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REVIEW

LATEST TECHNIQUES FOR CAROTID REVASCULARIZATION

Effect of plaque morphological characteristics on the outcomes of carotid artery stenting

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ABSTRACT

Carotid artery stenting (CAS) represents today an accepted option for the treatment of severe carotid artery stenosis. The evolution of materials, techniques, perioperative medical management and patients' selection, has allowed to progressively reduce CAS complications. However, the main drawback of CAS is still represented by the risk of cerebral embolization, that may occur during several steps of the procedure and also in the early postoperative period. Preoperative carotid plaque morphological characteristics may have a great role in determining the risk of embolization during CAS. This review summarizes the current knowledge on carotid plaque characteristics that may influence the risk of complication during CAS. This information may be important for the optimization of CAS patients' selection and adaptation of the materials and techniques.

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Carotid artery stenting (CAS) represents today a valid option for the treatment of carotid stenosis, in particular in patients considered at high risk for carotid endarterectomy (CEA), owing to a high surgical risk or hostile neck anatomy.[1-3] The Achille's heel of CAS is represented by the risk of cerebral embolization, that may responsible of clinically significant cerebral ischemic complications leading to periprocedural stroke or transient ischemic attack (TIA). During CAS, distal embolization may occur during several steps of the procedure: aortic arch manipulation, lesion crossing with the guidewire and filter, predilatation, stent deployment, post-dilatation, and device retrieval. Also, an early postoperative embolization may occur as a result of stent malapposition or plaque prolapse.[4] Among these several possible sources, stent deployment represents the most critical step, accounting for the majority of embolic events.[5]

Therefore, the morphology and quality of the carotid plaque is of mainstay importance in determining the risk of embolization during the procedure, and the identification of plaques at increased risk may be important for the optimization of patients' selection and adaptation of the materials and techniques.

The aim of this narrative review was to summarize the evidence regarding the effect of primitive plaque morphological characteristics on the outcomes of CAS.

Modalities of assessment of perioperative embolization

Assessment of perioperative embolization may be performed using different outcomes criteria. A clinically evident embolization, manifesting as stroke or TIA, are reported in 2-8% of CAS procedures,[6] but with a high variability among series. This may be related to the inconsistency between centres of neurological evaluation modalities of patients, since minor neurological deficits may remain overlooked if a systematic postoperative neurological evaluation is not performed.

Post-operative diffusion-weighted (DWI) magnetic resonance (MRI) is a sensitive method that allows to detect new ischemic cerebral lesions after CAS. If performed routinely, this can reveal that up to 40-60% of patients have signs of new embolic cerebral lesions.[7]

While clinical outcomes and DWI-MRI represent a consequence of both intraprocedural and early post-procedural embolization events, transcranial doppler (TCD) and analysis of filter protection devices can be used to evaluate intraoperative embolization phenomena. TDC is typically performed monitoring embolic signals at the level of the middle cerebral artery. It carries the advantage to detect both microemboli and macroemboli, and to evaluate the exact timing of embolic events, discriminating between different CAS procedural steps; however the presence of embolic signals may not be directly related to clinical outcomes or new DWI-MRI lesions.[8-10]

Microscopic analysis of particles captured by embolic filters represent a direct method for analysing embolization events during CAS. After microscopic analysis, some embolic filter debris can be detected in up to 75% of filters in asymptomatic patients,[11] and the amount of particles captured by the filter (embolic filter debris load, EFD load) is related to the risk of clinically evident neurological complications.[11] Filter analysis is also the only method that allows for a qualitative examination of embolic debris.[12] However, the analysis of EPD does not account for embolization occurring before filter placement, and mostly reflects what happens during stent deployment and post-dilatation. Also possible micro or macroembolization occurring after the procedure completion cannot be assessed through filter analysis.

Plaque characteristics influencing embolic risk during cas with old-generation stents

Plaque length

Plaque length is defined as the as the longitudinal distance from the proximal to the distal shoulder of the carotid lesion in the most unforeshortened projection.[13] Although traditionally evaluated by angiography, plaque extension can be measured preoperatively by ultrasound, computed tomography angiogram (CTA), or MRI. Plaque length is directly correlated with the extension of plaque surface; the higher is the extent, the higher is the surface of attrition between the carotid lesion and the endovascular devices, justifying an increased risk of perioperative embolization.

The literature evidence is quite consistent in describing an association between plaque length and increased periprocedural neurological risk, in particular for plaque length >15 mm or 20 mm (Table I).[11, 14-23] Chaturvedi *et al.*[14] found a significant increased risk of ipsilateral stroke in patients with a plaque length >20 mm, using data on octogenarian patients from the Carotid ACCULINK/ACCUNET Post Approval Trial to Uncover Rare Events (CAPTURE 2). Moore *et al.*[15] investigated the effect of plaque angiographic characteristics on periprocedural stroke and death in the Carotid Revascularization Endarterectomy versus Stenting trial (CREST). A plaque length >12.85 mm was a major determinant of stroke and death. Also, worsened outcomes were described in case of sequential lesions affecting the extracranial internal carotid artery. Sayeed *et al.*[16] reported a higher incidence of any stroke in case of plaque length >15 mm.

A few studies assessed the impact of lesion length using as endpoint the occurrence of new DW-MRI brain lesions. Bijuklic *et al.*[17] reported an incremental risk for new ischemic lesions for each mm increase of lesion length; similarly Gröschel *et al.*[18] described an increased risk for lesions longitudinally extended for more than 1 cm; Sabat *et al.*[19] for lesions >2 cm.

Only scarce data exist on filter analysis in relation to plaque length. Piazza *et al.*[11] described a significantly increased amount of embolic debris (EFD load) in case of plaque length >15 mm. Kwon *et al.* performed a similar analysis, reporting only a non-significant trend of association between plaque length and the presence of large filter emboli. This study was limited by the inclusion of only 35 patients.

Among the several studies investigating the role of plaque length on CAS procedural risk, and an open cell stent was used in most cases. There are no studies describing the role of plaque length with the use of new-generation micromesh stents.

Plaque echogenicity

Plaque echogenicity is an important plaque morphological characteristic, that has been investigated for more than 20 years. Echogenicity reflects the histological composition of carotid plaques; echolucency (low echogenicity) is related to the presence of increased levels of triglyceride-rich lipoproteins and soft components, and hypoechogenic

TABLE I.—*Summary of evidences of the effect of plaque length on embolization risk in patients undergoing CAS with old-generation stents.*[11, 14-23]

Author	Year	N.	Stent design	Endpoint	Type of analysis	Covariate	Effect size (statistical significance)
Hofmann *et al.*[20]	2006	606	NA	Ipsilateral stroke	Bivariate comparison	Lesion length (mm)	P=.66
Sayeed *et al.*[16]	2008	429	397 OC 32 CC	Any stroke	Multivariate logistic regression	Lesion length >15 mm	OR 6.38; 95%CI 3.37-17.29 (P<.001)[a]
Chaturvedi *et al.*[14]	2010	1166	OC	Ipsilateral stroke	Multivariate logistic regression	Lesion length ≥20 mm	OR 2.34; 95% CI 1.13-4.85 (P=0.021)[a]
Moore *et al.*[15]	2015	570	OC	Ipsilateral stroke and death	Univariate logistic regression	Lesion length ≥12.85 mm	OR 3.42; 95% CI 1.19-9.78 (P<.05)[a]
Kastrupt *et al.*[23]	2008	62	59 OC 3 CC	New DWI ipsilateral ischemic lesion	Bivariate comparison	Lesion length ≥10 mm	P=.20
Gröschel *et al.*[18]	2008	176	173 OC 3 CC	Any new DWI ipsilateral ischemic lesion	Multivariate logistic regression	Lesion length >10 mm	OR 2.65; 95% CI 1.33–5.28 (P=0.006)[a]
Bijuklic *et al.*[17]	2013	837	NA	Any new DWI ischemic lesion	Multivariate logistic regression	Lesion length (mm)	OR 1.04; 95% CI 1.01–1.07 (P=0.018)[a]
Sabat *et al.*[19]	2019	107	OC	Any new DWI ischemic lesion	Univariate logistic regression	Lesion length ≥20 mm	OR 0.29; 95% CI 0.08-1.01 (P=0.05)[a]
Qu *et al.*[22]	2019	63	25 CCS 38 OCS	Any new DWI ischemic lesion	Bivariate comparison	Lesion length (cm)	P=.600
Kwon *et al.*[21]	2013	35	OC	Large emboli on filter microscopic analysis	Multivariate logistic regression	Lesion length (mm)	OR 1.12; 95% CI 0.95-1.31 (P=.181)
Piazza *et al.*[11]	2017	278	67 CC 211 OC	Embolic filter debris load	Multivariate logistic regression	Plaque length >15 mm	OR 1.79, 95%CI 1.02-3.61 (P=0.047)[a]

[a]Statistically significant.
CC: closed cell; OC: open cell.

plaques are associated with the development of neurological events also in asymptomatic patients undergoing best medical therapy only.[24, 25]

The most clinically used classification of echogenicity was proposed by Geroulakos *et al.*[26] in 2005, and includes five plaque types: type 1 plaques are uniformly echolucent, type 2 predominantly echolucent, type 3 predominantly echogenic, type 4 uniformly echogenic, and type 5 consist of plaques that cannot be classified owing to heavy calcification and acoustic shadow. In scientific studies, also Grey Scale Median (GSM) is used as echogenicity measure. However, this is less useful from the clinical standpoint, as it implies a computer-based analysis of the grey scale of pixels composing the carotid plaque, where the median value is used as an overall measure of plaque echolucency.[27]

Table II[11, 14, 27-31] summarizes the major studies investigating the impact of plaque echogenicity on CAS outcomes. Data from the Imaging in Carotid Angioplasty and Risk of Stroke (ICAROS) Study,[27] including a series of 418 patients undergoing CAS, described an increased risk for ipsilateral stroke in case of GSM<25. The design of the used stent was not specified, and embolic protection devices were used in approximately 50% of the study cohort. Consistent outcomes were reported by Tegos *et al.*,[28] showing an inverse correlation between the amount of emboli detected by TCD and plaque GSM. Giannakopulos *et al.*,[29] Piazza *et al.*,[11] and Malik *et al.*,[30] published the analysis of embolic particles captured by filters using CAS. These studies are concordant in reporting a significant increased amount of embolic filter debris in patients treated for an echolucent plaque.

Overall there is a high consistency in indicating echogenicity as an important factor influencing the risk of embolization during CAS. Also in this case, and an open cell stent was used in most cases and there are no studies describing the role of plaque echogenicity with the use of micromesh stents.

Plaque calcification

Carotid plaque calcification may be characterized in several ways. Grade of calcification is inversely related to echolucency, and ultrasound Geroulakos classification is someway related to calcifications. However, ultrasound is not the ideal diagnostic modality for the classification of plaque calcifications, as these may cause substantial im-

TABLE II.—*Summary of evidences of the effect of plaque echogenicity on embolization risk in patients undergoing CAS with old-generation stents.*[11, 14, 27-31]

Author	Year	N.	Stent design	Endpoint	Type of analysis	Covariate	Effect size (statistical significance)
Biasi *et al.*[27]	2004	418	NA	Ipsilateral stroke	Multivariate Logistic regression	GSM ≤25	OR 7.11; 95% CI 2.06-24.57 (P=0.002)[a]
Chaturvedi *et al.*[14]	2010	1166	OC	Ipsilateral stroke	Univariate logistic regression	Soft *vs.* calcified-mixed plaque	OR 0.64; 95%CI 0.25, 1.66
Tegos *et al.*[28]	2001	80	NA	TCD emboli	Spearman correlation	GSM	r = –0.22 (P =0.045)[a]
Stojanov *et al.*[31]	2012	47	26 OCS 21 CCS	Ipsilateral new DWI ischemic lesion	Bivariate analysis	Fibrolipid *vs.* fibrocalcified plaque	P=0.041[a]
Malik *et al.*[30]	2010	56	NA	Number and size of embolic particles	Bivariate analysis	GSM ≤20	P=0.007[a]
Giannakopoulos *et al.*[29]	2012	53	OC	Embolic material in filter	Multivariate Logistic regression	Gray-Weale scale	OR 2,26; 95% CI 1.02-5.02 (P=0.04)[a]
Piazza *et al.*[11]	2018	278	67 CCS 211 OCS	Embolic filter debris load	Multivariate logistic regression	Hypoechogenicity	OR 6.05; 95%CI 2.47-15.71 (P<.001)[a]

[a]Statistically significant.
CC: closed cell; OC: open cell.

age artifacts. Grade of calcification is better investigated by CTA; the Society for Vascular Surgery reporting standards[13] classify carotid calcifications into four categories: calcium absence, mild non-circumferential calcifications, moderate multifocal calcifications, and severe circumferential calcifications.

Elsayed *et al.*[32] compared plaques with calcifications <50% of the circumference *vs.* >50% after CTA evaluation, reporting an increased risk of ipsilateral stroke in case of calcified plaques. Sabat *et al.*[19] used ultrasound imaging to define the presence of calcifications, and described a higher incidence of new DWI lesions in presence of calcifications.

Bijuklic *et al.*[17] defined calcified plaques as those with angiographically visible calcifications; these were associated with an increased risk of new DW-MRI ischemic lesions in a cohort of 837 patients. Brightwell *et al.*[33] reported a quantitative and qualitative analysis of filter used during 20 CASs with closed cell stents: more calcified plaques were more likely to produced significantly more emboli, but characterized by smaller particles.

Differently, Chatourvedi *et al.*,[14] Sayeed *et al.*,[16] and Hoffman *et al.*[20] did not find a significant impact of calcifications on CAS clinical outcomes. Also other direct analysis of filters[11, 21, 22] did not find a significant impact of grade of calcifications on EFD load.

In conclusion, there is a high heterogenicity in the methods for calcification evaluation (by ultrasound, CTA, or angiography) and classifications, and this may influence the inconsistency of the results between series (Table III).[14, 16, 17, 19-22, 32, 33] Also, the inverse relation existing between calcification and echolucency, probably complicates the assessment of calcifications as an independent determinant of emboli. It is our opinion that heavy calcifications alone may not be an important source of clinically evident embolization during the procedure, but definitely can be responsible of inadequate stent expansion and incomplete apposition to the carotid wall, that in turn could facilitate early postoperative embolization and ischemic events.

Degree of carotid stenosis

Grade of carotid stenosis can be easily assessed by preoperative ultrasound or CTA. Although there generally is a is a good concordance between different imaging modalities, assessment of stenosis based on luminal area on CTA may overestimate the degree of stenosis compared to NASCET criteria, potentially leading to erroneous indications and preoperative risk evaluation.[34, 35] The presence of a severe grade of stenosis (*i.e.* >90%) may increase the number of attempts needed for lesion crossing and the plaque attrition with the guidewire and embolic protection device during lesion passage. Degree of stenosis is considered as a possible determinant in many studies on CAS outcomes; however only a few were specifically focused on this morphologic factor. In 2004 Biasi *et al.*[27] described an increased risk of periprocedural ipsilateral stroke in case of carotid stenosis >85% (OR 5.76, 95%CI 1.51-21.91; P=0.01). However, this result was not confirmed by more recent studies using either clinical outcomes,[14, 20] new DWI ischemic lesions,[22, 31] or filter debris load[29] as primary endpoint (Table IV).[14-16, 18, 20-22, 27, 29, 31]

Overall most studies did not find a significant impact of the grade of carotid stenosis on embolization risk. Nev-

TABLE III.—*Summary of evidences of the effect of plaque calcification on embolization risk in patients undergoing CAS with old-generation stents.*[14, 16, 17, 19-22, 32, 33]

Author	Year	N.	Stent design	Endpoint	Type of analysis	Covariate	Effect size (statistical significance)
Hofmann *et al.*[20]	2006	606	NA	Ipsilateral stroke	Bivariate comparison	Lesion calcification	P=0.3
Sayeed *et al.*[16]	2008	429	397 OC 32 CC	Any stroke	Bivariate analysis	Lesion calcification	P=.35
Chaturvedi *et al.*[14]	2010	1166	OC	Ipsilateral stroke	Univariate logistic regression	Target lesion calcification	
						Heavy-mild *vs.* none	OR 1.34; 95% CI 0.56-3.22 (P=0.509)
						Heavy *vs.* mild-none	OR 1.15; 95% CI 0.59-2.22 (P=0.686)
Elsayed *et al.*[32]	2022	4416	NA	Ipsilateral stroke	Multivariate logistic regression	Heavy calcification (CTA)	OR 1.7; 95% CI 1.01-2.8 (P=0.046)[a]
Bijuklic *et al.*[17]	2013	837	NA	Any new DWI ischemic lesion	Multivariate logistic regression	Lesion calcification (angiography)	OR 0.68; 95% CI 0.48-0.96 (P=0.028)[a]
Sabat *et al.*[19]	2019	107	OC	Any new DWI ischemic lesion	Univariate logistic regression	Lesion calcification (ultrasound)	OR, 5.68; 95% CI, 1.12-28.79 (P=0.04)[a]
Qu *et al.*[22]	2019	63	25 CCS 38 OCS	Any new DWI ischemic lesion	Univariate logistic regression	Percentage of plaque calcification (CTA)	OR 0.31; 95%CI 0.06-1.50 (P=0.146)
Brightwell *et al.*[33]	2011	20	CC	Embolic filter debris load	Bivariate comparison	Lesion calcification (Ca_{Score}>288.08 mean value)	P=0.02[a]
Kwon *et al.*[21]	2013	35	OC	Large emboli on filter microscopic analysis	Univariate logistic regression	Lesion calcification	OR 3.60; 95% CI 0.76-17.01 (P=0.106)

[a]Statistically significant.
CC: closed cell; OC: open cell.

ertheless the association of a high grade of stenosis with other potential embologenic factors, such as lesion length and echogenicity, may be an important morphological aspect to be considered during patients selection for CAS.

Plaque ulceration

Plaque ulceration is defined as an interruption of the intimal layer determining a crater from the lumen into the stenotic plaque.[16] Ulceration can be assessed through ultrasound, CTA, MRI or angiography. The presence of plaque ulcerations is a well-known risk factor for stroke in asymptomatic patients under best medical therapy alone.[2] This is related to a damage of the intima that may expose thrombogenic material to the blood flow, causing plaque thrombosis or embolization. However, the impact of ulceration on CAS outcomes is controversial.

Hofmann *et al.*[20] found an increased risk of ipsilateral stroke in case of treatment of ulcerated plaques, and this result was confirmed also after multivariate analysis. Other two clinical studies[15, 16] evaluating plaque ulceration either by angiography or ultrasound, did not find a significant impact on the stroke/death risk.

Also looking at new DWI-MRI ischemic cerebral lesions, the results are conflicting: Bijuklic *et al.*[17] included 837 CAS procedures, being 41% of these performed on ulcerated plaques; plaque ulceration was not included as covariate in the final multivariate logistic regression model. Gröschel[18] and Qu *et al.*[22] described a higher incidence of embolic infarcts in case of ulcerated plaques.

Kwon *et al.*[21] showed a significant univariate association between ulceration and presence of large emboli on filter analysis, but this was not confirmed after multivariate analysis.

Malik *et al.*,[30] in their examination of embolic filters, did not analyzed the impact of ulceration alone, but reported a detrimental effect in case of association of echogenicity, heterogenicity, and luminal irregularity/ulceration (P<0.02, 95% confidence interval, 4.5-27.6).

Overall there is a heterogenicity of results across different studies (Table V).[15, 16, 18-23] It is likely that plaque ulceration is an hallmark of plaque instability, that often comes with other associated characteristics as soft component, thin fibrous cap, and irregular surface, that may contribute to embolization risk during CAS.

Other plaque characteristics

Other morphological plaque characteristics, such as eccentric morphology, surface irregularity, MRI density,

TABLE IV.—*Summary of evidences of the effect of degree of stenosis on embolization risk in patients undergoing CAS with old-generation stents.*[14-16, 18, 20-22, 27, 29, 31]

Author	Year	N.	Stent design	Endpoint	Type of analysis	Covariate	Effect size (statistical significance)
Biasi *et al.*[27]	2004	418	NA	Ipsilateral stroke	Multiple Logistic regression	Target lesion stenosis (≥85%, *vs.* <85%)	OR 5.76; 95% CI, 1.51-21.91 (P=0.01)[a]
Hofmann *et al.*[20]	2006	606	NA	Ipsilateral stroke	Bivariate comparison	Target lesion stenosis (%)	P=0.26
Sayeed *et al.*[16]	2008	429	397 OC 32 CC	Any stroke	Bivariate analysis	Target lesion stenosis (%)	P=0.75
Chaturvedi *et al.*[14]	2010	1166	NA	Ipsilateral stroke	Univariate Logistic regression	Target lesion stenosis (≥90%, *vs.* <90%)	OR 0.95; 95% CI 0.52-1.74 (P=0.880)
Moore *et al.*[15]	2015	570	OC	Ipsilateral stroke and death	Univariate logistic regression	Target lesion stenosis (tertiles)	P=NS
Gröschel *et al.*[18]	2008	176	173 OC 3 CC	Any new DWI ipsilateral ischemic lesion	Bivariate comparison	Target lesion stenosis (%)	P=0.713
Stojanov *et al.*[31]	2012	47	26 OCS 21 CCS	Ipsilateral new DWI ischemic lesion	Bivariate analysis	Degree of stenosis (%) 50-70% *vs.* >70-99%	P=0.835
Qu *et al.*[22]	2019	63	25 CCS 38 OCS	Any new DWI ischemic lesion	Univariate logistic regression	Target lesion stenosis (moderate *vs.* severe)	P=0.581
Giannakopoulos *et al.*[29]	2012	53	OC	Embolic material in filter	Multivariate Logistic regression	Target lesion stenosis 70-80% >80%	 OR 7.81; 95% CI, 0.60-101.90 (P=0.12) OR 5.3; 95% CI, 0.50-57.50 (P=0.17)
Kwon *et al.*[21]	2013	35	OC	Large emboli on filter microscopic analysis	Univariate logistic regression	Target lesion stenosis (%)	OR 0.97; 95%CI 0.91-1.94 (P=.433)

[a]Statistically significant.
CC, closed cell; OC, open cell.

TABLE V.—*Summary of evidences of the effect of grade of plaque ulceration on embolization risk in patients undergoing CAS with old-generation stents.*[15, 16, 18-23]

Author	Year	N.	Stent design	Endpoint	Type of analysis	Covariate	Effect size (statistical significance)
Hofmann *et al.*[20]	2006	606	NA	Ipsilateral stroke	Multivariate logistic regression	Lesion ulceration	OR 2.5; 95%CI 1.1–5.8 (P=0.035)[a]
Sayeed *et al.*[16]	2008	429	397 OC 32 CC	Any stroke	Bivariate comparison	Lesion ulceration	P=.62
Moore *et al.*[15]	2015	570	OC	Ipsilateral stroke and death	Univariate logistic regression	Lesion ulceration	OR 2.21; 95%CI 0.88-5.51
Kastrupt *et al.*[23]	2008	62	59 OC 3 CC	New DWI ipsilateral ischemic lesion	Multivariate logistic regression	Lesion ulceration	OR 1.8; 95% CI 0.99-3335; (P=0.05)[a]
Gröschel *et al.*[18]	2008	176	173 OC 3 CC	Any new DWI ipsilateral ischemic lesion	Multivariate logistic regression	Lesion ulceration	OR 2.28; 95%CI 1.10-4.75 (P=0.027)[a]
Qu *et al.*[22]	2019	63	25 CCS 38 OCS	Any new DWI ischemic lesion	Univariate logistic regression	Irregular surface or ulceration	OR 1.92, 95%CI 1.00-3.67 (P=0.049)[a]
Sabat *et al.*[19]	2019	107	OC	Any new DWI ischemic lesion	Univariate logistic regression	Lesion ulceration	P=NS
Kwon *et al.*[21]	2013	35	OC	Large emboli on filter microscopic analysis	Univariate logistic regression	Lesion ulceration	OR 5.00; 95% CI 0.63-39.72 (P=0.128)

[a]Statistically significant.
CC, closed cell; OC, open cell.

and positron emission tomography-CT captation, may be important in determining the risk of embolization during CAS, but only limited data are available and the overall results are inconclusive. Plaque hemorrhage detected by MRI has been described as a marker of plaque instability, with an increased risk of stroke in patients addressed to best medical therapy only.[36] Also other morphological hallmarks of plaque instability, such as micorembolic signals at transcranial doppler, impaired cerebrovascular reserve, mural thrombus, and plaque neovascularization, that are associated to an increased risk of stroke in asymptomatic patients,[37] may impact on the outcomes of CAS. However the role of these morphological feature in patients undergoing CAS has not been clearly investigated, and further studies are needed to determine their effect on perioperative risk of embolization.

Plaque characteristics influencing embolic risk during cas with new-generation stents

New-generation carotid stents are characterized by a double-layer structure with a significantly smaller cell area (75-500 µm) compared to traditional open-cell (≥5 mm^2) and closed-cell (approximately 1 mm^2) stents. The rational for this design is to reduce cerebral embolization deriving from plaque crashing and prolapse, maintaining a good flexibility and conformability.[38] In preliminary clinical experiences, the use of double-layer stents has demonstrated a lower incidence of clinically relevant embolization[39] and amount of material captured by protection filters[40] compared to first-generation stents. However, there still is a paucity of comparative data and up to date there are no studies specifically assessing the role of morphological plaque characteristics on the outcomes of CAS using new-generation stents. Two studies compared the embolization potential of new-generation *vs.* old-generation stents in specific types of lesion. Nakagawa *et al.*[41] described a significant reduction in cerebral embolization – defined by new MRI cerebral lesions – with the use of new-generation compared to closed-cell stents, especially in cases with highly lipidic lesions. Another study from our group[40] compared EFD load between different carotid stent designs, and found a significant decreased amount of embolized material with the use of micromesh stents; this result was driven mostly by a protective effect of new-generation stents in case of hypoechoic plaques or plaque length >15 mm, that typically are at higher risk for embolization with closed or open cell stents.

Impact of plaque characteristic on patients management

Patients at risk for embolic risk during CAS may be considered for dedicated treatment protocols. If the patient carries an acceptable surgical risk, CEA should represent the first treatment option. Alternatively, if the patient is at high risk for open surgery owing to general comorbidities, best medical treatment alone may be considered in asymptomatic patients: in this case the risk of CAS adverse events should be balanced with the risk of stroke under best medical therapy, and a tailored decision should be done based on patients' specific risk factors and comorbidities. If CAS is indicated although the presence of potentially embologenic features, selection of adequate technique and materials is mandatory. Unprotected predilatation of the carotid plaque should be avoided, and the use of an embolic protection device should be considered to avoid embolization related to lesion crossing, stent deployment, and post-ballooning. A proximal occlusion device may be preferred over a distal filter to prevent from possible embolization originating from filter advancement over the carotid stenosis. Finally, new-generation micromesh stents should be considered to reduce embolization during stent deployment, postdilatation, and plaque prolapse after CAS.[40] However, there is still a lack of evidence in this field and future studies are required to clarify the role of micromesh stent design in high risk carotid plaques, including highly calcific lesions.[42]

Conclusions

The literature is consistent in identifying plaque length >15 mm and ultrasound hypoechogenicity as risk factors for embolization during CAS. Calcified plaques, high-grade stenosis, and ulcerated lesions may be treated by CAS without a substantial increase in the risk for embolization, but should be still regarded as potentially harmful if associated with other risk factors for embolization. A substantial limitation of existing studies is that virtually all reports investigating the effect of plaque morphological characteristics on the outcomes of CAS are based on the use of open cell or closed cell stents. Initial clinical experiences seem to show a protective effect of new-generation stents in those plaque that typically are considered at risk for embolization with old-generation stents, such as highly lipidic lesions, hypoechoic plaques, and long plaques. Further studies will clarify the role of new-generation micromesh stents in the endovascular treatment of high-risk carotid plaques.

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Conflicts of interest
The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

Authors' contributions
Francesco Squizzato: conception and design, data collection, interpretation, writing, final approval; Alessandra Turcatel: data collection, writing, final approval; Michele Piazza, Elda C. Colacchio, Franco Grego and Michele Antonello: conception and design, critical revision, final approval. All authors read and approved the final version of the manuscript.

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