Cardiovasc Intervent Radiol (2019) 42:812–819
https://doi.org/10.1007/s00270-019-02173-1

CIRSE

CLINICAL INVESTIGATION ARTERIAL INTERVENTIONS

Early Embolization After Carotid Artery Stenting with Mesh-Covered Stent: Role of Diffusion-Weighted Magnetic Resonance Imaging as Pre-procedural Predictor and Discriminant Between Intra- and Post-procedural Events

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Received: 15 September 2018 / Accepted: 30 January 2019 / Published online: 19 February 2019

Abstract

Objectives To evaluate the incidence and the time of onset of early micro-embolism after CAS (carotid artery stenting) with two different mesh-covered stents and to assess the role of DW-MRI (Diffusion-weighted magnetic resonance imaging) in their prediction.

Methods Single-institution prospective study including 50 patients (33 male, median age 74 years) who underwent CAS with Roadsaver® or CGuard™. All patients with primary stenosis (37/50, 74%) had carotid plaque DW-MRI pre-procedure, with both qualitative evaluation of the hyperintensity and ADC (apparent diffusion coefficient) measurement of the plaque. All patients had brain DW-MRI pre-procedure, at 1 h, 24 h and 30 days post-procedure to evaluate the appearance of hyperintense lesions over time. Imaging analysis was performed in a double-blinded fashion by two radiologists.

Results There were no statistically significant differences between the two stents both in the incidence at 1 h ($P = 0.23$) and 24 h ($P = 0.36$) and in the volume of new DWI hyperintense brain lesions at 24 h ($P = 0.27$). Thirty-four new asymptomatic lesions in 19 patients (38%) were reported: 4 (11.8%) at 1 h, 30 (88.2%) at 24 h. The 30-day DWI-MR showed complete resolution of all lesions and no evidence of new lesion. The incidence of new lesions at 24 h resulted significantly higher in patients with DWI hyperintense carotid plaques (12/16, 75% vs. 0/21, 0%, $P < 0.0001$). This result was paralleled by the difference in ADC value (0.83 ± 0.21 vs. 1.42 ± 0.52).

Conclusion The majority of early asymptomatic brain lesion occurred during the first 24 h after CAS. Pre-procedure high DWI signal of the plaque was associated with an increased incidence of post-procedure microembolizations.

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Keywords Internal carotid artery stenosis · Carotid stenting · Micromesh stent · Diffusion-weighted magnetic resonance · Ischemic brain lesions

Abbreviation

CAS	Carotid artery stenting
CEA	Carotid endarterectomy
DUS	Duplex ultrasound
MRI	Magnetic resonance imaging
DWI	Diffusion-weighted imaging
NIHSS	National Institute of Health Stroke Scale
NASCET	North American symptomatic carotid endarterectomy trial
ASA	Acetylsalicylic acid
ADC	Apparent diffusion coefficient
CT	Computed tomography

Introduction

Carotid endarterectomy (CEA) and carotid artery stenting (CAS), the two currently available interventions for carotid artery stenosis, demonstrated to be equally effective in preventing strokes in the long term (> 30 days) [1, 2]. The higher incidence of peri-procedural brain embolisms and short-term (< 30 days) non-disabling strokes was for a long time Achille's heel of CAS [3, 4] with an incidence of 37% (9–70%) for CAS detected by diffusion-weighted magnetic resonance imaging (DW-MRI) versus 10% (0–27%) after CEA [5]. The risk of embolism is not limited to the procedure time, but it extends to a "stent healing" time interval of about 30 days after the procedure [6, 7]. The higher incidence of perioperative ischemic lesions could be related to a higher incidence of plaque protrusion (PP) in patients with unstable plaques [8]. The prevention of perioperative ischemic brain lesions is essential, since they are markers of increased risk of recurrent cerebrovascular events [9], and recurrent strokes have a strong association with post-stroke dementia [10]. To overcome this issue, much research focused on the development of embolic protection devices and mesh-covered stents designed to offer a better coverage of the plaque by the stent after its deployment. Furthermore, the characterization of vulnerable carotid plaques, both with duplex ultrasounds (DUS) and magnetic resonance imaging (MRI), demonstrated to have good diagnostic power for short-term intracranial embolization after carotid interventions [11–14].

The aims of this paper are to investigate: i) the performance of two different mesh-covered stents, i.e., Roadsaver® Carotid artery stent system (Terumo, Japan) and CGuard™ Embolic Prevention System (InspireMD, Tel Aviv, Israel); ii) the incidence of intraprocedural embolization, using the timing of appearance on brain DW-MRI to distinguish them from those related to the "healing time" of the stent; iii) the role of DW-MRI in the preoperative assessment of vulnerable plaques.

Methods

Study Design and Patient Population

The study is a single-center prospective non-randomized examination of 50 CAS procedures performed between September 2016 and December 2017 with either Roadsaver® (Terumo, Japan) or CGuard™ (InspireMD, Tel Aviv, Israel) carotid stents. Part of the data obtained with Roadsaver® was already analyzed for a different purpose in a previous paper [15]. Symptomatic stenosis > 50% and asymptomatic stenosis > 80%, according to NASCET criteria [16], were included after multidisciplinary evaluation. Patients with age > 80 years, carotid obstruction, endoluminal thrombus, acute stroke within the last 30 days, myocardial infarction within 72 h and intracranial hemorrhage in the previous 12 months were excluded. All patients underwent: brain DW-MRI evaluations at baseline, 1 h, 24 h and 30 days after stenting and clinical evaluation and DUS at baseline, 24 h and 30 days after stenting. The clinical evaluation included a neurological examination by an independent neurologist using the National Institute of Health Stroke Scale (NIHSS). All patients, but 13 (26%) with restenosis after endarterectomy (to limit confounding factors), underwent a carotid plaque DW-MRI evaluation at baseline. Procedural success was defined as residual stenosis after stenting < 30% and no complications. The outcomes of interest were: incidence, volume and timing of new ischemic brain lesions. Predictors were: type of stent used and hyperintensity of the carotid plaque in the preoperative DWI-MRI.

Patients' information was anonymized prior to the analysis. The study was piloted in agreement with the 1964 Helsinki Declaration and its later amendments and approved by the ethics committee of our institution.

Devices

The Roadsaver® carotid artery stent (Terumo, Japan) is a nitinol double-layer micromesh stent, with an inner nitinol micromesh woven into an external closed-cell stent, forming a cell size of 375–500 μm. This structure joins the flexibility of an open-cell stent with the benefits of a closed-cell stent in preventing plaque protrusion and release of emboli after stent implantation. It is a 0.014-inch guidewire compatible device with rapid exchange delivery system and an outer diameter of 5 Fr, allowing a high crossability. The stent is resheathable and repositionable up to 50% deployment.

The CGuard™ EPS (InspireMD, Tel Aviv, Israel) is an open-cell nitinol carotid stent wrapped with a MicroNet mesh of single-knitted polyethylene terephthalate (PET) fiber 20 µm thick, forming mesh cells of 150–180 µm. Its structure allows for the densest closed-cell area currently available. It is a 0.014-inch guidewire compatible device with rapid exchange delivery system and an outer diameter of 6 Fr. The range of lengths is 20 to 60 mm, while the range of diameters is 6–10 mm.

Carotid Artery Stenting Procedure

CAS was performed according to the Clinical Practice Guidelines of the European Society for Vascular Surgery (ESVS) [17]. Patients were treated with Roadsaver® or CGuard™ EPS according to their availability at the time of the procedure. The intracranial circulation was evaluated before and after the procedure. Before the procedure, all patients, but those already under DAPT, received 100 mg acetyl-salicylic acid (ASA) and a loading dose of 375 mg clopidogrel. After the procedure, patients received a daily dose of 100 mg ASA and 75 mg clopidogrel for one month, and only ASA thereafter. During the procedure, ACT-based heparinization was administered using weight-adjusted initial dosing; 1 mg of atropine was administered after stent dilatation. Despite the conflicting evidence regarding the role of cerebral protection devices, their use is generally recommended [17] (Class IIa, Level B); in our study, even if procedures were performed with a dual mesh stent, we used a distal protection device to limit the incidence of distal embolization during the first crossing of the lesion with the stent delivery system. All CAS were performed with the same distal embolic protection device (Emboshield NAV, Embolic Protection System, Abbott Vascular, Temecula, CA), by the same four operators with extensive experience (at least 50 CAS/year as first operators in the last 10 years). No case required a pre-dilation of the stenosis.

MRI Protocol

All MRI studies were performed with a 1.5 T scanner (Achieva, Philips, Best, The Netherlands), with a 16-channel PMS SENSE Neurovascular MRI Coil (Philips, Best, The Netherlands). Brain MRI studies, before and after the stenting, included high-resolution DW sequences (TE 89 ms; TR 4143 ms; voxel size RL 2.05 mm × AP 2.56 mm × FH 5 mm; b values 0–1000), gradient echo T2-weighted axial sequences (TE 23 ms; TR 932 ms; voxel size RL 0.9 mm × AP 1.12 MS × FH 5 mm) and fluid attenuation inversion recovery (FLAIR) axial sequences (TE 140 ms; TR 11,000 ms; voxel size RL 0.99 mm × AP 1.86 mm × FH 5 mm). Baseline plaque DW-MRI studies included three-dimensional multichunk inflow sequences (3DI-MC-WATS: TE 6.9 ms, TR 20 ms, voxel size RL 0.293 mm × AP 0.293 mm × FH 0.7 mm) on the region of the neck, to visualize the anatomy of the supra-aortic vessels (Fig. 1), and DW sequences (TE 63 ms; TR 3000 ms; voxel size RL 2.5 mm × AP 2.5 mm × FH 2.5 mm; 0–300–600 mm/s^2 b values) centered on the carotid bifurcation.

MR Extended Work Space 2.6.3.2 2009 software (Philips Medical Systems, Best, The Netherlands) was used for imaging interpretation. Two radiologists (R.F. and M.G., with 10 and 5 years of experience), double blinded to the study timing and the patient data, evaluated all MRI images qualitatively and quantitatively. In case of disagreement, the examinations were submitted to a senior radiologist (P.F.). The apparent diffusion coefficient (ADC) map (b values 0–600 mm/s^2) was calculated on a separate workstation (ADC Map Calculator plug-in, OsirixMD, Pixmeo), placing manually a polygonal region of interest (ROI, mean size 15.88 mm^2, SD 9.47 mm^2) on the carotid plaque at the level of maximal narrowing, based on 3DI-MC-WATS and DWI sequences (Figs. 2, 3). Acute ischemic lesions were defined as areas of high signal intensity on DW images and low ADC values. To be considered indicative of acute injury, a lesion had to have been absent in the pre-procedure imaging (Fig. 4). Ischemic lesion location (ipsilateral, contralateral and bilateral hemisphere) and size (volume in cc) were recorded. Volume analysis of acute ischemic lesions was performed on a separate workstation (Volume Calculator, Osirix, Pixmeo). The acute ischemic brain lesions which appeared at 1 h after stenting were considered related to the procedure, while lesions visible only after 24 h were considered related to the interaction between the plaque and the stent remodeling.

Statistical Analysis

Continuous variables which passed the Shapiro–Wilks test for normality were expressed as average ± standard deviation, otherwise as median (first quartile–third quartile). Dichotomic variables were represented as counts and percentages. The analysis used nonparametric tests: Mann–Whitney test (independent variables), Wilcoxon's test

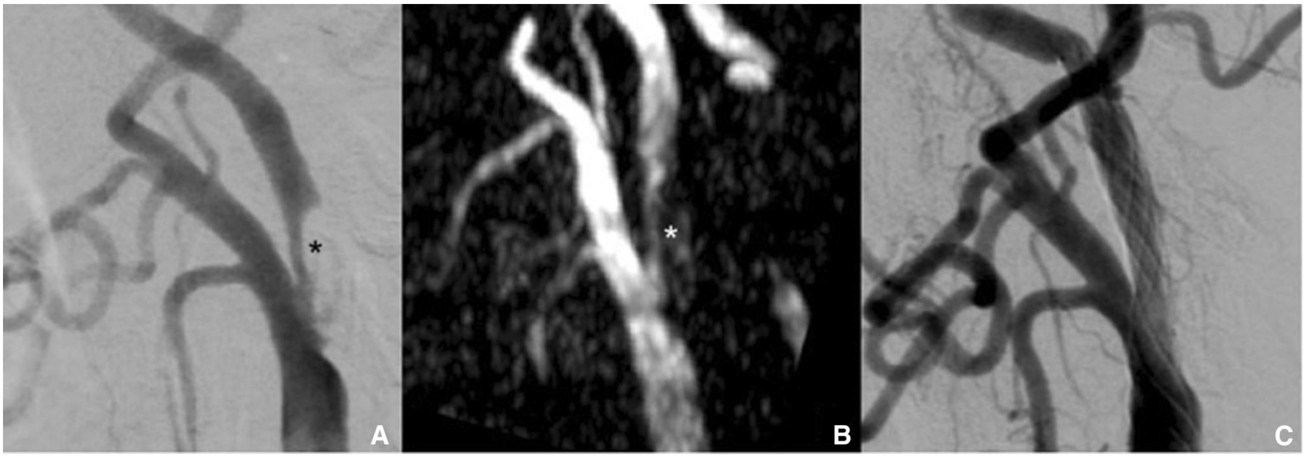

Fig. 1 Maximum intensity projection (MIP) reconstruction of the 3DI-MC-WATS (three-dimensional multichunk inflow) sequence on the region of the neck. Comparison between pre- and post-procedural angiographies (**A**, **C**) and 3DI-MC-WATS (three-dimensional multichunk inflow) sequence (**B**), showing the carotid artery stenosis (asterisk) in a patient treated with a Roadsaver® stent

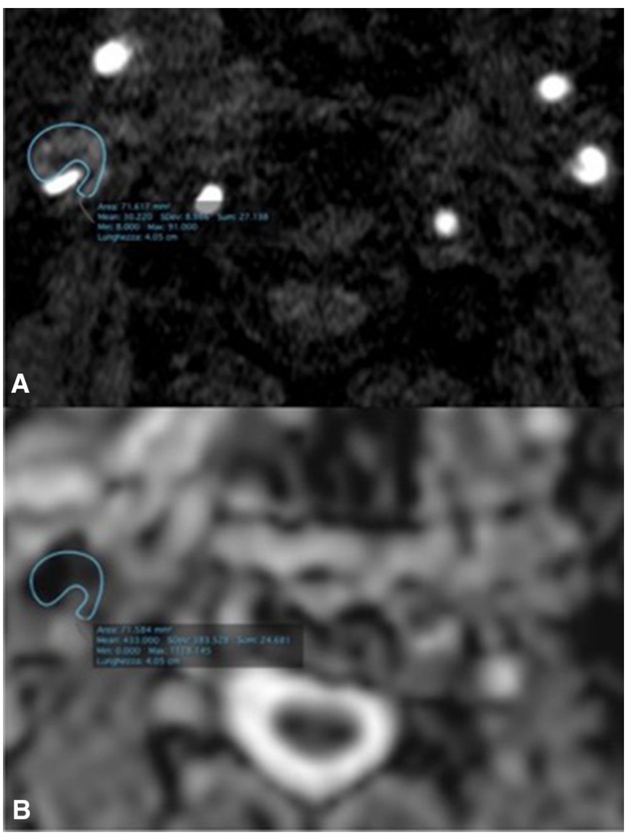

Fig. 2 Carotid plaque with high signal intensity in DW (diffusion weighted) images. Positioning of a polygonal ROI (region of interest) on the 3DI-MC-WATS (three-dimensional multichunk inflow) sequence (**A**) and automatic reproduction on the ADC (apparent diffusion coefficient) map (**B**). The ADC value (433.000×10^{-3} mm^2/s, SD 383.528×10^{-3} mm^2/s) confirms the restricted diffusion

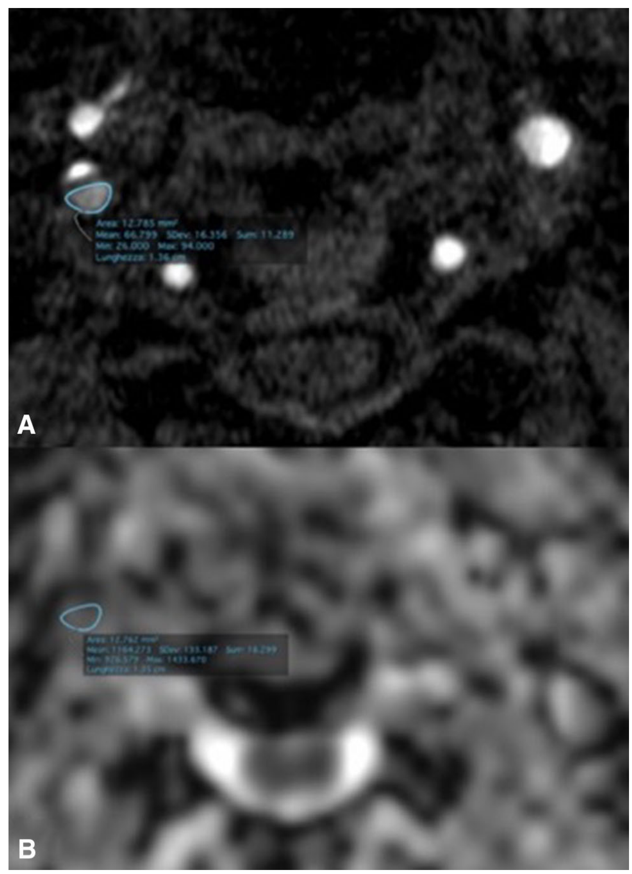

Fig. 3 Carotid plaque without high signal intensity in DW (diffusion weighted) images. Positioning of a polygonal ROI (region of interest) on the 3DI-MC-WATS (three-dimensional multichunk inflow) sequence (**A**) and automatic reproduction on the ADC (apparent diffusion coefficient) map (**B**). The ADC value (1164.273×10^{-3} mm^2/s, SD 133.187×10^{-3} mm^2/s) confirms the absence of restricted diffusion

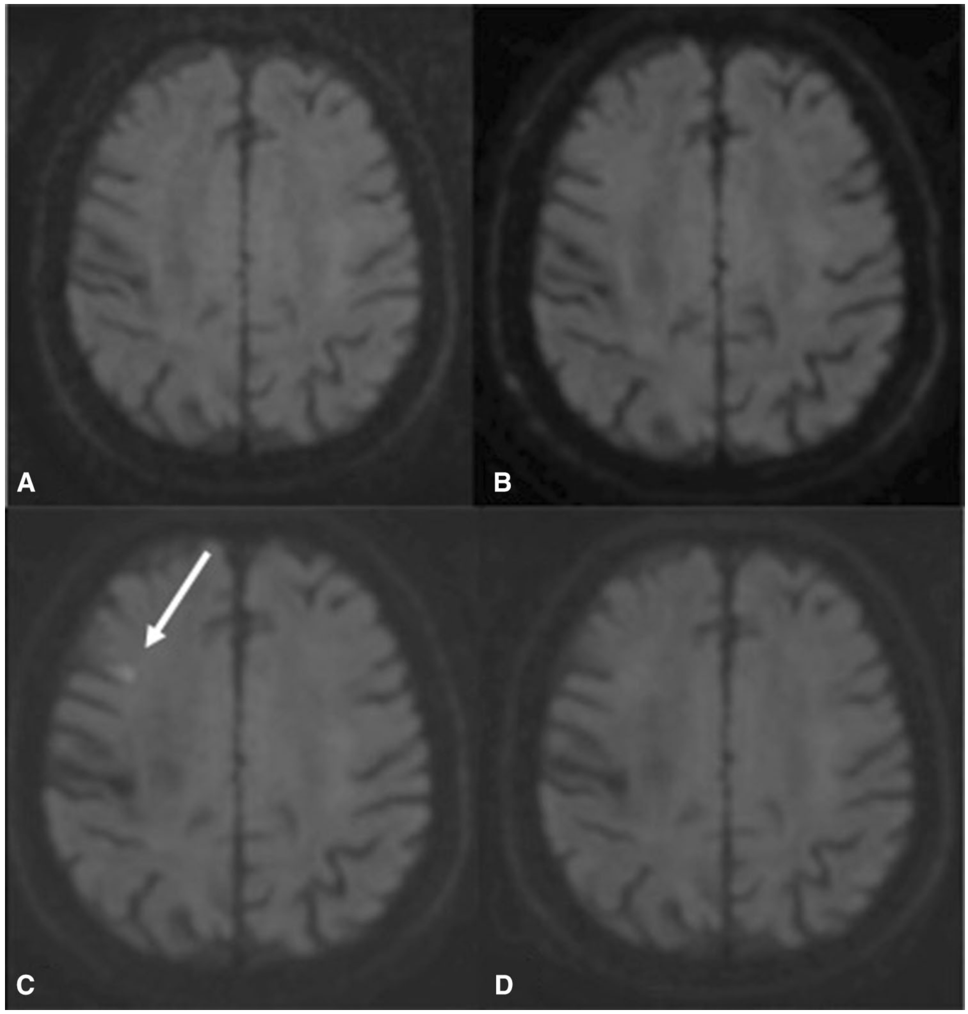

Fig. 4 Early brain embolization after CAS (carotid artery stenting). The brain MRI (magnetic resonance imaging) performed 24 h after the procedure (**C**) shows a focal area of high signal intensity on DW (diffusion weighted) images in the right frontal lobe (arrow), not visible in both baseline (**A**) and 1 h post-procedure (**B**) examinations. The 30-day post-procedure MRI shows the complete resolution of the ischemic lesion (**D**)

(correlated variables), ANOVA (η^2 coefficient) and Fisher's test.

Results

The baselines of patients treated with the two devices showed no significant differences (Table 1). The pretreatment brain DW-MRI did not evidence acute ischemic lesions in any patient. The procedural success was 100% (50/50), and no serious device-related and procedure-related adverse events were recorded. The cumulative incidence of new ischemic lesions after CAS was 38% (19/50), with a total burden of 34 lesions (1.8 lesions/patient): 28 (82%) were ipsilateral to the carotid stenosis, while 6 (18%) were contralateral. The DW-MRI at 1 h after CAS showed that 3/25 patients (12%) in the CGuard group developed 4 ipsilateral ischemic lesions (1.3 lesions/patient), with volume 0.15 (0.18–0.23) cm^3 versus zero within the 25 patients in the Roadsaver group. At 24 h, the DW-MRI (Fig. 1) evidenced that 10/25 patients (40%) in the CGuard group developed 17 ischemic lesions (2 lesions/patient), with volume 0.05 (0.04–0.11) cm^3. In the Roadsaver group, 6/25 patients (24%) developed 13 new ischemic lesions (2 lesions/patient), with volume 0.045 (0.03–0.05) cm^3. Thirty new lesions (88%) appeared at 24 h, while only 4 at 1 h. No statistically significant differences were found for the incidence of new ischemic lesions at 1 h ($P = 0.23$) and 24 h ($P = 0.36$), or their volume at 24 h ($P = 0.27$). The 30-day DWI-MR showed complete resolution of all post-CAS lesions and no evidence of new acute ischemic lesion. The 30-day DUS showed that all ECA and stents were patent without any in-stent restenosis (PSV < 100 cm/s and ICA/CCA ratio < 2). Clinical and neurological evaluations excluded major cerebrovascular event or a worsening of the neurological and cognitive conditions. No major adverse cardiovascular and cerebrovascular event (MACCE) was observed.

Since both baseline and 24 h lesion variables showed no significant differences between the patients treated with the two different stents (Table 1), the two samples were grouped for investigating the carotid plaque DW-MRI

Table 1 Baseline characteristics of the two groups

	CGUARD		ROADSAVER		
	Mean	SD	Mean	SD	*P*
Age	73.7	4.7	74.4	8.9	0.7
Stenosis (%)	84.0	6.3	84.6	5.0	0.7
	N	%	*N*	%	*P*
Sex (M)	16	66.7	17	68.0	≥ 0.99
Symptomatic	14	56.0	15	60.0	0.78
DAPT	19	76.0	22	91.7	0.27
Single APT	3	12.0	1	4.0	0.6
LOAD DOSE	6	24.0	3	12.0	0.46
DAPT POST	25	100.0	25	100.0	≥ 0.99
Smoker	11	45.8	6	24.0	0.19
Former smoker	5	20.0	8	32.0	0.52
Diabetes	6	25.0	6	24.0	≥ 0.99
Dyslipidemia	13	52.0	15	60.0	0.77
Hypertension	16	64.0	20	80.0	0.34
Atrial fibrillation	3	12.0	2	8.0	≥ 0.99
Previous TIA	4	16.0	8	32.0	0.32
Previous MI	5	20.0	4	16.0	≥ 0.99
NIHSS 0	9	36.0	10	40.0	≥ 0.99
NIHSS 1	13	54.2	10	40.0	0.48
NIHSS 2	3	12.0	4	16.7	0.95
Right ICA	11	44.0	13	52.0	0.78
Left ICA	14	56.0	12	48.0	0.78
Primary stenosis	17	68.0	20	80.0	0.52
Contralateral stenosis	9	36.0	7	28.0	0.76
Contralateral occlusion	2	8.0	1	4.0	≥ 0.99

DAPT dual antiplatelet therapy, *APT* antiplatelet therapy, *TIA* transient ischemic attack, *MI* myocardial infarction, *NIHSS* National Institute of Health Stroke Scale, *ICA* internal carotid artery

features. Sixteen patients with primary stenosis (43%) had high signal intensity of the plaque on DW images: among them, the incidence of new ischemic lesions at 24 h was 12/16 while none of the 21 patients without high signal intensity of the plaque had new ischemic lesions (75% vs. 0%, $P < 0.0001$).

The quantitative analysis of the carotid plaque ADC map showed a significantly lower ADC value in patients with high signal intensity on DW (DW +) than in those without high DW signal (DW-): 0.83 ± 0.21) vs. $1.42 \pm 0.52 \times 10^{-3} mm^2/s$, with $P = 0.0004$ (Fig. 5). The ADC values measured by the two readers were in agreement according to both Wilcoxon's test for matched data ($P = 0.72$) and η^2 coefficient (0.95).

Discussion

Our study on 50 cases of CAS with two different mesh-covered stents (Roadsaver® and CGuard™) yielded an incidence of asymptomatic brain embolization after CAS of 38% (19/50) with an overall median volume of $0.049 cm^3$. We found no significant differences between the two devices for incidence of new ischemic lesions, either at 1 h ($P = 0.23$) or 24 h ($P = 0.36$), and the volume of new lesions at 24 h ($P = 0.27$). Our results are consistent with other studies, which reported an incidence of post-procedural micro-embolization between 20% [18] and 37% (average volume $0.039 cm^3$) [19] for CGuard™.

Since brain DW-MRI evaluation was shown to be positive within minutes of injury [20], we performed both 1 h and 24 h post-procedure examinations to distinguish strictly intraprocedural from post-procedural events.

The large majority of events occurred after the procedure, 88% (30/34) vs. 12% (4/34), confirming a previous study on CAS with both open- and closed-cell stents [21].

A high signal intensity of the plaque on DW images was associated with a higher risk of post-procedural new ischemic brain lesions (12/16, 75% vs. 0/21, $P < 0.0001$).

The high intensity of DW signal of the plaque was associated with an ADC value significantly lower than for plaques without high DWI signal (0.83 ± 0.21 vs. $1.42 \pm 0.52 \times 10^{-3} mm^2/s$, $P = 0.0004$).

These findings suggest the importance of the interaction of the plaque with the stent and may be explained by the capability of DW-MRI to detect a wide spectrum of

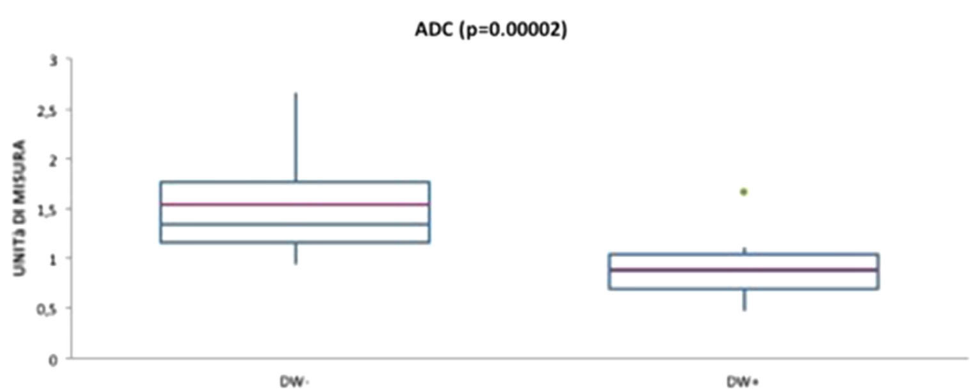

Fig. 5 Box plot of ACD (apparent diffusion coefficient) values for DW + (diffusion weighted +) and DW carotid plaques. The bottom and top hinges of the boxes are the first (Q1) and third (Q3) quartile; the blue band is the second quartile (median), and the red line is the sample mean

structural features of unstable atherosclerotic lesions, including both intraplaque hemorrhage and inflammatory infiltrate. Unstable plaques are known to have certain cellular, molecular and structural features, including inflammatory processes, angiogenesis, intraplaque hemorrhage and thinning of the fibrous cap [22]. In particular, intraplaque hemorrhage is a common feature of unstable carotid atherosclerotic lesions and is associated with rapid changes in plaque volume and the development of ischemic neurological events [23], while inflammation modulates the evolution of the atheroma through the recruitment of macrophages and lymphocytes by endothelial cells, resulting in a potent inflammatory cascade which leads to plaque instability [24]. In this scenario, various imaging techniques were investigated as preoperative predictors of vulnerable plaques and subsequent post-procedure embolic events, such as DUS [11], computed tomography [25] and MRI [12–14].

Preliminary in vitro studies suggest that high field DW-MRI can identify vulnerable plaques, intended as plaques containing mobile lipids [26] and a necrotic core [27]. Furthermore, a recent in vivo study [28], evidenced significant differences in ADC values between hemorrhagic and non-hemorrhagic plaques, and for the former, between hemorrhagic and non-hemorrhagic regions; in the same study, with an even higher difference for plaques with intramural hematoma.

Besides identifying the presence of hemoglobin degradation products, through the T1 and T2 sequences, DW-MRI is also routinely applied in various districts to detect the presence of an inflammatory infiltrate, another common feature of unstable plaques [29].

This study has several limitations: It is a non-randomized study conducted on a relatively small sample of patients; the positioning of ROIs in carotid plaque DW-MRI was indirectly performed on the basis of the WATS sequences, due to the poor visibility of carotid plaques on the ADC map; the study was conducted with a 1.5 T scanner; carotid plaque MRI was performed only with DW images and without other useful sequences (like T1 e T2 weighted) to characterized hemorrhage and inflammation.

Conclusions

Even after the introduction of dual-layer stents, most early asymptomatic brain embolization events after CAS occur after the procedure. No significant differences were evidenced between Roadsaver® and CGuard™ stents in terms of incidence and volume of intra- and post-procedural ischemic lesions. The preoperative DW-MRI evaluation of the carotid plaque was a reliable predictor of early post-procedural embolization events after CAS.

Compliance with Ethical Standards

Conflict of interest All authors have declared that they have no conflicts of interest.

Informed Consent Patients' information was anonymized prior to the analysis. The study was piloted in agreement with the 1964 Helsinki declaration and its later amendments and approved by the ethics committee of our institution.

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