 30-day periprocedural mortality, stroke, MI, and combined outcome (mortality, stroke, or MI) were not significantly different between CEA and CAS, like Jalbert et al [59] who found similar rates of death,stroke/TIA, periprocedural MI, and a composite of these endpoints.

But as a result, perioperative stroke is an important complication and should be prevented. The major postulated mechanism is the post-dilatation of the stent after implantation. A retrospective study of 3,772 CAS procedures demonstrated a 2.4-fold increase in the risk of perioperative stroke and death rates associated with post-dilatation compared with no post-dilatation strategies.[60] This increased risk is likely mediated by two distinct mechanisms, the principal one likely being an increased embolic showering, causing ischemia during the procedure, whereas on occasion persistent hemodynamic depression related to procedure-related carotid baroreceptor stimulation may lead to neurologic events related to reduced cerebral blood flow. Double-layer nitinol [60] or mesh-covered stents [61], hybrid stents has been under evaluation to minimize/eliminate plaque prolapse.

Use of EPDs may reduce the peri-procedural stroke rate following CAS. A systematic review reported a reduced 30- day death or stroke rate from 5.5% to 1.8% in patients undergoing CAS without and with EPDs respectively.[62] Data from a large registry have also confirmed the finding that EPDs reduce the death or stroke rate in patients undergoing CAS, with the use of EPDs being an independent protective factor.[63] The benefit of EPDs was also evident in a prospective registry of 1455 patients: in those treated with EPD, in-hospital death/ stroke rates were at 2.1% vs. 4.9% in patients treated without EPD. [64] The best results within RCTs were seen in the CREST and ACT-1 trials, where cerebral protection was mandatory and CAS practitioners were trained in its use.[47,55] In contrast, the SPACE trial observed lower ipsilateral stroke rates in CAS patients without EPD (6.2%) vs. with EPD (8.3%).[36] Although EPDs have been widely accepted as necessary adjuncts during CAS and the risk of stroke in this study is similar to the risks reported in other high-risk registries, it is important to em-

phasize that strokes may occur despite the use of EPDs and failures may be due to the inability to deliver the device, device-induced complications such as vessel dissection, and incomplete capture or retrieval of debris leading to acute stroke. We observed grossly visible debris in 41.1% of the patients and in one of them we had difficulty recovering the filter. We claim that the clustering of strokes after prolonged and complex interventional procedures, and the relationship between filter deployment duration and stroke, suggests that some adverse events may be potentially avoidable by careful patient selection. That important result brings us to the beginning: patient-tailored therapy including clinical, anatomical risks

Also new techniques like proximal balloon occlusion protection was advocated as superior to distal filters in reducing embolization or in 2019 Langhoff et al [65] addressed a new device combining a balloon with an integrated embolic protection filter designed to increase embolic protection during post-dilation and reported promising results. Schermerhorn MD et al, compared transcrotid artery revascularization with flow reversal technique with transfemoral CAS, and concluded that among patients undergoing treatment for carotid stenosis, transcrotid artery revascularization, compared with transfemoral CAS, was significantly associated with a lower risk of stroke or death.[66]

Factors that influence the choice of stent include device availability, clinical trial or postmarketing registry participation, stent cell structure, stent shape and specific EPD characteristics. Considering this factors, we preferred to use the Protégé RX Carotid Stent System, which is a nitinol open cell-tapered stent that comes pre-mounted on a 6 F, 0.014" rapid exchange delivery system and the safety and efficacy of the Protege RX carotid stent system in the carotid indication has not been demonstrated with EPDs other than with the SpiderFX™ EPD.

Open-cell stents have a free cell area of >5 mm<sup>2</sup> and adapt well to the contour of the vessel making delivery easier but physically cover less of the target lesion, potentially posing a higher risk of embolization as atherosclerotic material may prolapse through the stent struts. Closed-cell stents may kink the vessel if placed inappropriately. No published high-quality RCTs compare open-cell to closed-cell stents and available evidence is conflicting. Published studies have shown a variety of results.[67] Wisgott et al., evaluated eight stent systems including Protégé RX Carotid Stent System and drew attention to its high radial force (collapse observed at 0.20 bar) and good wall adjustment.[68] Also with regard to the re-stenosis rate, a significant difference between the open-cell and closed-cell

stents could not be demonstrated from the literature.[68]

We have to pay attention to the fact that periprocedural stroke is more likely with CAS; however, this difference has reduced with time with increasing skills of the operators and emerging endovascular techniques and technology. From 1991 to 2010, published data have shown a 6% annual reduction in operative stroke/death.[69] This reduction also exists for CEA and BMI. In a meta-analysis of 41 studies, the rate of ipsilateral stroke was 2.3/100 person-years in studies completing recruitment before 2000, compared with 1.0/100 person-years during the 2000–2010 period ( $P < 0.001$ ). [70] A 60–70% decline in annual stroke rates was also observed in medically treated patients in both trials over the recruitment period from 1995 to 2010.[20,53] Moreover, we have to remember that periprocedural stroke after carotid revascularization is not always secondary to thromboembolism and often occurs due to haemodynamic disturbance. Because of the learning curve associated with CAS, as well as it being performed in low numbers by multiple specialties, there are concerns as to whether the death/stroke rates reported for CAS in these trials can be replicated in 'real-world' practice.[71] Since CAS is a technically demanding procedure, establishing minimum volume requirements is important. Nallamothu BK et al. evaluated CAS in the United States among elderly patients between 2005 and 2007 and found higher 30-day mortality in patients treated by operators with lower annual volumes of CAS, reported the median annual operator volume as only 3.0 per year. They classified an annual operator volume with a 12–23 CAS procedures/year as medium experience, and did not find any significant difference with high experience (>24 procedures / year) centers.[72] We performed 17 CAS procedures in one year, which can be classified as a medium experience. Patients treated by operators with <6 procedures per year were found to have an elevated risk of 30-day mortality.[72]

Previous meta-analyses have shown that the superiority of CEA over CAS disappears in patients aged <70 years.[1,5]. Lindström et al also found the results for CAS to be better in younger patients, although not significant in this relatively small series in the Swedish study.[73] Increased age is an independent predictor of poor outcome after CAS.[74,75] We performed CEA in older patients and this preference reflected into the results as a significant difference among the groups in terms of age.

Naggara et al [76] reported the results of a pooled analysis of 34,398 CAS patients and showed that CAS for left ICA stenosis was associated with higher 30-day perioperative stroke/death rates compared with CAS for right CS (7.5% vs 6%). They sug-



gested that this higher rate was secondary to the difficult access from the aortic arch to the left common carotid artery. However, other studies, including our study, have not found a significant difference in 30-day stroke or death rates, or both, between right- and left-sided CAS.[74,77]

Target site calcification has also been correlated with a higher 30-day stroke rate.[18] A single-center study by Setacci et al [39] noted that the presence of target site calcification was associated with a higher 30-day perioperative stroke rate of 6.5% in contrast to 2.3% in patients without calcification. Because of this fact, CEA was performed more often in patients with target site calcification in our study as 50% of patients in CEA vs 11.7% of patients in CAS. This algorithm may have prevented the possible difference in rates of stroke and technical success between two procedures.

Female sex, hypertension, DM and dyslipidaemia were reported as independent predictors of restenosis or reocclusion at 2 years after CAS whilst smoking was statistically significantly associated with restenosis after CEA.[75] Following CEA only, 5.2-9.5% developed restenosis at 1-5 years.[78] On the other hand, in a systematic review, the cumulative restenosis rate (>70%) was about 4% in the first 2 years after CAS, and this compares well with CEA.[79] In our study, patients in the CEA group were older, but risk factors including hyperlipidemia, chronic renal insufficiency requiring hemodialysis and left ventricular dysfunction were more frequent among patients in CAS group. Our rate of restenosis within 12-months and the concomitant risk factors are consistent with the literature -5.71% all study group- as during follow-up, we diagnosed restenosis in 2 patients (1 from each group) who were female with DM and hyperlipidemia.

Taking perioperative stroke and death rates, following a comprehensive Medline search of over a 15-year period, Khan and Qureshi [80] reported that clinical factors, including age of >80 years, DM, chronic renal failure, and symptomatic indications, are associated with high risk. Considering the angiographic variables, they also reported ulcerated and calcified plaques, left carotid artery intervention, >10-mm target lesion length, >90% stenosis, ostial involvement, type III aortic arch, >60°-angulated internal carotid and common carotid arteries, and PTA without EPDs as predictors of increased perioperative stroke.

A few other studies [18,77] have analyzed the correlation of CAS outcome and the target lesion length and concluded that longer lesions were associated with a higher 30-day perioperative stroke rate. Mathur et al [52] reported a 30-day stroke

rate of 11.4% for lesions longer than 10 to 15 mm vs 3.8% for lesions shorter than 10 mm; whereas Sayed et al [81] reported a stroke rate of 17% vs 2.1%, and Setacci et al [39] reported a stroke rate of 5.6% vs 2.6% for these lesions, respectively. Lal BK et al [38] specified a threshold for lesion length and reported that plaque length > 13 mm was associated with a 6.1% death/stroke after CAS vs. 1.9% after CEA. We preferred to perform CEA in long lesions to prevent this risk; as this choice was reflected in the results of our study.

Since the lesion severity for each type of intervention need to be reported to assess periprocedural risk and precise classification methodology for reporting lesion characteristics affecting outcomes have not been defined and universally accepted; we decided to use CDSS system which allows the calculation of a global disease severity score for the carotid lesion before CEA or CAS. In our study, CDSS of group 1 was significantly lower than group 2, as lesions which were more calcified, longer and stenotic were preferred to be treated with CEA.

On the other hand, extended neck surgery has been shown to significantly increase the complexity of surgical intervention resulting in a higher risk of cranial nerve injury as well as more challenging dissection when compared to de novo open carotid intervention. Radiation into the cervical region has been shown to have various effects on the extent of fibrosis scarring as well as injury to the carotid artery itself.[29] Contralateral carotid stenosis or occlusion has traditionally been considered a predictor for adverse outcome after CEA according to NASCET data.[28] The location of the lesion relative to the carotid bifurcation and the base of the skull are anatomic variables that may increase the complexity of CEA. Those previously described anatomical factors, as well as the clinical criteria that had been reported to increase the risk after CEA formed the high-risk inclusion criteria for CAS. After detailed investigation of the literature, we developed an algorithm for enrolling the patients -evaluating risks- to the groups and providing a patient-tailored treatment.

Moreover, there are studies in the literature that pointed out the risk about CAS was procedure dependent; not clinical.[82] The same group also did not find any significant difference in the risk of MI between the two procedures.

Prior studies of carotid revascularization procedures estimate 30-day re-admission rates at a range of 4.2% to 11.1% .[82,83] In our study, 30-day re-admission rate was 2.85%. ACT trial had suggested that CAS was not inferior to CEA in asymptomatic patients in terms of readmission.[47] Dakour A et al, collected data from 700 hospitals and after evaluating 95,687 patients

they concluded that 30-day all-cause readmission rates were lower with CAS than CEA.[84]

In initial studies comparing CEA to CAS, rates of MI were <1% for both procedures, likely because cardiac biomarkers were not measured routinely (BE-36,37,38). The high-risk SAPHIRE trial, which systematically collected cardiac biomarkers, was the exception, reporting MI rates of 5.9% for CEA and 2.4% for CAS (46). In the average-risk group studied in CREST, the incidence of MI after CAS was 1.7%; 3.4% with CEA under general anaesthesia; and 1.8% with CEA under locoregional anaesthesia.[85] It was also reported that any type of perioperative stroke was associated with a threefold poorer long-term survival, similar to the poorer 4-year survival observed in patients suffering a perioperative MI.[8] MI was found more associated with CEA, likely due to the periprocedural anaesthetic risk, as are cranial nerve injuries (CNI) and haematomas (although many CNIs are non-permanent).[5] In CREST, the rate of cranial nerve injury for CEA was 4.6%.[55] However, 34% of deficits had resolved at 1-month follow-up and 81% resolved by 1 year. No difference in quality of life associated with cranial nerve injury was detected at 1-year follow-up. In our study, no patients experienced major stroke, myocardial infarction, or death.

The most common complications are vasovagal or vasodepressor responses, possibly due to stretching the carotid baroreceptor during balloon inflation and stent deployment, or mobilizing the bifurcation before clamping which was reported up to 20% in the literature. Our results are consistent with the literature and all patients treated medically.

Concomitant administration of warfarin and dual antiplatelet therapy may predispose elderly patients to serious bleeding complications, including intracranial hemorrhage which Safian et al. reported a prevalence of 1.3%.[22]

Stent thrombosis is a feared complication of CAS that we did not observe in our study group. Stent insertion may cause intimal injury leading to platelet adhesion and thrombus formation. Guidelines suggest administration of dual antiplatelet therapy pre and post procedurally along with antihypertensives, beta-blockers and lipilowering agents. We administered those medications as a standard for all patients. Novel medical therapies may also show benefit in reducing the long-term stroke risk in asymptomatic patients. A subgroup analysis of the Cardiovascular Outcomes for People using Anticoagulation Strategies (COMPASS) RCT showed that addition of low-dose rivaroxaban to aspirin (in 1919 patients with previous carotid artery revascularisation or asymptomatic CS of at least

50% reduced the overall major adverse cardiovascular event rate without increasing the bleeding risk.[86]

### Study Limitations

First, this is a retrospective observational study. Therefore, only associations but not causal relationships can be derived from the data. Another limitation of the study was that the data were self-reported by the operator performing the procedure. The number of patients included in our trial was too small to permit precise conclusions with regard to the relative benefit of each technique.

### Conclusion

This study showed similar short and mid-term results for CEA and CAS in asymptomatic patients with significant carotid disease. CAS is a maturing procedure and has improved significantly over the past several years with the addition of protection devices and greater experience of the operators. Future developments of stents and protection devices will achieve better perioperative results. Till that time, although we have shown good results for both carotid surgery and stenting, CAS procedure should be limited to those cases that are not suitable for open surgery and treatment of asymptomatic carotid artery disease with CEA should be considered for patients with few risk factors and long life expectancy. Although, it is clear that both CEA and CAS reduce the long-term stroke risk in asymptomatic patients, the appropriate treatment strategy should be selected according to the patient's individual risk factors and imaging data.

### Declaration of conflict of interest

The authors received no financial support for the research and/or authorship of this article. There is no conflict of interest.

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