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Risk factors for peri-procedural stroke or death in internal carotid artery stenting: A neurology team experience

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Abstract

Background and Objectives: Suitable cases of extracranial internal carotid artery (ICA) stenosis can be treated with carotid artery stenting (CAS) or carotid endarterectomy. However, major complications in the peri-procedural period, like stroke and death, are more common with CAS. We therefore investigated the risk factors for stroke and death during the peri-procedural period following CAS. *Methods:* In this study, the files of patients who were treated with CAS by a neurology team during 2020–2022 were retrospectively analyzed. Patient age, gender, vascular risk factors, use of antiplatelet therapy, type of carotid artery stenosis (symptomatic or asymptomatic), measured stenosis degrees, contralateral carotid stenosis, types of aortic arch, balloon angioplasty, use of a filter-type embolism protection device, stent cell design (open or closed), and peri-procedural death, stroke, or myocardial infarction (MI) were recorded. All patients were followed up for the first 30 days after CAS. *Results:* The mean age of 219 patients included in our study was 67.8 ± 8.38 years and 68.5% were male. The most common comorbid diseases in the patients were hypertension (76.7%), hyperlipidemia (53.4%) and diabetes mellitus (DM) (43.4%). Stroke or death occurred in the peri-procedural period in 15 (6.85%) of the patients, but MI did not occur. No statistically significant difference was observed in terms of age or gender when comparing with the cases without stroke or death. Of the patients suffering stroke or death, ischemic stroke developed in 13 (86.67%), cerebral hemorrhage in two (13.33%) and two patients (13.33%) died. Two-thirds of the strokes were either minor (n=7, 46.67%) or moderate (n=4, 26.67%); 13 (86.67%) were ipsilateral, and 14 (93.33%) were in the anterior circulation. The complication risk was found to be significantly higher in patients with prior stroke (OR=3.865; 95% CI 1.282 to 11.652 p=.016), DM (OR=3.634; 95% CI 1.102 to 11.992 p=.034) and pre-dilation angioplasty (OR=13.100; 95% CI 1.762 to 97.422 p=.012).
Conclusion: Prior stroke, DM and pre-dilation angioplasty increase peri-procedural stroke and death in CAS. However, even if a stroke complication develops after CAS, it is often not severe.

Keywords: Carotid artery stenting, stroke, death, myocardial infarction, peri-procedural risk factors

INTRODUCTION

Stroke is the second most common cause of death and the most common cause of disability in the world.[1] Large vessel atherosclerosis (LVA) is etiologically responsible for 30% of strokes, which cause serious social and economic damage.[2] Extracranial internal carotid artery (ICA) stenosis, which is a type of LVA, is 13.4 per 100.000 people per year, which represents 8% of all strokes of strokes and is observed much more frequently than ICA occlusion, intra/extracranial stenosis, or other occlusions.[3] The treatment of ICA stenosis is therefore very important for the prevention of stroke. In addition to defining the risk factors for ICA stenosis and recommending the best medical treatment, European Society for Vascular Surgery (ESVS) also presented revascularization treatment options, such as carotid artery stetting (CAS) and carotid artery endarterectomy (CAE), for suitable cases.[4]

An analysis of randomized controlled trials (RCT) suggests CAS as an alternative to CAE,

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especially in patients who are not candidates for surgery[5], but the most important factor against recommending CAS as the primary treatment method is the more frequent occurrence of peri-procedural (first 30 days) complications. Large RCTs comparing CAS and CAE (EVA-3S, SPACE, ICSS, CREST) suggest that ICA stenting in symptomatic patients has a significantly higher peri-procedural risk of stroke or death (OR=1.72; 95% CI: 1.29–2.31).[6-9] The risk of stroke or death is greater in CAS than CEA, especially after the age of 70, and also, unlike in CEA, shows a significant correlation with age.[10,11] This increase in risk is dependent upon the degrees of stenosis, symptomatic or asymptomatic stenosis type, novelty, surgeon or interventionist experience, patient age, plaque characteristics (length, calcification, etc.), arterial structure (tortuosity, kinking), comorbid diseases, presence of contralateral occlusion, and aortic arch type.[12] Although the risk of stroke and death in the peri-procedural period is against CAS, it is similar to CEA in the long term. In addition, MI, cranial nerve injury, and severe hematoma are less common in CAS during the peri-procedure period.[5]

Current guidelines recommend analyzing outcomes after treatment with CAS or CEA at the local, national, and international levels to reduce peri-procedural complications and guide future treatment selection strategies.[13] In the current study, we investigated the incidence of and risk factors for peri-procedural stroke or death in patients who underwent CAS in a tertiary hospital in Turkey.

METHODS

The files of patients who underwent extracranial proximal ICA stenting due to carotid artery stenosis (CS) were evaluated retrospectively for complications of death, stroke, or MI in the first 30 days (peri-procedural) after revascularization. Patient age, gender, vascular risk factors, use of antiplatelet therapy, CS type (symptomatic or asymptomatic), measured stenosis degree, aortic arch type, contralateral CS, balloon angioplasty procedure, use of a filter-type embolism protection device (EPD), stent design (open or closed cell), and peri-procedural development of major complications, including death, stroke, and myocardial infarction (MI), were extracted from the records. Stroke after ICA stenting was defined as ischemic or hemorrhagic stroke in any area, transient ischemic attack (TIA), or ocular ischemia (transient monocular blindness, amaurosis fugax, or retinal infarction).

Endovascular procedure

In all cases, the femoral artery was used to reach the stenosis. Femoral 6F introducer sheath was exchanged for a 6 Fr × 80 cm or 6 Fr × 90 cm sheath using 0.35-inch support wire. The long sheath was placed proximal to the common carotid artery bulb, and the stenosis was passed with soft-tipped 0.014-inch micro guidewires. In cases in which distal embolism shielding was used, a 5 Fr SpiderFX™ EPD Irvine/USA was placed in the distal ICA, under the petrous segment. Protege™ RX SEPX 8-6×40 mm 135 cm stent Heerlrn/Netherlands or Boston Scientific 7×40 mm 75 cm closed-cell Carotid WALLSTENT Galway/Ireland was inserted into the stenosis. When sufficient clearance could not be achieved, based on the images taken, balloon angioplasty was performed on the stenosis area, first using a 4×20 Simpass Endo Balloon Dilation Catheter Tuzla/Istanbul if the stenosis could not be passed, then—or instead—using a 5×20 Simpass Endo Balloon Dilation Catheter Tuzla/İstanbul in the stent, with a pressure of 10–12 Atm. If used, the 5 Fr SpiderFX EPD was then duly collected and removed. The procedure was terminated once it was determined that sufficient flow was provided through the stent and the stenosis had been opened according to NASCET (North American Symptomatic Carotid Endarterectomy Trial) criteria. During the procedure, 5000 U heparin and 150 cc contrast agent were administered intraarterially to all patients. All the procedures were managed by a neurology team that included interventional neurologists.

Ethics

Written permission to conduct this study was obtained from the Ankara City Hospital Ethics Committee (date: 27/07/2022, number: E1-22-2610). The study was conducted in accordance with the Helsinki Declaration and with research and publication ethics.

Statistical analyses

The data were analyzed using SPSS Version 26 Chicago/USA. Descriptive statistics are shown as either n (%) for categorical variables or mean ± standard deviation (SD) for continuous variables. Student's t-test was used to compare independent groups, while Fisher's exact test and chi-squared tests were used to compare categorical variables; $p<0.05$ was considered statistically significant. Backward stepwise regression was performed using all variables significant to $p<0.1$.

RESULTS

Two hundred and nineteen patients were included in our study. The mean age of all patients was 67.8 ± 8.38 years and 68.5% were male. The comorbid fastnesses of the patients were listed as follows; HT in 76.7% (n:168), HL in 53.4% (n:117), DM in 43.4% (n:95), CAD in 26%, and stroke history in 19.6% (n:43) and AF in 3.7% (n:8). Stroke or death occurred in the peri-procedural period in 15 (6.85%) of the 219 patients included in the study, but MI did not occur at all. The mean age of patients who developed stroke or death was 69.6 ± 8.31 years, 60% of whom were men ($\frac{\text{female}}{\text{male}}=0.67$), while the mean age of patients who did not develop stroke or death was 67.63 ± 8.38 years and 69.1% were men ($\frac{\text{female}}{\text{male}}=0.45$). No statistically significant difference was observed in terms of age ($p=0.381$) or gender (p=0.565) when comparing with the cases without stroke or death, and when categorizing patients as either below or above 70 years of age, there was no significant difference between the groups ($p=0.337$).

There were ten (7.81%) instances of stroke or death in symptomatic patients and five (5.49%) in asymptomatic patients. Of the patients suffering stroke or death, ischemic stroke (IS) developed in 13 (86.67%) and cerebral hemorrhage (CH) in two (13.33%); two patients (13.33%) died, one of whom was diagnosed with IS and the other with CH secondary to cerebral hyperperfusion syndrome (CHS). All strokes and stroke complications were detected during hospitalization.

For the 15 patients who experienced a stroke, the severity scores, according to the National Institutes of Health Stroke Scale (NIHSS), were minor (NIHSS 0–4) for seven (46.67%), moderate (NIHSS 5–15) for four (26.67%), moderate–severe (NIHSS 16–20) for two (13.33%), and severe (NIHSS 21–42) for two (13.33%). Of the stroke cases, 13 (86.67%) were ipsilateral to the CS and 14 (93.33%) were in the anterior circulation. While the complication rate was found to be significantly higher in patients with stroke ($p=0.013$) and diabetes mellitus (DM) ($p=0.015$), other vascular risk factors, dual antiplatelet therapy use rates, symptomatic or asymptomatic stenosis, degrees of stenosis, contralateral CS, aortic arch types, pre- or post-balloon angioplasty procedure, use of a filter-type EPD, and stent cell type were not associated with stroke or death in the peri-procedural period (Table 1).

Backward stepwise regression was performed using all variables significant to p <0.1 [stroke history, diabetes mellitus (DM), pre-dilation angioplasty, stent cell design (open or closed cell)]. Model statistical significance was found p=0.10. The complication risk was found to be significantly higher in patients with prior stroke (OR=3.865; 95% CI 1.282 to 11.652 p=.016), diabetes mellitus (DM) (OR=3.634; 95% CI 1.102 to 11.992 p=.034) and pre-dilation angioplasty (OR=13.100; 95% CI 1.762 to 97.422 p=.012) (Table 2).

DISCUSSION

Carotid artery stenting, in comparison to carotid endarterectomy, is emerging as a viable and minimally invasive revascularization technique for ICA stenosis.[14] While CAS remains an attractive intervention, randomized controlled studies indicate that peri-procedural stroke or death are higher following CAS in comparison to CAE.[6-9] Furthermore, these studies have underscored that patient outcomes following CAS are influenced by factors related to the patient, procedure, or operator.[12,15,16] Our study results showed that prior stroke, diabetes and pre-dilation angioplasty are risk factors for stroke or death in CAS, stroke after CAS is mostly ischemic type and mild or moderate stroke severity. In addition, none of our CAS cases occurred MI in the peri-procedural period, indicating that the risk of MI is low in CAS during the peri-procedural period.

A meta-analysis of large RCTs reported a stroke or death rate of 8.7% in symptomatic patients and 3.1% in asymptomatic patients treated with CAS in the first 30 days[13]; in the current study, this rate was 6.85% in the whole patient group, while it was 7.81% for symptomatic patients and 5.49% for asymptomatic patients. MI was not observed in any of the cases. In this study, all stroke or death complications occurred during hospitalization, while other studies have reported that two-thirds of peri-procedural complications developed while the patients were still in the hospital and especially in the first two days after the procedure.[17]

ESVS report that the risk of stroke or death after revascularization therapy is less than 3% for asymptomatic patients and less than 6% for symptomatic patients.[13] We believe that the higher risk of stroke or death in the current study is related to the patient selection criteria. In a study

Table 1: CAS case characteristics and comparison between cases with and without stroke or death.

	Stroke or death						
	Yes (n=15)			No (n=204)			
	n	%	Mean ± SD	n	%	Mean ± SD	*p*
Age			69.6 ± 8.31			67.63 ± 8.38	0.381*
<70 or >70 years	7:8	46.7:53.3		121:83	59.3:40.7		0.337*
Sex (female or male)	6:9	40:60		63:141	30.9:69.1		0.565
Stroke or death	15	6.85		204	93.15		
Death	2	13.3					
Stroke	15	100					
IS	13	86.7					
CH	2	13.3					
Vascular risk factors							
HT	13	86.7		155	76		0.529
DM	11	73.3		84	41.2		0.015**
HL	9	60		108	52.9		0.597**
Stroke	7	46.7		36	17.6		0.013
CAD	5	33.3		52	25.5		0.545
AF	1	6.7		7	3.4		0.439
DAPT	15	7.2		194	92.8		0.484
Symptomatic or asymptomatic	10:5	66.7:33.3		118:86	57.8:42.2		0.503
Stenosis grade							0.568
50–69%	3	20		38	18.6		
70–99%	11	73.3		159	77.9		
Near occlusion	1	6.7		7	3.4		
Contralateral CS, >50%	1	6.7		8	3.9		0.478
Arcus Type							0.544
Type 1	13			181			
Type 2	2			22			
Type 3				1			
Filter wire EPD use	14	93.3		171	84.2		0.478
Pre-dilation angioplasty	2	13.3		4	2		0.057
Post-dilation angioplasty	14	93.3		201	99		0.193
Stent cell design	8:7	53.3:46.7		102:102	50:50		0.062**

IS: ischemic stroke, CH: cerebral hemorrhage, HT: hypertension, DM: diabetes mellitus, AF: atrial fibrillation, CAD: coronary artery disease, DAPT: dual antiplatelet therapy, CS: carotid artery stenosis, EPD: embolism protective device Student's t-test was used to compare independent groups. Fisher's exact test and chi-squared tests were used to compare categorical variables. $p < 0.05$ was considered statistically significant.

*independent samples t-test; **chi-squared test, Fisher's exact test was used for the p-values without asterisks.

examining the importance of patient selection, Two hundred and seventy one CAS procedures conducted on 231 patients were evaluated, in which 6.2% experienced minor strokes and 0.7% major strokes. When the authors revised the inclusion criteria for the patients according to the NASCET study and excluded asymptomatic stenos, advanced age, serious comorbid diseases,

Table 2: Regression analysis results for peri-procedural stroke or death risk factors in internal CAS

Variables	OR	95% Cl		*p* value
		Lower	Upper	
Stroke history	4.349	1.234	15.331	0.022
DM	4.231	1.363	13.129	0.013
Pre-dilation angioplasty	13.100	1.762	97.422	0.012
Stent cell design	1.001	0.319	3.147	0.998

DM; diabetes mellitus
Model *p*: 0.001

cardioembolic stroke etiology, and a history of endarterectomy, the number of CAS procedures decreased from 271 to 37 and the complication rate decreased to 2.7%.[18] Making the same revisions to the current study would exclude 112 patients, including 91 asymptomatic patients, ten over 79 years of age, five with serious comorbid diseases, three with severely disabling stroke, two with suspected cardioembolic stroke etiology, and one with ipsilateral CEA; the number of procedures would then decrease to 107 and the stroke or death rate to 3.7%. Another important reason for the high rate of stroke detected in the current study may be the neurologist in our team, who performed the CAS procedure, and the team's awareness of stroke or death, which would be consistent with previous studies that have shown a significant increase in the rate of neurological deficit detection when a neurologist participates in the CAS procedure.[19]

The incidence of peri-procedural TIA as 2.4 per 100 CAS procedures, and the incidence of stroke was 2.7 per 100 CAS procedures. Perioperative stroke drastically increases the risk of peri-procedural mortality (20), but stroke that develops after CAS is usually minor (81%), ischemic (90%), ipsilateral (88%), and in the anterior circulation (88%).[21] In the current study, approximately half of the strokes that occurred were minor, 86.7% were IS, 93% were ipsilateral, and 93% were in the anterior circulation.

CH is a relatively rare but potentially fatal complication of CAS, reported as occurring in between 0.36% and 6.67% of patients after CAS, with a mortality rate of about 75%.[22] Of the important causes of stroke after CAS, CH was observed in two cases in the current study (0.9%). In one of these cases, the diagnosis was CHS, which reportedly occurs at a rate of 3.1–6.8% after CAS, particularly in the peri-procedure period[23], and is fatal, especially when CH then develops, as with our patient.[24]

Stroke in CAS is not only related to stenting, but may also be related to angiographic examination. In the Asymptomatic Carotid Atherosclerosis Study, which compared medical treatment and CEA in asymptomatic patients, the perioperative stroke or death rate in the CEA group was 2.3%, while more than half of the strokes were associated with angiography.[25] To prevent embolisms that may develop due to the stent procedure, the guidelines recommend—with a low level of evidence—the use of an EPD with closed-cell stents at the discretion of the operator.[13] Prevention of embolic strokes is important using EPDs, but embolisms can still occur as a result of incomplete insertion, misplacement, or incomplete aspiration of debris. A meta-analysis of three major RCTs (Carotid Stenosis Trialists' Collaboration) found, similar to our study, that EPDs do not reduce the risk of stroke or death in the first 30 days.[26] Other studies have produced similar results for the use of closed-cell stents and we found no differences in terms of complication development.[27,28] Efforts to reduce embolism-related complications in CAS continue, with positive data emerging for newly developed techniques like transcervical carotid artery stenting[29] and robotic endovascular revascularization[30], which should be reflected in future studies.

A review of the existing literature shows several categories of risk factors for stroke or death following CAS: demographics (advanced age, female gender)[31-33], anatomical variables (arch type 2 or 3, tortuous carotid arterial system)[34], clinical features (comorbid diseases, symptomatic stenosis, severe stenosis rate, contralateral CS, stenosis side, ulcered/calcified/long plaque structure)[31,35,36], technical aspects (non-use of EPD or closed-cell stent, pre-dilatation, post-dilatation, primary intervention versus intervention for restenosis, angioplasty without stent, heparin dosage greater than 5000 IU)[31,37,38], and timing of the CAS.[39,40] However, considering that each study reported different risk factors, features of the studies themselves might be explanatory, such as the patient selection criteria or differences in the team or the center performing the procedure.[39]

DM increases the risk of IS in the general population[41] and can also aggravate the severity of extracranial atherosclerotic disease.[42] It was also found to be a risk factor for stroke or death during the peri-procedural period of CAS in our study, which is consistent with a meta-analysis of 14 studies that found DM to be associated with procedural stroke, death, and poor long-term prognosis.[43] DM also increases the risk of stent stenosis in the post-procedural period.[44] One of the findings showing the negative effects of diabetes on carotid stenosis is that it can cause an increase in intima-media thickness (IMT) was observed in diabetic patients and the relative risk of MI and stroke was found to be increased by approximately 40%.[45] Consistent with this, it has been shown that tight glycemic control reduces abnormal IMT[46] and is associated with lower cardiovascular mortality.[47] Therefore, the lack of data on the glycemic control of the patients in our study is a limitation.

Another important comorbidity in cases with stroke or death in the current study was previous stroke history, as in prior research[48], and a history of severe stroke is an exclusion criterion for revascularization studies.[49] Both the patient history of stroke and the timing of post-stroke revascularization and acute treatment regimens may increase the risk of stroke or death after CAS. Guidelines recommend that CAS or CEA be performed as early as possible (first 14 days) after the neurologic index event in patients with symptomatic carotid stenosis (≥50% stenosis), but the first seven-day period after stroke was found to be risky for stroke or death after CAS.[39] The same risk has been found for the first six-day period after thrombolytic therapy[40], but the data in our study do not provide information on this topic. Our study also has other limitations: the follow-up period was limited to 30 days, the number of cases was relatively small, there was no comparison with CAE, the complications investigated were limited to stroke and death, and several parameters, such as the timing of the procedure, were not evaluated.

In our study, although predilatation angioplasty was an independent risk factor for stroke or death in the peri-procedural period, it was applied only in six patients, hemorrhagic stroke in one patient and death in one patient. Guidelines also recommends avoiding aggressive predilatation angioplasty (balloon diameters <5 mm should be considered) and postdilatation angioplasty in less than 30% residual stenosis in order not to impair hemodynamic stability.[13] In the recent study, performing predilatation alone, postdilatation alone, or both predilatation and postdilatation were not significantly associated with differences in the rate of stroke and/or death. The results of the meta-analysis study on this subject indicate an increased risk of neurologic deficit in the early period, independent of the angioplasty method.[50] In our study, all six patients with predilatation angioplasty had severe occlusion (70-99% CAS in 4 cases, near occlusion in 2 cases). In a study comparing pre- or post-dilatation angioplasty in 265 patients with severe CAS, predilatation angioplasty was associated with increased early cardiovascular and cerebrovascular complications.[51] There are studies in the literature showing that predilatation angioplasty is associated with fewer side effects. These studies argue that predilatation reduces the risk of intimal damage and embolism.[52] In addition, there are studies that emphasize that without the use of EPD during pre-dilation angioplasty, there is an increased risk of stroke or mortality.[51,53-54] However, in our study, EPD was used in all cases of pre-dilation angioplasty.

In conclusion, stroke history, diabetes and pre-dilation angioplasty were found to be significantly higher in patients affected by stroke or death in the peri-procedural period following CAS. The CAS patient selection criteria also directly affected mortality and morbidity. Nevertheless, even if a stroke complication develops after CAS, it is often not severe.

DISCLOSURE

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