Plaque morphology effect on periprocedural asymptomatic cerebral embolism in carotid artery stenting using first-generation carotid stents: A diffusion-weighted magnetic resonance imaging study

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ABSTRACT

Background: Silent cerebral embolism with carotid artery stenting (CAS) may contribute to dementia and cognitive decline. Moreover, clinically silent embolism is an important index of peri-procedural stroke risk.

Aims: The purpose of this study was to compare the periprocedural asymptomatic cerebral embolism rates of CAS procedures performed for noncalcified and calcified carotid artery plaques using diffusion-weighted magnetic resonance imaging (DW-MRI).

Methods: Five hundred and seventy clinically uncomplicated patients who underwent CAS at our center from December 2010 to June 2020 (mean [standard deviation, SD] age 69.3 [8.2 years]) were analyzed retrospectively. The patients were divided into 2 groups with noncalcified (268 patients) and calcified (302 patients) plague. Cerebral DW-MRI was performed for the patients before and after CAS and compared. The presence of periprocedural new ipsilateral diffusion limitations detected on cerebral DW-MRI was noted as a significant finding. Ipsilateral diffusion limitations of the non-calcified and calcified plaque groups detected on cerebral DW-MRI were compared.

Results: The presence of periprocedural asymptomatic ipsilateral DW-MRI lesions was higher in patients in the noncalcified plaque group (45 [16.8%]) than in patients in the calcified plaque group (31 [10.3%]; $P = 0.02$).

Conclusion: This study demonstrated that the rate of ipsilateral asymptomatic cerebral embolism detected on cerebral DW-MRI was higher in the CAS procedures performed for noncalcified carotid artery plaques than in those performed for calcified plaques.

Key words: carotid artery stenting, diffusion-weighted magnetic resonance imaging, embolism, new ischemic cerebral lesions, plaque morphology

INTRODUCTION

With the development of interventional devices and techniques, carotid artery stenting (CAS) has become an alternative to carotid endarterectomy (CEA) for the treatment of carotid artery stenosis [1]. The most important complications of carotid artery stenting include new ischemic cerebral lesions associated with distal embolization and neurological symptoms [2]. Silent cerebral embolism associated with CAS has been demonstrated to cause dementia, cognitive decline [3], and even ischemic stroke [4, 5].

Cerebral diffusion-weighted magnetic resonance imaging (DW-MRI) is a very sensitive method to detect silent brain lesions formed during CAS [6, 7]. The use of embolic protection devices (EPD) in CAS has decreased the incidence of new cerebral ischemic lesions associated with the procedure and detected through DW-MRI [8]. Therefore, EPD is strongly recommended during CAS procedures [9].

WHAT'S NEW

Carotid artery stenting (CAS) plays an important role in the preventive treatment of ischemic stroke, which is one of the top causes of disability and mortality. Asymptomatic cerebral embolism, best detected by diffusion-weighted magnetic resonance imaging, is an index of peri-procedural stroke risk, and it may enhance cognitive decline. We have evaluated, for the first time in a patient series exceeding 500, the relationship between plaque morphology and CAS-related asymptomatic cerebral embolism. With our routine use of first-generation (single-layer) carotid stents under transient cerebral protection, we found that the risk of cerebral embolism was larger in the case of soft, non-calcified plaques. Our findings suggest that patients at increased risk of CAS-related cerebral embolism, in particular, might benefit from novel plaque-sequestrating carotid stent systems that require further research.

Even though the CAS procedure is performed with the use of EPD, cerebral embolism may yet develop. New ischemic cerebral lesions caused by distal emboli that occur during CAS may develop due to several factors. Some of these factors include the cerebral status of patients, their vasculature, aortic arch type, devices used, the experience of operators. There is increasing recognition of the role of plaque morphology in the risk of cerebral embolism with CAS [10, 11]. Hence patients, lesions, and appropriate material selection play an important role in decreasing distal emboli associated with CAS.

Vulnerable atherosclerotic plaques are more likely to get ruptured and cause thrombotic and embolic effects [12]. Studies with small series demonstrated that carotid plaques with a noncalcified morphology resulted in more cerebral embolism in CAS compared to fibrocalcific plaques [13]. Except for carotid artery plaque nature, carotid ultrasound indices (carotid intimamedia thickness, extramedia thickness, intraabdominal thickness, and the combined PATIMA index) may play an important role in decision-making for coronary revascularization in patients with high cardiovascular risk [14, 15]. The purpose of our study was to compare the periprocedural asymptomatic cerebral embolism rates in CAS procedures in patients with noncalcified and calcified carotid artery plaques using DW-MRI.

METHODS

We obtained the approval of the ethics board of our center for this study (no. 2020-321). We included 570 clinically uncomplicated patients (mean [standard deviation, SD] age, 69.3 [8.2] years) who were admitted to our center from December 2010 to June 2020 and referred for CAS after consultation in the multidisciplinary carotid council consisting of neurology, cardiology, cardiovascular surgery, and radiology clinics. The patients were divided into 2 groups: the noncalcified (268 patients) and calcified (302 patients) plaque groups. Symptomatic patient (284 patients [50%]) was defined as one that had a history of the ischemic cerebrovascular event with or without sequela, transient ischemic attack (TIA), amaurosis fugax in the previous six months. Patients who were symptomatic and had more than 50% stenosis on digital subtraction angiography (DSA), according to the North American Symptomatic Carotid Endarterectomy Trial (NASCET) formulation, and those who were asymptomatic and had more than 80% stenosis were included in the assessment. All patients who had a glomerular filtration rate (GFR) greater than 60 ml/min/1.73 m^2 underwent computed tomography angiography (CTA) for the carotid after carotid Doppler ultrasonography (CDUS). The nature of patients' carotid artery plaques was determined using imaging techniques. The medical follow-up, CAS or CEA, was decided by the multidisciplinary team depending on the clinical features, comorbidities, and characteristics of carotid artery lesions of the patients. Table 1 shows the inclusion and exclusion criteria in our study. Table 2 shows the patients who were considered to be at risk for CAS and referred

Table 1. Inclusion and exclusion criteria

Inclusion criteria
Symptomatic ICA stenosis ≥50% on DSA
Asymptomatic ICA stenosis ≥80% on DSA
The ipsilateral external carotid artery is not totally occluded
Patent contralateral ICA
A complete circle of Willis (assessed by CTA)
Filter able to pass through the lesion without the need for predilatation (assessed by CTA)
Presence of adequate landing zone for the filter (4 cm) (assessed by CTA)
Informed consent form for the procedure signed by patients
Exclusion criteria
Symptomatic complications (23 patients)
Periprocedural hemodynamic instability (>10 minutes) (17 patients)
Distal ICA spasm (14 patients)
>30% residual stenosis (12 patients)
Procedure time >45 min (11 patients)
Diffusion limitation in the watershed area of the collateral carotid artery on cerebral DW-MRI after CAS, bilateral diffusion limitation and watershed diffusion limitation (26 patients)
Need for repeated pre/postdilatation (10 patients)
Balloon dilatation under an atmosphere pressure 20% greater than the nominal balloon pressure (5 patients)
CEA restenosis, history of radiotherapy, routine use of anticoagulants (37 patients)
Type III aortic arch (88 patients)
Ischemic stroke in the past 48 hours (15 patients)
Poor image quality of cerebral DW-MRI, contraindication for DW-MRI (pacemaker, claustrophobia) (23 patients)
History of rheumatic diseases (11 patients)
Diagnosis of cancer (14 patients)

Abbreviations: CAS, carotid artery stenting; CEA, carotid endarterectomy; CTA, computed tomography angiography; DSA, digital subtraction angiography; DW-MRI, diffusion-weighted magnetic resonance imaging; ICA: internal carotid artery

Table 2. Patients who were at risk for carotid artery stenting and thus underwent CEA

Patient or lesion characteristics
• Femoral access problem
• Arcus aorta is severely atherosclerotic or calcified
• Common carotid artery is severely tortuous
• Carotid artery lesion length >40 mm
• Diameter of carotid artery closer to the bifurcation > 10 mm
• Dense calcification in the carotid artery in the area of stenosis (Gray-Weale type IV)
• Carotis artery plaque is severely ulcerated or densely thrombotic
• GFR <30 ml/min/1.73 m^2
• Resistance to acetylsalicylic acid and clopidogrel

Abbreviations: GFR, glomerular filtration rate; other — see Table 1

for CEA. The criteria shown in Table 2 were based on our center's experience. In the cases excluded by the criteria outlined in Table 2, a stent procedure was applied to the carotid artery stenosis.

Preparation of patients for carotid artery stenting

Patients were informed about the details of CAS and signed informed consent forms. Antihypertensive, antihyperlipidemic, and antiplatelet medications that the patients had been taking were regulated. The procedure was initiated after their blood pressure values were regulated down below 135/80 mm Hg. We made sure that the patients had been taking dual antiplatelet therapy consisting of 100 mg acetylsalicylic acid (ASA), in particular, and 75 mg clopidogrel at least for 7 days. Otherwise, additional loading dose (ASA 300 mg, clopidogrel 600 mg), and maintenance antiplatelet therapy were planned. A resistance test was performed on venous blood for both antiplatelet agents in the morning of the procedure. CAS was performed after a loading dose of 2 tablets of 90 mg ticagrelor and 2 × 1 maintenance regimen if they had resistance only to clopidogrel.

Carotid artery stenting procedure

All procedures were performed by 2 operators: an invasive cardiologist and an interventional vascular neurologist. They were performed under local anesthesia with percutaneous transfemoral access. The patient's oxygen saturation, electrocardiographic, and blood pressure parameters were monitored throughout the procedure. The procedure was initiated with a femoral 8 F sheath. A 9F sheath was used when proximal protection was preferred as an embolic protection method. After the sheath was placed, all patients were given 75 IU/kg unfractionated heparin. Depending on the arcus aorta type of the patient evaluated in the council, a 5 F hydrophilic headhunter or sim 1.2 diagnostic catheter was used. CAS was performed with the anchor method in most of the patients. The telescopic method was used only in a few patients. Following bilateral carotid and cerebral DSA, we determined the embolic protection method, balloon and stent diameters, and if predilatation/postdilatation would be performed. The stent design was not selected according to either the lesion or vascular structure. The available stent design was placed in the stenotic carotid artery. For predilatation, 3.0–5.0 × 20 mm balloons (Invader; Alvimedica, Simpass; Simeks) were used. For the postdilatation procedure after carotid stent, 5.0–5.5 × 20 mm balloons (Viatrac; Guidant) were preferred. The balloon diameter for predilatation was calculated as around 1 mm smaller than the diameter of the distal intact ICA. When the residual stenosis was <30% after stenting, postdilatation was not performed. Tapered stents were used for all patients. The self-expandable stent diameter was adjusted so it was 20% larger than the diameter of the carotid artery measured digitally. The stent designs used at our clinic so far are closed-cell stent (20%), Xact carotid stent (Abbott, Santa Clara, CA, US), open-cell stents (67%); Sinus-carotid-conical RX stent (Optimed, Ettlingen, Deutschland), RX Acculink stent (Abbott), protege RX stent (Ev3, Medtronic, Plymouth, MN, US), a hybrid-cell stent (13%), and Cristallo idealE SE stent (İnvatec, Medtronic). In the following lesion groups, the proximal blockage system (Mo.MA®) was preferred as EPD. In the case of symptomatic and >90% carotid artery stenosis, ICAs after bulbous area are tortuous, the lesion was ulcerated and slightly thrombotic. For the other lesions, a distal protection method (filter [Emboshield, Filterwire, spider FX]) was used. Patients with a heart rate of <60/min were administered 1 mg atropine intravenously (IV) before carotid ballooning. Atropine was given to other patients if their heart rate went below <60/min after ballooning/stenting. To make sure if there had been distal embolization associated with CAS, bilateral cerebral DSA was performed and compared with pre-CAS scans. For all patients who did not undergo coronary artery angiography (CAG) beforehand, CAG was performed after CAS.

Follow-up after carotid artery stenting

All patients were followed up for hemodynamic and clinical parameters at the coronary intensive care unit for 24 hours following CAS. Cerebral DW-MRI was performed to be able to see possible asymptomatic cerebral DW-MRI lesions in patients 3–7 days before and 12–24 hours after the CAS procedure (Figure 1). A routine cardiac enzyme test was not made. The patients were followed up by the vascular neurologist for minor and major neurological complications for 24 hours following the procedure. On discharge, all patients were prescribed dual antiplatelet and statin therapy (if low-density lipoprotein [LDL] cholesterol was >70 mg/dl). Dual antiplatelet therapy was continued for 6–12 months if the patients did not have any other specific conditions.

Carotid plaque characterization

Carotid artery stenosis was first evaluated by CDUS and then by CTA. Plaque morphology, which is defined as predominantly fibrolipid (noncalcified) or fibrocalcific, and the degree of stenosis were initially determined through a sonography/DUS evaluation and CTA of supra-aortic vessels during the inclusion period. All lesions were eval-

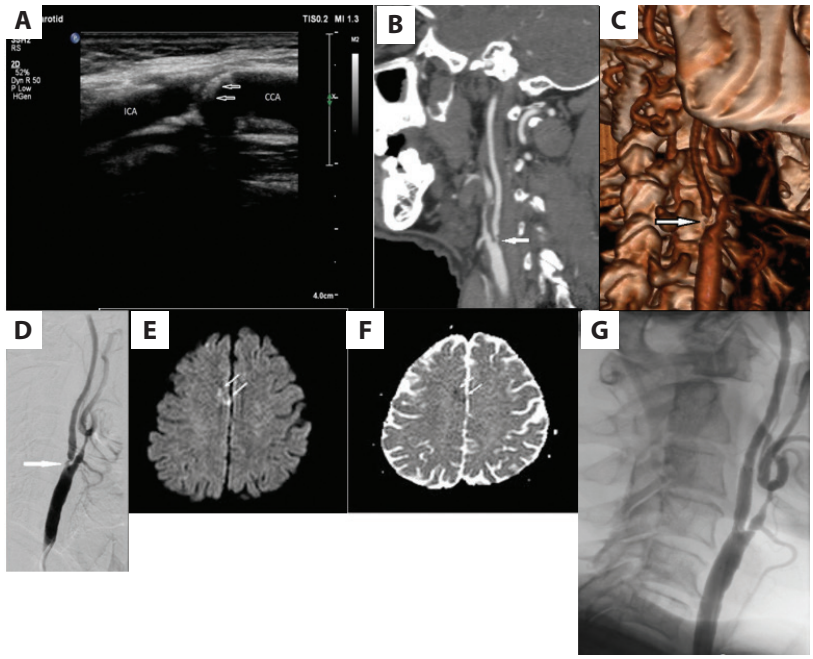

Figure 1. Noncalcified plaque-causing severe stenosis in the internal carotid artery (arrow). B-mode sonography (**A**), computed tomography angiography (**B**) 3D computed tomography angiography (**C**), and digital subtraction angiography (**D**). Postinterventional cerebral diffusion-weighted magnetic resonance imaging (**E**) shows the anterior cerebral artery territory high-signal intensity lesion (arrow). On ADC map (**F**), the lesion shows low-signal intensity (arrow) indicating its acute nature. Digital subtraction angiography after stenting (**G**)

uated with CDUS and CTA. Plaque morphology defined by CDUS was confirmed by CTA in lesions with severe stenosis in CDUS according to flow rate. Final plaque morphology before CAS was decided according to CTA findings. CDUS examination was performed using the Esaote SpA MyLab-Class C (Esaote SpA, Florence, Italy) device with the linear array probe, which allows the selection of frequencies between 3 and 11 MHz. The severity of carotid stenosis was evaluated by measuring the peak systolic velocity (PSV), with angle correction, at the narrowest point of stenosis. If PSV was in the range of 125–240 cm/s, carotid stenosis was considered to be 50%–70%. Stenosis was classified at more than 70% if PSV was more than 240 cm/s. The classification of Gray-Weale [16] was used for ultrasonography plaque characterization as follows: Type I, predominantly echolucent plaque with a thin echogenic cap; Type II, substantially echolucent lesions with small areas of echogenicity; Type III, predominantly echogenic lesions with small areas of echolucency; and Type IV, uniform echogenic lesions (equivalent to homogeneous). Type I and Type II were predominantly soft plaques with fibrolipid structure; Type III and Type IV were predominantly fibrotic and partly calcified plaques (hard plaques). In our study, Types I and II were classified as noncalcified plaque (Figure 1), and Type III as calcified plaque (Figure 2). Patients with Type IV plaque (dense calcification) were excluded from the study.

CTA examination was performed using the Philips Brilliance 64 detector CT (Holland) device (Philips Healthcare, 5680 DA Best, The Netherlands). After venous access was established through the antecubital vein and 80 ml nonionic contrast agent was administered at a rate of 4.5 ml/sec, axial-plane computed tomography images of the carotid and cerebral arteries were obtained using the tracking method. Acquired slices were transferred to the Workstation (Philips IntelliSpace Portal, Philips Healthcare) and multiplane images, maximum intensity projection, and volume rendering 3-dimensional images were developed by postprocessing the original slices via appropriate software (AVA). Plaque type was classified according to attenuation measurements from the previously reported criteria [17]. Predominantly lipid or fibroid plaques were defined as soft intermediate plaques with a median attenuation of ≤130 HU (Figure 1). Calcified plaques consisted of lesions having a median attenuation >130 HU (Figure 2). When there was a disagreement in plaque characterization between CTA and DUS, we used the data obtained by CTA. The stenosis caused by plaques as detected using CDUS was assessed according to the criteria developed by the Internal Carotid Artery Stenosis Criteria Consensus Committee. The severity of stenosis detected on CTA was evaluated according to the criteria of the NASCET.

DW-MRI

Cerebral DW-MRI images were obtained using a 1.5 Tesla Magnetom Sonata (Siemens, Erlangen, Germany). Cerebral MRI (DWI and ADC [apparent diffusion coefficient]) maps of patients were compared before and after CAS by an experienced interventional neurologist (ESG). New ipsilateral hyperintense DW-MRI lesions not seen before CAS were considered silent cerebral embolisms. The diffusion-weighted sequence was acquired with three different *b*-values (b = 0.500, and 1000 s/mm^2). A positive DWI scan

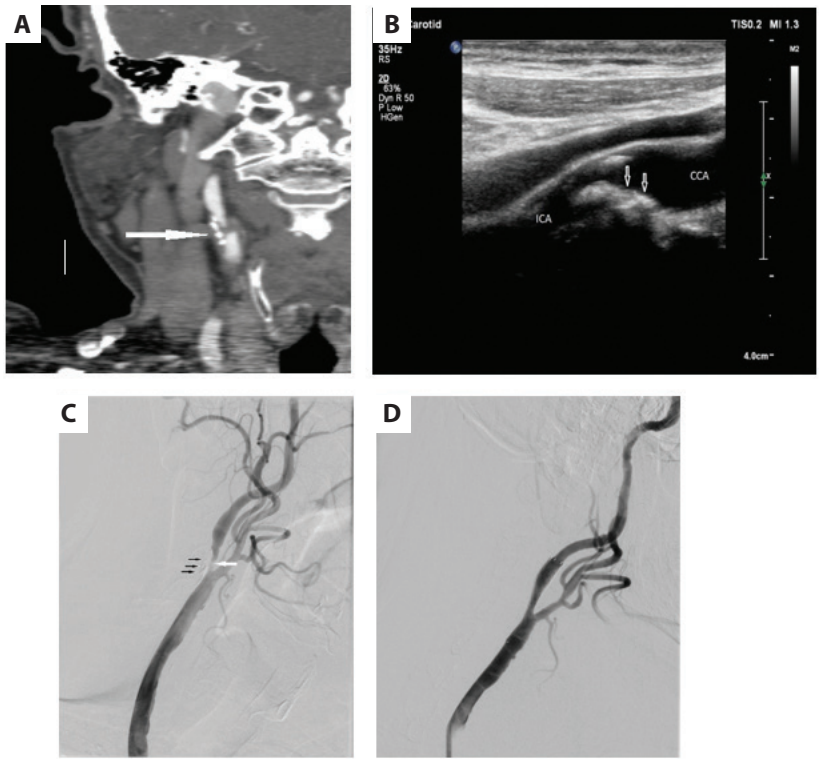

Figure 2. Calcified plaque-causing severe stenosis in the internal carotid artery (arrow). B-mode sonography (**A**), computed tomography angiography (**B**), and digital subtraction angiography before stenting (**C**), after stenting (**D**)

was defined as a high signal on the b1000 image. In the cases with a lesion on DWI, we also reviewed the ADC map and noted whether high-signal areas on the b1000 image showed low, high, or normal signal on the ADC map when comparing the affected area to the corresponding contralateral area. Furthermore, we assessed whether the lesions visible on DWI were also present on the T2 image.

Statistical analysis

The data obtained in this study was recorded with SPSS 24.0 (IBM Corp., Armonk, NY, US) software. The categorical variables were expressed as numbers and percentages while continuous variables were expressed as means and standard deviation. The Shapiro-Wilk test was used to analyze the concordance of the continuous variables with the normal distribution. For inter-group comparison, the Student's t-test was used for normally distributed parameters while the Mann-Whitney U test was used for other parameters that did not have the normal distribution. To analyze the categorical variables, the χ^2 test or Fisher's test was used. P <0.05 was considered to be statistically significant.

RESULTS

When the baseline characteristics of the noncalcified and calcified groups were compared, the mean age of the patients in the calcified group was found to be statistically significantly higher (mean [SD] age in the noncalcified and calcified groups, respectively, was 68.10 [9.9] vs. 70.86 [9.1] years; P <0.001). The rate of smokers was statistically significantly higher in the noncalcified group (the number of smokers in the noncalcified and calcified groups, was 110 [41.0%] vs. 93 [30.8%] respectively, P =0.011). No difference was found between the two groups as regards the other clinical characteristics (Table 3).

As for the procedural characteristics, balloon postdilatation was performed statistically significantly more in the calcified group (the number of patients undergoing balloons postdilatation in the noncalcified and calcified groups, was 96 [35.8%] vs. 137 [45.4%], respectively, P = 0.021). As for the other procedural characteristics, both groups were similar (Table 4).

When the two groups were compared for periprocedural asymptomatic ipsilateral cerebral DW-MRI lesion, which was the primary endpoint of our study, the lesion was detected in 45 (16.8%) patients in the noncalcified group and 31 (10.3%) patients in the calcified group. Periprocedural asymptomatic ipsilateral cerebral DW-MRI lesion was detected more often in the noncalcified plaque group than in the calcified plaque group, which was statistically significant (P = 0.022) (Table 5).

DISCUSSION

In this study, periprocedural ipsilateral cerebral DW-MRI lesion rates of calcified and noncalcified carotid plaques associated with CAS were compared with cerebral DW-MRI findings. The findings of this study demonstrated that carotid stents implanted into the noncalcified plaques were associated with a higher rate of periprocedural

Table 3. Clinical characteristics of the study groups

Variables	Noncalcified plaque (n = 268)	Calcified plaque (n = 302)	*P*-value
Age, years, mean (SD)	68.10 (9.9)	70.86 (9.1)	<0.001
Male, n (%)	209 (78.0)	230 (76.2)	0.605
Hypertension, n (%)	189 (70.5)	223 (73.8)	0.377
Diabetes mellitus, n (%)	108 (40.3)	119 (39.4)	0.828
Coronary artery disease, n (%)	180 (67.2)	222 (73.5)	0.097
Peripheral artery disease, n (%)	13 (4.9)	14 (4.6)	0.904
Smoking, n (%)	110 (41.0)	93 (30.8)	0.011
Chronic renal failure, n (%)	11 (4.1)	7 (2.3)	0.223
Symptomatic ICA stenosis, n(%)	134 (50.2)	151 (50.2)	0.996
LDL, mg/dl, median (IQR)	105.0 (77.2–136.0)	107.0 (83.7–136.2)	0.757
Statin intake, n (%)	249 (92.9)	274 (90.7)	0.345
Drug resistance, n (%)			
Absent	236 (88.1)	275 (91.1)	0.080
ASA	5 (1.9)	5 (1.7)	
Clopidogrel	27 (10.1)	18 (6.0)	

Data are expressed as median (interquartile range [IQR]) for non-normal distributed data and percentage for categorical variables

Abbreviations: ASA, acetylsalicylic acid; LDL, low-density lipoprotein; other — see Table 1

Table 4. Procedural characteristics of the study groups

Variables	Noncalcified plaque (n = 268)	Calcified plaque (n=302)	*P*-value
Stent length, n (%)			
30 mm	130 (48.5)	128 (42.4)	0.143
40 mm	138 (51.5)	174 (57.6)	
Stent diameter, n (%)			
6&8, 6&9, 7&9	114 (42.9)	119 (39.4)	0.404
7&10, 8&10	152 (57.1)	183 (60.6)	
Filter/ MoMA®, n (%)			
Protected	22 (8.2)	12 (4.0)	0.078
MOMA	99 (36.9)	126 (41.7)	
Filter	147 (54.9)	164 (54.3)	
Stent type, n(%)			
Open-cell	179 (66.8)	202 (66.9)	0.932
Closed-cell	54 (20.1)	58 (19.2)	
Hybrid-cell	35 (13.1)	42 (13.9)	
Predilatation, n (%)	172 (64.2)	197 (65.2)	0.793
Postdilatation, n (%)	96 (35.8)	137 (45.4)	0.021
Debris, n (%)	55 (20.6)	55 (18.2)	0.472

Abbreviations: MoMA, proximal embolic protection device; other — see Table 1

Table 5. Periprocedural ipsilateral cerebral DW-MRI lesion of all groups

	Noncalcified plaque, n (%)	Calcified plaque, n (%)	Total, n (%)	*P*-value
DW-MRI lesion absent	223 (83.2)	271 (89.7)	494 (86.7)	0.022
DW-MRI lesion present	45 (16.8)	31 (10.3)	76 (13.3)	
Total	268	302	570 (100)	

Abbreviations: DW-MRI, diffusion-weighted magnetic resonance imaging

asymptomatic ipsilateral DW-MRI lesions compared to the calcified plaques.

In the ACST-2 (second asymptomatic carotid surgery trial) study, which was published in 2021, procedure-related complications and long-term results were found to be similar between CAS and CEA in asymptomatic carotid stenosis [18]. Despite these large-scale randomized trials, the safety of CAS is still controversial [1, 19]. Stroke and transient ischemic attack after CAS are rare complications observed at high-volume and experienced centers [20]. Symptomatic or asymptomatic periprocedural cerebral embolism is one of the most important limitations of CAS [21, 22]. Silent cerebral embolism associated with CAS was demonstrated to cause dementia, cognitive decline [3], and even ischemic stroke in the subsequent years [4].

DW-MRI is a very sensitive method to detect cerebral lesions that develop during CAS [6, 7]. The rate of silent cerebral embolism associated with CAS and detected on DW-MR was reported to be up to 40% in some series [2, 23]. Thirty percent of these embolic events are observed in the contralateral hemisphere [24]. Unless an embolic protection method is used (unprotected), the rate of cerebral

embolism is 45%, which can be reduced to 33% with an embolic protection method [2, 10].

There is a need to find the cause of silent cerebral embolism, which is still common and clinically significant in protected CAS procedures and to reduce the incidence of embolism. In a study [10], age, hypertension, lesion eccentricity, and type III aortic arch were shown to cause cerebral ischemic lesion associated with CAS with the use of DW-MRI. Xiaoyu Xu et al. demonstrated in the study they conducted in 2020 that diabetes mellitus, ipsilateral calcified plaque, ulcerated plaque, predilatation, and use of open-cell stent were independent risk factors for silent cerebral lesions during CAS [25].

Some variables in CAS may increase the risk of embolism in the brain tissue fed by the stented carotid artery and some others may increase the risk of bilateral cerebral embolism. Long-term periprocedural hemodynamic instability may lead to bilateral cerebral embolism and especially watershed infarcts. Type III aortic arch, severely atherosclerotic and calcified aortic arch, inappropriate catheter use prolong the procedure time and increase the risk of bilateral embolism [26]. Severely tortuous carotid artery, severe ICA spasm, complex carotid plaques (long, ulcerated, thrombotic plaques), and the use of inappropriate antiplatelets increase the risk of embolism on the same side with the stent. In our study, to determine the risk associated with the nature of carotid artery plaque-causing cerebral embolism, we determined several exclusion criteria such as symptomatic complications, hemodynamic instability during the procedure, difficult and risky arcus aorta, severely tortuous carotid arteries, severely ulcerated, heavily thrombotic and heavily calcified circular carotid artery plaques, watershed infarcts, and a history of repeated ballooning. The goal was to find significant associations between these brain emboli fed by the stented artery and the nature of calcified and noncalcified plaques. Our study is different from other studies because statin was initiated for most of the patients before CAS and dual antiplatelet therapy was adjusted according to the antiplatelet resistance test results. A multidisciplinary team is crucial to decide on the right patients, right lesions, and the right procedure. The fact that all CAS procedures recommended by the multidisciplinary team were performed by the same operators and with the same method using similar materials is considered to be the main factor that kept the procedure-associated cerebral embolism rate at a very low level (13.3%) and increased the reliability of our results.

The most important step in implementing CAS to decrease cerebral embolism is to use an embolic protection device. Most of the studies investigating cerebral embolism with DW-MRI used the distal protection method. Contrary to these studies, we used the proximal blockage method for embolic protection in 39% of the study group. Before the proximal blockage system was used, intracerebral blood circulation was assessed, and a balloon intolerance test was performed. The PROFI trial demonstrated that the proximal blockage system was more advantageous than the distal protection method to reduce cerebral embolism in CAS [24]. If filters are smaller than the diameter of the vessel, distal particle embolization may occur between the vessel wall and filter. If it is larger than the vessel diameter, it may lead to spasm in the distal carotid artery. Filters cannot hold particles that are smaller than the pore sizes. Besides, they may also pour back their content if the technique is not used properly while retracting the filters. All the above-mentioned reasons may lead to diffusion limitation in the brain tissue on the distal side of the stented artery. Such risk associated with filters can be minimized at high-volume and experienced centers.

The mean age of the patients in the calcified plaque group was found to be statistically significantly higher. Calcification of vessel walls is known to increase with age [27]. We do not think that a higher mean age in the calcified group than in the noncalcified group would affect the result of our study.

The rate of smokers was found to be statistically significantly higher in the noncalcified group. Smoking is a general risk factor for vascular atherosclerosis. Studies with small series (33 patients) have demonstrated that smoking is an independent risk factor for stent restenosis [28]. In light of this information, we do not know to what extent smoking could affect the results of our study.

Balloon postdilatation after CAS increases the likelihood of periprocedural cerebral embolic events [29]. Predilation with high atmosphere before carotid stenting and avoiding post-stent postdilation may reduce the incidence of periprocedural cerebral embolism [30]. The number of patients undergoing balloon postdilatation after carotid stenting was higher in the calcified group than in the noncalcified group in our study. This might slightly increase the rate of cerebral embolism in the calcified group.

In our study, first-generation self-expandable carotid stents were used. In the literature, studies are investigating cerebral embolism using DW-MRI regarding different protection methods and mesh-covered stents. Each stent and protection method has a certain risk of periprocedural cerebral embolism. Currently, the ideal stent in terms of silent cerebral embolism risk has not been determined yet [31–33]. In the study by Karpenko et al. [34] in 2021, it was shown that CAS procedures performed with MicroNet-covered stents significantly reduce both periprocedural and first 30-days' cerebral embolism compared to first-generation stents. Another important result from the same study is that the cerebral DW-MRI quantitative volume analysis is extremely important in detecting and interpreting CAS-related cerebral embolisms [34].

The clinical effects of calcified atherosclerotic plaques were analyzed with pathological and imaging methods. Calcium hardens atherosclerotic plaque and makes it resistant to rupture [35]. Hunt et al. [36] showed with endarterectomy materials that calcified carotid plaques in symptomatic and asymptomatic carotid patients were

associated with fewer cerebrovascular events compared to noncalcified plaques. Neutrophilia to lymphocyte rate, which is an inflammatory marker, was found to be higher in the symptomatic and noncalcified carotid plaques with a stenosis of 50%–70% while it was lower in asymptomatic and calcified plaques [37, 38]. Echo-rich carotid plaques detected on CDUS typically have more calcium and fibrous tissue while echolucent plaques have more lipid content. Using these criteria, the Tromso trial revealed that echo-rich plaques were at a lower risk for neurological symptoms [39]. Therefore, more unstable noncalcified carotid plaques may cause more cerebral embolisms in CAS procedures. It may be useful to use intravascular ultrasonography (IVUS) to reveal the nature of the carotid plaque more clearly and to optimize the placement of the stent on the carotid artery wall [40].

Our study had certain limitations. It was a retrospective and single-center study. A total of 170 patients who may be at high risk of cerebral embolisms, such as symptomatic complications after CAS (23 patients), were excluded from the analysis for various reasons (Table 2). CEA, not CAS, was performed on 88 patients with target artery access difficulties. Quantitative volume analysis could not be performed for new embolic lesions detected in DW-MRI after CAS. Carotid lesions with circular heavily calcified plaques were not included in the study. IVUS could have been performed to determine the carotid artery plaque morphology more clearly and rule out the complications associated with stent location. Cerebral DW-MRI cross-sections could have been thinner.

CONCLUSIONS

The rate of periprocedural asymptomatic ipsilateral cerebral embolism detected on cerebral DW-MRI is higher in CAS performed for noncalcified carotid artery plaques compared to the calcified plaques. There is a need for further prospective, multi-center studies with a higher number of patients to validate the results of this study.

Article information

Conflict of interest: None declared.

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