REVIEW

Clinical update

Carotid artery stenting: an update

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In patients with carotid disease, the purpose of carotid artery revascularization is stroke prevention. For >50 years, carotid endarterectomy has been considered the standard treatment for severe asymptomatic and symptomatic carotid stenoses. Carotid artery stenting (CAS) has emerged in the last 15 years as minimally invasive alternative to surgery. However, the value of the endovascular approach in the management of carotid disease patients remains highly controversial. The aims of this review are to elucidate the current role of CAS, to describe the major technology advancements in the field, and to speculate about the future of this therapy.

Keywords   Carotid artery stenosis   •   Carotid artery stenting   •   Carotid endarterectomy   •   Randomized controlled trials   • Emboli protection

Introduction

Ten to 15% of all ischaemic strokes originate from a stenosis at the level of the internal carotid artery. In patients with carotid disease, the purpose of carotid revascularization is the prevention of (recurrent) stroke. For >50 years carotid endarterectomy (CEA) has been considered the standard treatment for severe asymptomatic and symptomatic carotid stenoses. Carotid artery stenting (CAS) has emerged in the last 15 years as minimally invasive alternative to surgery.[1] However, its role remains highly controversial. The debate has been fuelled by the multiples medical specialties involved as well as by the disappointing results of CAS in randomized comparisons with CEA. While some have interpreted those findings as clear-cut clinical evidence, other have suggested that most of the trials may have compared the two revascularization modalities in an unfair way.[2] Aims of this review are to elucidate the current role of CAS in the management of patients with advanced carotid disease, to describe the major technology advancements in the field, and to speculate about the future of this therapy.

Clinical data

Major randomized trials of carotid artery stenting vs. carotid endarterectomy and meta-analysis

Six major trials have randomized a total of 6780 patients to CAS vs. CEA. While the SAPPHIRE (Stenting and Angioplasty with

Protection in Patients at High Risk for Endarterectomy) trial[3] included patients, both symptomatic and asymptomatic, at high risk for surgery, CAVATAS (Carotid and Vertebral Artery Transluminal Angioplasty Study),[4] SPACE (Stent-Protected Percutaneous Angioplasty of the Carotid Artery vs. Endarterectomy),[5] EVA-3S (Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis),[6] and ICSS (International Carotid Stenting Study) enrolled symptomatic patients at standard surgical risk.[7] Finally, the Carotid Revascularization Endarterectomy vs. Stenting Trial (CREST) enrolled both symptomatic and asymptomatic patients at standard surgical risk.[8] The randomized studies were, to different degrees, burdened by several limitations, the most important being the limited endovascular expertise requirements for operators performing CAS.[2]

The CAVATAS trial, performed in the late 1990s, randomized 504 symptomatic patients at low-to-moderate risk for surgery to CEA or carotid angioplasty.[4] The incidence of death or stroke at 30 days was 10.0% in the endovascular group and 9.9% in the surgical group. The study was criticized by the interventional community for the low stenting rate (26%). Accordingly, in the study initially all patients in the endovascular arm were treated with balloon angioplasty, while later the implantation of (balloon expandable) stents was allowed. Embolic protection devices (EPD) were unavailable at the time. At 8 years, no difference in ipsilateral stroke, ipsilateral stroke or transient ischaemic attack, or any stroke between the two arms was observed.[9] The SAPPHIRE study randomized 334 patients at a high

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risk for surgery to CAS with the systematic use of EPD or CEA.[3] The trial included asymptomatic (71%) and symptomatic (29%) patients. The primary endpoint, a composite of death, stroke, or myocardial infarction (MI) within 30 days after the intervention or death or ipsilateral stroke between 31 and 1 year showed a trend in favour of CAS, occurring in 12.2% in the CAS group and in 20.1% in the CEA group (*P* = 0.053). Patients who underwent CAS had significantly fewer MI at 30 days compared with those allocated to CEA (1.9 vs. 6.6%, *P* = 0.04). At 3-year follow-up, CAS and CEA were equally effective in terms of stroke prevention.[10]

The SPACE study, which included 1200 participants and was terminated because of slow enrolment and lack of funding, found no difference in the incidence of ipsilateral stroke or death at 30 days between patients allocated to CAS or CEA, with an event rate of 6.8 and 6.3%, respectively.[5] Embolic protection devices were used in a minority of CAS patients. At 2 years, the outcomes of the two groups were comparable.[11] The EVA-3S trial, which included 527 patients, was stopped prematurely because of a significantly increased event rate among patients allocated to endovascular treatment (death or stroke 9.6% in the CAS arm and 3.9% in the CEA arm).[6] At 6 months, the incidence of any stroke or death was 11.7% in the CAS group and 6.1% in the CEA group (*P* = 0.02). At 4-year follow-up, the death or stroke rate still favoured CEA, driven by the 30 day events. However, beyond 30 days, no difference in adverse outcomes between CAS and CEA was observed.[12]

The ICSS study randomized 1713 symptomatic patients to CAS or CEA, and the primary endpoint was the long-term rate of any fatal or disabling stroke. The authors reported first an interim safety analysis showing that the 120-day rate of stroke, death, or procedural MI occurred in 8.5% in the CAS group and 5.2% in the CEA group [hazard ratio (HR) 1.69; 95% confidence intervals (CI) 1.16–2.45; *P* = 0.006]. The incidence of disabling stroke or death at 120 days did not differ (4.0% in the CAS group and 3.2% events in the CEA) but there was an excess of overall strokes in the endovascular arm (HR 1.92, 95% CI 1.27–2.89; *P* = 0.002).[7] The use of EPD was not mandatory in this trial. The final results of the study were just published recently showing that the 5-year risk incidence of fatal or disabling stroke did not differ between CAS (6.4%) and CEA (6.5%).[13] Beyond 30 days after treatment, there was no difference in the rates of ipsilateral stroke in the territory of the treated carotid artery (4.7% for CAS vs. 3.4% for CEA, HR 1.29, 95% CI 0.74–2.24). However, overall an excess of strokes in the CAS arm persisted, with a 5-year cumulative risk of 15.2 vs. 9.4% in the CEA group (HR 1.71, 95% CI 1.28–2.30; *P* < 0.001), although this did not translate into differences in functional disability and quality of life, as assessed by the modified Rankin scale and EQ-5D questionnaire.

The CREST trial randomized 2502 symptomatic and asymptomatic patients to CAS with embolism protection or CEA. The primary composite endpoint was stroke, MI, or death from any cause during the periprocedural period or ipsilateral stroke within 4 years after randomization. Over a median follow-up period of 2.5 years, there was no significant difference in the estimated 4-year rates of the primary endpoint between CAS and CEA groups (7.2 and 6.8%, respectively; HR 1.11; 95% CI 0.81–1.51; *P* = 0.51).[8] The 4-year rate of stroke or death was 6.4% with CAS and 4.7% with CEA (HR 1.50; *P* = 0.03); the rates among symptomatic patients were 8.0 and 6.4% (HR 1.37; *P* = 0.14), and the rates among asymptomatic patients were 4.5 and

2.7% (HR 1.86; *P* = 0.07), respectively. Periprocedural event rates differed between the CAS and CEA for stroke (4.1 vs. 2.3%, *P* = 0.01) and MI (1.1 vs. 2.3%, *P* = 0.03). Beyond 30 days, the incidence of ipsilateral stroke with both CAS and CEA was low (2.0 and 2.4%, respectively; *P* = 0.85). Importantly, in the second half of the study, the rate of stroke in the CAS arm, but not in the CEA arm, showed a significant reduction, suggesting a learning curve effect in the endovascular arm.[14] Finally, in CREST, there was an association between the presence of periprocedural MI, more common in the CEA arm, and long-term mortality. This was not the case for the endpoint of minor stroke, which was as mentioned more common in the CAS arm.[14]

A meta-analysis of randomized controlled trials including 3754 patient treated with CAS and 3723 patients undergoing CEA showed that at 30 days, CAS was associated with an significantly elevated risk of stroke [Odds Ratio (OR) 1.53, 95% CI 1.23–1.91; *P* < 0.001], death or stroke (OR 1.54, 95% CI 1.25–1.89; *P* < 0.001) while MI (OR 0.48, 95% CI 0.29–0.78; *P* = 0.003) and cranial nerve injuries (OR 0.09, 95% CI 0.05, 0.16; *P* < 0.001) were significantly reduced compared with CEA.[15] Beyond 30 days, the efficacy of the two revascularization strategies in terms of ipsilateral stroke prevention and their safety in terms of restenosis and need for repeat revascularization was comparable in all trials.

Ongoing randomized carotid revascularization trials

The randomized, controlled, open, multi-centre three-armed SPACE-2 study started in 2009 aiming to compare state-of-the-art medical prevention including lifestyle modification with CEA and CAS in patients with severe asymptomatic carotid stenosis. Due to low recruitment, the steering committee decided in 2012 to modify the protocol and to split this three-arm trial into two separate two-arm clinical trials [CEA + best medical treatment vs. best medical treatment alone (SPACE-2A) and CAS + best medical treatment vs. best medical treatment alone (SPACE-2B)].[16] The Asymptomatic Carotid Surgery Trial-2 (ACST-2) is enrolling up to 5000 patients with severe asymptomatic carotid stenosis randomly allocated to CEA or CAS. In an interim safety analysis of the first 691 patients enrolled, the investigators reported a disabling stroke, fatal MI, and death rate of 1.0%.[17]

The Carotid Stenting vs. Surgery of Severe Carotid Artery Disease and Stroke Prevention in Asymptomatic Patients (ACTI) trial randomized asymptomatic patients to CAS vs. CEA in a 3:1 ratio. The study has been prematurely halted after the enrolment of ~1600 patients and the results have not been presented yet. The carotid revascularization for primary prevention of stroke (CREST-2) study is composed of two independent multi-centre, randomized controlled trials of carotid revascularization and best medical management vs. medical management alone in patients with asymptomatic high-grade carotid stenosis. One trial will randomize patients in a 1:1 ratio to CEA vs. no CEA and another will allocate patients in a 1:1 ratio to CAS vs. no CAS. Medical management will be uniform for all groups. The study plans to include 2480 patients and enrolment is supposed to start at the end of 2014.

In summary, no trial is planned to address the most relevant issue, namely the comparative value of CAS and CEA in symptomatic patients. For asymptomatic patients some, but likely non-conclusive

Table I 30-day event rates in carotid artery stenting registries enrolling over 1000 patients

Name	Year	Country	N	Industry sponsored	Surgical high risk	EPD	Sympt patients (%)	Neuro[a]	CEC adjud.	D/S	D/S/MI	D/S sympt	D/S asymp
CAPTURE[31]	2007	USA	3500	Yes	Yes	Mandatory	14	Yes	Yes	5.7%	6.3%	10.6%	4.9%
CASES PMS[32]	2007	USA	1493	Yes	Yes	Mandatory	22	Yes	Yes	4.5%	5.0%	NR	NR
PRO-CAS[33]	2008	D	5341	No	No	75%	55	70%	No	3.6%[b]	NR	4.3%[b]	2.7%[b]
SAPPHIRE-W[34]	2009	USA +	2001	Yes	Yes	Mandatory	28	No[c]	Yes	4.0%	4.4%	NR	NR
SVS[35]	2009	USA	1450	No	Yes	95%	45	No	No	NR	5.7%	NR	NR
EXACT[36]	2009	USA	2145	Yes	Yes	Mandatory	10	Yes	Yes	4.1%	NR	7.0%	3.7%
CAPTURE-2[36]	2009	USA	4175	Yes	Yes	Mandatory	13	Yes	Yes	3.4%	NR	6.2%	3.0%
Mercogliano[b,f,37]	2010	I	1300	No	No	Mandatory[d]	28	No	No	1.4%	1.4%	3.0%	0.8%
Krakow[b,f,38]	2012	P	1081	No	No	Mandatory	51	No	No	NR	2.6%	3.6%	1.5%
CABANA[39]	2014	USA	1025[e]	Yes	Yes	Mandatory	32	Yes	Yes	4.1%	4.6%	NR	NR

EPD, emboli protection devices; sympt, symptomatic; asympt, asymptomatic; CEC adjud., clinical event committee adjudication; D, death; S, stroke; MI, myocardial infraction; NR, not reported; D, Deutchsland 7 (country); I, Italy; P, Poland.
+ USA and Canada.
[a]Neuro, independent pre- and post-procedural assessment by a neurologist.
[b]In-hospital events.
[c]Neurologic assessment performed by stroke scale certified staff member.
[d]Mo.Ma proximal protection.
[e]1097 patients enrolled and 1025 patients evaluable for 30-day events.
[f]Single-centre study.

data should be soon available from the ACT-I trial, while from the most important trial, namely ACST-2, no data will be available for several years to come. Finally, both SPACE-2 and CREST-2, if completed, will allow due to their design only indirect comparisons between CAS and CEA.

Large-scale registries

The results of 10 CAS large-scale registries (i.e. enrolling over 1000 patients) have been published, for a total of 23 511 patients treated (*Table 1*). The use of EPD was mandatory in the majority of the studies. The highest quality studies came from the Unites States, with most of the registries being mandated by the FDA and having independent neurologic assessment pre- and post-procedure as well as clinical event committee adjudication of adverse outcomes. The main limitation of the registries is that the proportion of symptomatic patients was modest. Overall, the outcomes can be considered favourable, with a 30-day death, stroke, or MI rate ranging from 1.4 to 6.3%, especially if considered that several registries included only patients at high surgical risk and that the event rates have decreased over the years.

Technology advancements

Although the insufficient expertise, both in terms of skills and in patient selection, may be the main factor leading to stroke excess in CAS compared with CEA, CAS as it was performed in the randomized trials carried some intrinsic limitations:

(i) distal EPD (filters) may not adequately protect the brain in all settings, due to incomplete apposition to the vessel wall, lack of protection during placement of the EPD, and the passage of micro-emboli smaller that the pore size of the filter;

(ii) current stent frames may have insufficient lesion scaffolding properties and allow for intra-strut plaque prolapse;

(iii) catheter manipulations at the level of the aortic arch may be an important source of emboli not prevented by current EPD technology.

Some of those limitations have been addressed by recent technology advancements described below.

Proximal cerebral protection

Proximal EPD protects the brain by interrupting or reversing the blood flow at the level of the carotid bifurcation at the time of the procedure. This approach as emerged as alternative to distal EPD (filters). The main advantages of proximal protection include crossing of the lesion under protected conditions as well as the blockage of both macro- and micro-emboli. Finally, with proximal protection there is no placement of a device in the distal internal carotid artery, and this may reduce the risk of arterial spasm, dissection, or intimal damage. Drawbacks of this technique include the larger sheath size required, which may be problematic in patients with advanced peripheral arterial disease and may be associated with an increased rate of vascular access complications, as well as the interruption of brain perfusion leading to an intolerance with transient neurologic symptoms in 3–8% of the patients.[18] Proximal protection should not be used in patients with advanced external or common carotid disease and its applicability in patients with contralateral carotid occlusion depend on the extent of the collateralization through the Circle of Willis. Finally, the procedure is somehow less
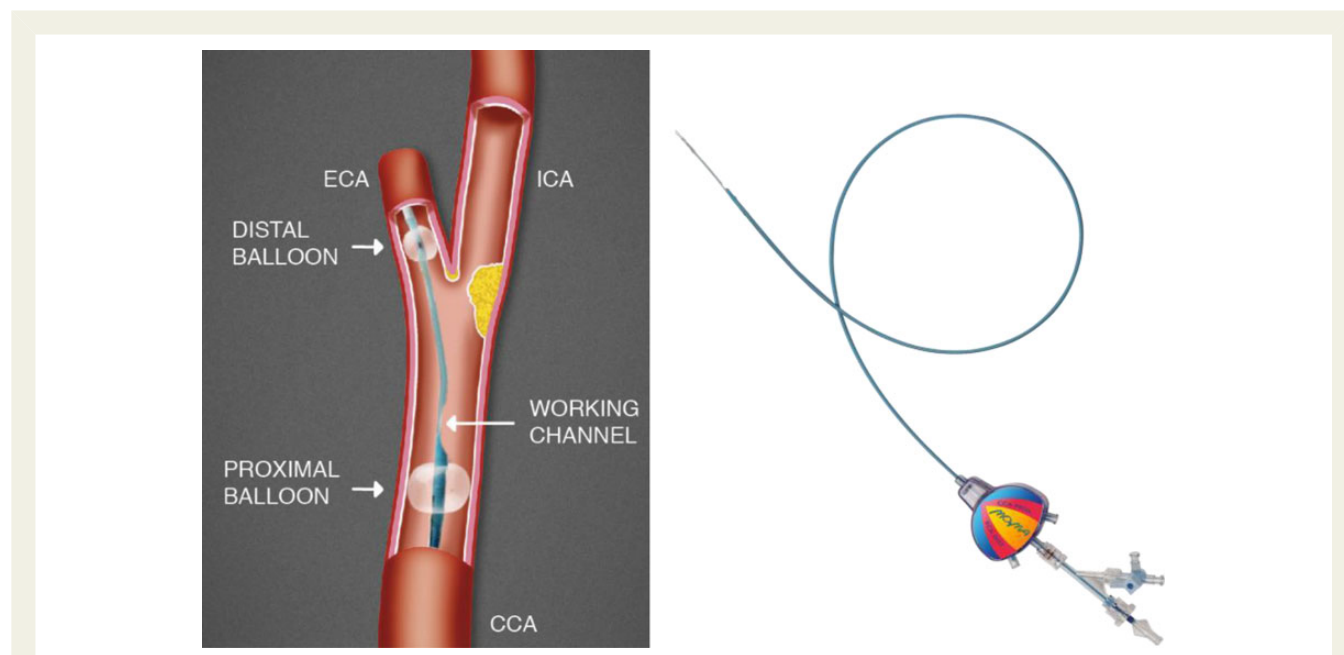

Figure I Mo.Ma™ working concept and device. The distal and the proximal balloons occlude the external carotid artery and the common carotid artery (left panel). The contemporary inflation of both balloons prevents flow in the internal carotid artery coming antegradely from the common carotid artery and retrogradely from the external carotid artery. Through the working channel the carotid lesion can be crossed and treated under flow blockage, preventing cerebral embolization. The device is illustrated in the right panel.
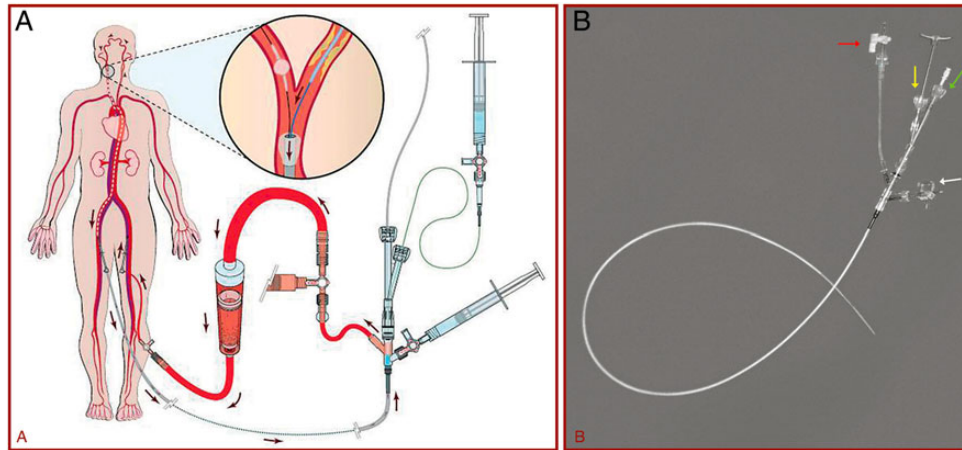
Figure 2 NeuroProtection System™ working concept (*A*) and device (*B*) with its multiple ports (arrows).

straightforward than filter-protected CAS and requires additional skills. Two proximal protection EPD systems are available.

Mo.Ma™ (Medtronic-Invatec, Roncadelle, Italy)

The Mo.Ma system consists of an 8F or 9F sheath with an effective working channel of a 5F and 6F sheaths, respectively, and two independently inflatable balloon catheters (*Figure 1*). The distal balloon is located close to the sheath tips and occludes the external carotid artery. The proximal balloon is positioned in the common carotid artery. When inflated, both balloons prevent flow in the internal carotid artery coming both antegradely from the common carotid artery and retrogradely from the external carotid artery. As a result, the carotid lesion can be crossed and treated under flow blockage, preventing cerebral embolization. After the lesion is treated, three 20 mL syringes of carotid blood are aspirated and checked for debris before deflating the distal and then the proximal balloons, reestablishing cerebral blood flow.

NeuroProtection System™ (WL Gore and Associates, Flagstaff, AZ, USA)

The NeuroProtection System is a distal EPD that promotes passive reverse flow in the internal carotid artery. It is composed of two independent systems: the balloon wire and the 9F sheath which has an effective working channel of a 6F sheath and contains an inflatable balloon at its tip (*Figure 2*). The sheath is positioned in the common carotid artery and the balloon wire is inserted through the sheath and positioned at the external carotid artery. When both balloons are inflated, the blood flow through the common and external carotids is blocked. The proximal part of the sheath is connected to the contralateral femoral vein, allowing blood flow reversal of blood from the cerebral circulation (i.e. the Circle of Willis) down the internal carotid artery and through the sheath into the venous system. The blood flows through a filter with a pore size of 180 μm which collects debris before the blood re-enters the circulation through the femoral vein. As a consequence, the carotid lesion can be crossed and treated in reverse-flow mode. At the end of the procedure, 10–20 mL of carotid blood are actively
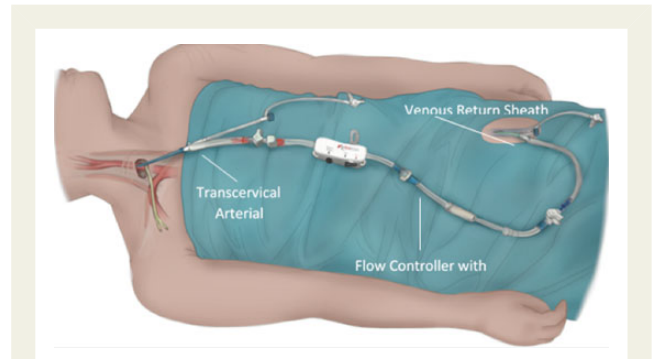

Figure 3 Schematic diagram of the component parts and layout of the ENROUTE™ system.

aspirated and then the balloons are deflated while active suction is applied to retrieve any particle contiguous to the balloon occluder.

Clinical data on proximal protected carotid artery stenting

The available clinical experience consisted of five multi-centre registries and one large-scale single-centre registry and has been summarized in a meta-analysis.[18] Among 2397 patients, 31% of them being symptomatic, the 30-day rate of composite stroke, MI, or death was 2.25%. Stroke, MI, and death were encountered in 1.71, 0.02, and 0.40%, respectively. Age and diabetic status were found to be the only significant independent risk predictors and stroke rates below 2.6% were found in all subgroups, including symptomatic octogenarians. In this analysis, gender, symptomatic status and contralateral carotid occlusion were not associated with adverse events.

ENROUTE™ neuroprotection system (formerly MICHI™ neuroprotection system, Silk Road Medical, Sunnyvale, CA, US)

The ENROUTE™ system is a flow reversal circuit consisting of two sheaths, one placed below in the common carotid via a transcervical approach connected to a transfemoral venous line (*Figure 3*).
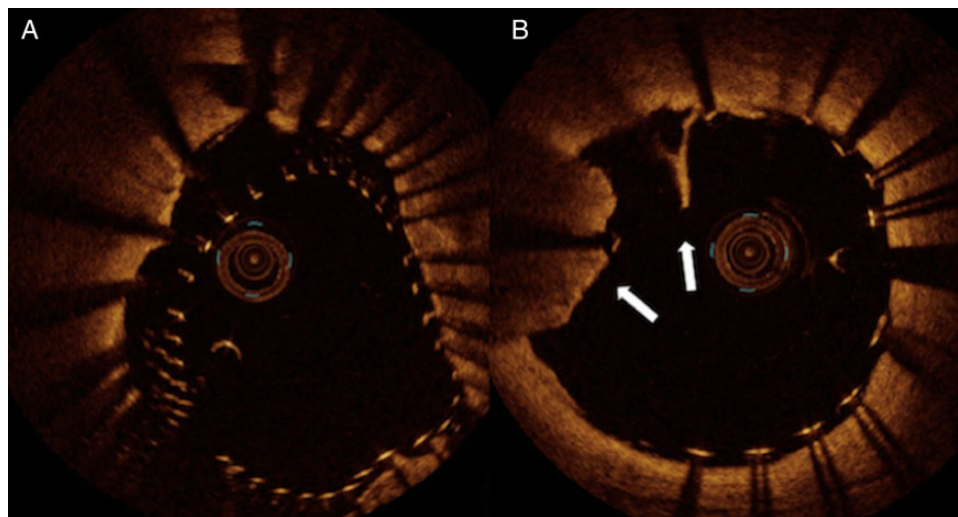
Figure 4 Optical coherence tomography findings inside an open-cell carotid stent. (*A*) Malapposition of the stent to the vessel while (*B*) intra-strut plaque prolapse (arrows).

The arterial sheath is placed via a surgical incision of around 2 cm in length above the clavicle on the side to be treated while the venous sheath is inserted into the femoral vein and an arterio-venous shunt is created. When the carotid artery is occluded just proximal to the arterial sheath, the resulting pressure gradient induces flow reversal. No blockage of flow in the ipsilateral external carotid is necessary. The main advantage of this approach is the lack of catheter manipulations at the level of the aortic arch. Downsides include the need for a surgical incision as well as for a disease-free portion of common carotid artery at the site of cut-down. Finally, the working length between the access point in the common carotid and the carotid bifurcation needs to be at least five cm.

Clinical data on ENROUTE™ system protected carotid artery stenting

At this stage, the ENROUTE™ system has undergone only limited clinical evaluation and should be considered an experimental device. In a first-in-man single-arm feasibility study including 44 patients, no major stroke, MI, death, or cranial nerve injury was reported. At 30 days, one minor contralateral stroke occurred in a patient who was free of lesions on post-procedural DWMRI.[19] A total of 31 patients underwent pre- and post-procedure DWMRI investigations. Five patients (16.1%) had new lesions on the post-procedural scan, representing the lowest DWMRI rate of any carotid stenting strategy reported to date.

Double layer mesh stent technology

While in coronary interventions miniaturization and refinement of stent design has allowed the interventionalists to perform more complex procedures and to solve most of the limitations of stenting, in CAS little research and development efforts have been allocated to improve stent characteristics. Recently, it has been recognized that the stent itself may substantially add to embolic protection in CAS through adequate scaffolding of the plaque once the EPD has been
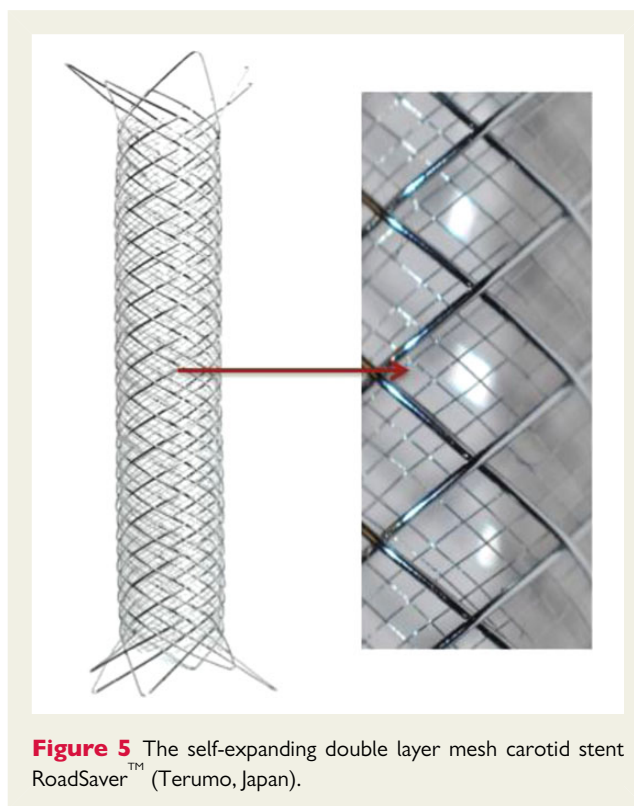

Figure 5 The self-expanding double layer mesh carotid stent RoadSaver™ (Terumo, Japan).

removed. The ideal properties of a carotid stent are a well-balanced mix of high flexibility and conformability, to accommodate tortuous anatomy, as well as high plaque coverage, to prevent late embolization of debris. Stents structure is characterized by sequential aligned annular rings interconnected by bridges and the design may be either open cell or closed cell, depending on the density of the bridges between the rings.

Open-cell design stents present some of the segments free from the adjacent rings allowing greater adaptation to the vessel anatomy at the price of less plaque coverage and higher risk of tissue prolapse. Closed-cell design stents are characterized by higher density of bridge interconnection, which reduces their conformability and increases the probability of malapposition but at the same time offers greater plaque coverage. A hybrid configuration with an open-cell design of the proximal and distal segments combined with a closed-cell design of the central segments has been recently developed. The impact of stent design on clinical outcome following CAS has not been adequately addressed. An observational study found a significant lower rate of post-procedural events in
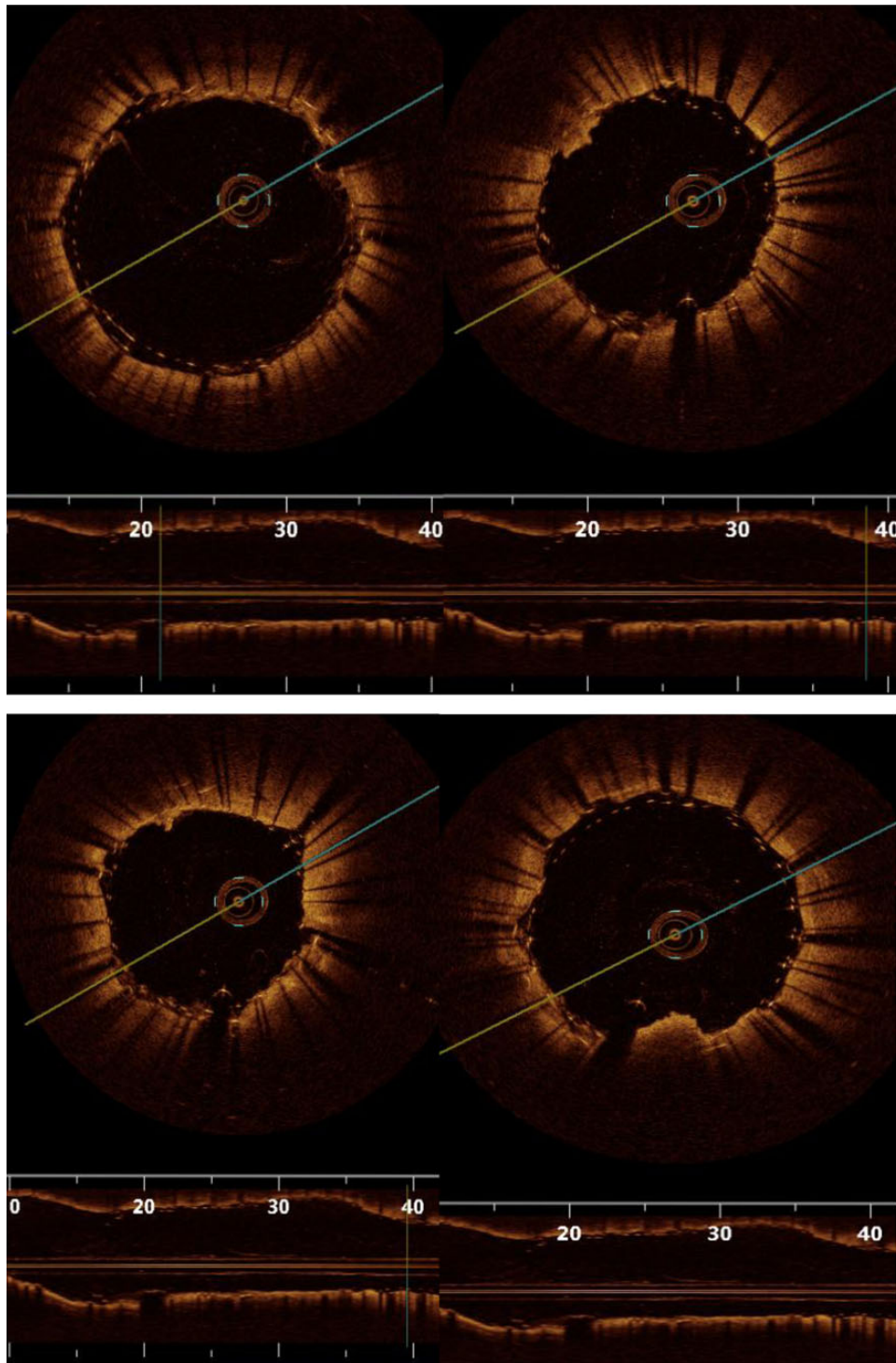

Figure 6 Optimal coherence tomography assessment of a RoadSaver™ stent showing no significant prolapse of plaque and good wall apposition.

patients undergoing closed-cell design stent implantation compared with individual allocated to open-cell design stenting, but these results were not confirmed by other registries showing poor correlation between in-hospital and 30 days mortality and stent design.[20–23]

A nice insight in the impact of stent design and in the pathophysiology at the lesion level at the time of CAS comes from a prospective single-centre study enrolling 40 consecutive patients and designed to evaluate the rate of stent malapposition, plaque prolapse, and thin cap fibro-atheroma rupture according to stent configuration by optical coherence tomography (OCT) (*Figure 4*).[24] Closed-cell design stents were used in 17 patients (42.5%), open-cell design stents in 13 patients (32.5%), and hybrid design stents in 10 patients (25%). No neurological complications occurred. On OCT analysis, the frequencies of malapposed struts were higher with closed-call compared with open-cell and hybrid design stents (34.5 vs. 15% and 16.3%, respectively; $P < 0.01$). Plaque prolapse was more frequent with open cell than closed cell (68.6 vs. 23.3%; $P < 0.01$) and hybrid stents (30.8%; $P < 0.01$). Significant differences were also noted in the rates of fibrous cap rupture between closed- and open cell (24.2 vs. 43.8%; $P < 0.01$), and between closed-cell and hybrid design (39.6%; $P < 0.01$) stents, but not between open-cell and hybrid design stents ($P = 0.4$). The authors concluded that micro-defects after stent deployment in CAS are frequent and are related to the design of implanted stents. While stent malapposition was more common following closed-cell design stent implantation, plaque prolapse was more common in patients treated with open-cell design devices. While these results are important, a correlation to clinical events remains to be demonstrated.

The mechanism of delayed cerebral embolization following CAS is unknown but may include tissue prolapsed through the stent struts and thrombus formation around malapposed stent struts. Despite the fact that current guidelines recommend carotid artery revascularization exclusively on the basis of stenosis severity, the importance of plaque characterization in stratifying stroke risk has been increasingly recognized. The weak correlation between the severity of stenosis and the risk of stroke in asymptomatic patients found in several trials together with recently published data that link complex plaques with stroke challenge the 'degree of stenosis-stroke risk' paradigm, highlight the importance of the morphology and composition of the carotid plaques beyond the degree of stenosis and of the investigation of the complex stent–plaque interaction after CAS.[24,25] In this respect, calcified lesions may favour stent malapposition while soft plaques may result in greater tissue prolapse though the stent struts.

Recently, a novel carotid stent design has been developed, namely the double layer mesh stent. The design should allow for high flexibility to accommodate tortuous anatomy and at the same time convey scaffold properties for optimal plaque coverage. This technology is characterized by an internal micromesh layer for plaque coverage and an external self-expanding nitinol layer for scaffolding offering the flexibility that characterize open-cell design stents. Currently, the only CE marked and commercially available double layer mesh stent is illustrated in *Figure 6*. The device is compatible with a 0.014″ guide wire and 7F guiding catheter or 6F long sheath. The cell size of the micromesh is extremely small (0.381 mm^2) allowing for extensive plaque coverage (*Figures 5* and *6*). It remains to be demonstrated whether this interesting concept will translate into a reduction of neurologic events associated with CAS.

Transradial approach

The transradial approach may be a valuable alternative to transfemoral access for CAS in patients with advanced peripheral vascular disease of with complex aortic arches such as the bovine or the type III arches.[26] Transradial access for CAS was first reported in 1999, and several case reports and few small case series followed.[27] The largest series so far published included 382 patients treated in two high-volume centres and documented an overall success rate of 91% and a stroke rate of 1.3%.[28] Recently, a randomized single-centre trial allocating 260 consecutive patients at high risk for CEA to transradial or transfemoral CAS reported excellent outcomes with both strategies with an incidence of procedural major adverse cardiac and cerebral events $< 1.0\%$ in both groups. From a transradial route, technical success was achieved in 90% of cases while 10% of patients required a crossover to a trasnfemoral access. Major vascular complications were rare ($< 1\%$ in both groups).[29]

Future directions

Carotid stenting, although it is a mature technique regularly applied with excellent outcomes in high-volume centres by expert operators, is struggling to find the consensus of the scientific community. The initial enthusiasm for CAS as a valuable and less invasive alternative to CEA has been mitigated by the undisputable gap in outcomes between the two strategies observed in randomized clinical trials. Inadequate requirements in terms of endovascular expertise, potentially leading to an increased event rate related to both insufficient technical skills and inadequate patient selection, has been proposed as the main reason for the unfavourable outcomes related to CAS. Despite the fact that high-quality multi-centre registries and high-volume single-centre experiences have consistently described favourable CAS outcomes, the evidence has not been considered sufficient in the neurologist community to recommend CAS. In addition, in some countries including the United States the procedure has been reimbursed only within research protocols. Overall, the number of procedures performed in recent years is stagnant if not decreasing and industry massively reduced funding for research, development, and clinical trials. Unfortunately, in the next years little additional randomized data comparing CAS and CEA are to be expected. The promising technologies described may reverse the currently unfavourable trend for CAS only if they will be given the chance to be tested in adequately powered clinical trials, which require major funding by either industry or private or public entities.[30]

References

1. Roffi M, Mukherjee D, Clair DG. Carotid artery stenting vs. endarterectomy. *Eur Heart J* 2009;**30**:2693–2704.
2. Roffi M, Sievert H, Gray WA, White CJ, Torsello G, Cao P, Reimers B, Mathias K, Setacci C, Schonholz C, Clair DG, Schillinger M, Grunwald I, Bosiers M, Abou-Chebl A, Moussa ID, Mudra H, Iyer SS, Scheinert D, Yadav JS, van Sambeek MR, Holmes DR, Cremonesi A. Carotid artery stenting versus surgery: adequate comparisons? *Lancet Neurol* 2010;**9**:339–341; author reply 341–332.

3. Yadav JS, Wholey MH, Kuntz RE, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Whitlow P, Strickman NE, Jaff MR, Popma JJ, Snead DB, Cutlip DE, Firth BG, Ouriel K. Protected carotid-artery stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2004;**351**:1493–1501.

4. Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* 2001;**357**:1729–1737.

5. Ringleb PA, Allenberg J, Bruckmann H, Eckstein HH, Fraedrich G, Hartmann M, Hennerici M, Jansen O, Klein G, Kunze A, Marx P, Niederkorn K, Schmiedt W, Solymosi L, Stingele R, Zeumer H, Hacke W. 30 day results from the SPACE trial of stent-protected angioplasty versus carotid endarterectomy in symptomatic patients: a randomised non-inferiority trial. *Lancet* 2006;**368**:1239–1247.

6. Mas JL, Chatellier G, Beyssen B, Branchereau A, Moulin T, Becquemin JP, Larrue V, Lievre M, Leys D, Bonneville JF, Watelet J, Pruvo JP, Albucher JF, Viguier A, Piquet P, Garnier P, Viader F, Touze E, Giroud M, Hosseini H, Pillet JC, Favrole P, Neau JP, Ducrocq X. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med* 2006;**355**:1660–1671.

7. Ederle J, Dobson J, Featherstone RL, Bonati LH, van der Worp HB, de Borst GJ, Lo TH, Gaines P, Dorman PJ, Macdonald S, Lyrer PA, Hendriks JM, McCollum C, Nederkoorn PJ, Brown MM. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): an interim analysis of a randomised controlled trial. *Lancet* 2010;**375**:985–997.

8. Brott TG, Hobson RW II, Howard G, Roubin GS, Clark WM, Brooks W, Mackey A, Hill MD, Leimgruber PP, Sheffet AJ, Howard VJ, Moore WS, Voeks JH, Hopkins LN, Cutlip DE, Cohen DJ, Popma JJ, Ferguson RD, Cohen SN, Blackshear JL, Silver FL, Mohr JP, Lal BK, Meschia JF. Stenting versus endarterectomy for treatment of carotid-artery stenosis. *N Engl J Med* 2010;**363**:11–23.

9. Ederle J, Bonati LH, Dobson J, Featherstone RL, Gaines PA, Beard JD, Venables GS, Markus HS, Clifton A, Sandercock P, Brown MM. Endovascular treatment with angioplasty or stenting versus endarterectomy in patients with carotid artery stenosis in the Carotid And Vertebral Artery Transluminal Angioplasty Study (CAVATAS): long-term follow-up of a randomised trial. *Lancet Neurol* 2009;**8**:898–907.

10. Gurm HS, Yadav JS, Fayad P, Katzen BT, Mishkel GJ, Bajwa TK, Ansel G, Strickman NE, Wang H, Cohen SA, Massaro JM, Cutlip DE. Long-term results of carotid stenting versus endarterectomy in high-risk patients. *N Engl J Med* 2008;**358**:1572–1579.

11. Eckstein HH, Ringleb P, Allenberg JR, Berger J, Fraedrich G, Hacke W, Hennerici M, Stingele R, Fiehler J, Zeumer H, Jansen O. Results of the Stent-Protected Angioplasty versus Carotid Endarterectomy (SPACE) study to treat symptomatic stenoses at 2 years: a multinational, prospective, randomised trial. *Lancet Neurol* 2008;**7**:893–902.

12. Mas JL, Trinquart L, Leys D, Albucher JF, Rousseau H, Viguier A, Bossavy JP, Denis B, Piquet P, Garnier P, Viader F, Touze E, Julia P, Giroud M, Krause D, Hosseini H, Becquemin JP, Hinzelin G, Houdart E, Henon H, Neau JP, Bracard S, Onnient Y, Padovani R, Chatellier G. Endarterectomy Versus Angioplasty in Patients with Symptomatic Severe Carotid Stenosis (EVA-3S) trial: results up to 4 years from a randomised, multicentre trial. *Lancet Neurol* 2008;**7**:885–892.

13. Bonati LH, Dobson J, Featherstone RL, Ederle J, van der Worp HB, de Borst GJ, Mali WPTM, Beard DJ, Cleveland T, Engelter ST, Lyrer PA, Ford GA, Dorman PJ, Brown MM. Long-term outcomes after stenting versus endarterectomy for treatment of symptomatic carotid stenosis: the International Carotid Stenting Study (ICSS) randomised trial. *Lancet* 2014. doi:10.1016/S0140-6736(14)61829-8.

14. Gray WA, Simonton CA, Verta P. Overview of the 2011 Food and Drug Administration Circulatory System Devices Panel meeting on the ACCULINK and ACCUNET Carotid Artery Stent System. *Circulation* 2012;**125**:2256–2264.

15. Economopoulos KP, Sergentanis TN, Tsivgoulis G, Mariolis AD, Stefanadis C. Carotid artery stenting versus carotid endarterectomy: a comprehensive meta-analysis of short-term and long-term outcomes. *Stroke* 2011;**42**:687–692.

16. Reiff T, Eckstein HH, Amiri H, Hacke W, Ringleb PA. Modification of SPACE-2 study design. *Int J Stroke* 2014;**9**:E12–E13.

17. Halliday A, Bulbulia R, Gray W, Naughten A, den Hartog A, Delmestri A, Wallis C, le Conte S, Macdonald S. Status update and interim results from the Asymptomatic Carotid Surgery Trial-2 (ACST-2). *Eur J Vasc Endovasc Surg* 2013;**46**:510–518.

18. Bersin RM, Stabile E, Ansel GM, Clair DG, Cremonesi A, Hopkins LN, Nikas D, Reimers B, Sievert H, Rubino P. A meta-analysis of proximal occlusion device outcomes in carotid artery stenting. *Catheter Cardiovasc Interv* 2012;**80**:1072–1078.

19. Pinter L, Ribo M, Loh C, Lane B, Roberts T, Chou TM, Kolvenbach RR. Safety and feasibility of a novel transcervical access neuroprotection system for carotid artery stenting in the PROOF Study. *J Vasc Surg* 2011;**54**:1317–1323.

20. Bosiers M, de Donato G, Deloose K, Verbist J, Peeters P, Castriota F, Cremonesi A, Setacci C. Does free cell area influence the outcome in carotid artery stenting? *Eur J Vasc Endovasc Surg* 2007;**33**:135–141; discussion 142–133.

21. Bosiers M, Deloose K, Verbist J, Peeters P. Carotid artery stenting: which stent for which lesion? *Vascular* 2005;**13**:205–210.

22. Jim J, Rubin BG, Landis GS, Kenwood CT, Siami FS, Sicard GA. Society for Vascular Surgery Vascular Registry evaluation of stent cell design on carotid artery stenting outcomes. *J Vasc Surg* 2011;**54**:71–79.

23. Timaran CH, Rosero EB, Higuera A, Ilarraza A, Modrall JG, Clagett GP. Randomized clinical trial of open-cell vs closed-cell stents for carotid stenting and effects of stent design on cerebral embolization. *J Vasc Surg* 2011;**54**:1310–1316 e1311; discussion 1316.

24. de Donato G, Setacci F, Sirignano P, Galzerano G, Cappelli A, Setacci C. Optical coherence tomography after carotid stenting: rate of stent malapposition, plaque prolapse and fibrous cap rupture according to stent design. *Eur J Vasc Endovasc Surg* 2013;**45**:579–587.

25. Abizaid A, Chamie D. A journey into the carotid artery microenvironment in high resolution: challenging the stenosis-symptoms paradigm. *JACC Cardiovasc Interv* 2014;**7**:685–687.

26. Lorenzoni R, Roffi M. Transradial access for peripheral and cerebrovascular interventions. *J Invasive Cardiol* 2013;**25**:529–536.

27. Castriota F, Cremonesi A, Manetti R, Lamarra M, Noera G. Carotid stenting using radial artery access. *J Endovasc Surg* 1999;**6**:385–386.

28. Etxegoien N, Rhyne D, Kedev S, Sachar R, Mann T. The transradial approach for carotid artery stenting. *Catheter Cardiovasc Interv* 2012;**80**:1081–1087.

29. Ruzsa Z, Nemes B, Pinter L, Berta B, Toth K, Teleki B, Nardai S, Jambrik Z, Szabo G, Kolvenbach R, Huttl K, Merkely B. A randomised comparison of transradial and transfemoral approach for carotid artery stenting: RADCAR (RADial access for CARotid artery stenting) study. *EuroIntervention* 2014;**10**:381–391.

30. Roffi M, Cremonesi A, Setacci C. Proving the safety of carotid artery stenting: now or never. *J Endovasc Ther* 2012;**19**:757–760.

31. Gray WA, Yadav JS, Verta P, Scicli A, Fairman R, Wholey M, Hopkins LN, Atkinson R, Raabe R, Barnwell S, Green R. The CAPTURE registry: results of carotid stenting with embolic protection in the post approval setting. *Catheter Cardiovasc Interv* 2007;**69**:341–348.

32. Katzen BT, Criado FJ, Ramee SR, Massop DW, Hopkins LN, Donohoe D, Cohen SA, Mauri L. Carotid artery stenting with emboli protection surveillance study: thirty-day results of the CASES-PMS study. *Catheter Cardiovasc Interv* 2007;**70**:316–323.

33. Theiss W, Hermanek P, Mathias K, Bruckmann H, Dembski J, Hoffmann FJ, Kerner R, Leisch F, Mudra H, Schulte KL, Sievert H. Predictors of death and stroke after carotid angioplasty and stenting: a subgroup analysis of the Pro-CAS data. *Stroke* 2008;**39**:2325–2330.

34. Massop D, Dave R, Metzger C, Bachinsky W, Solis M, Shah R, Schultz G, Schreiber T, Ashchi M, Hibbard R. Stenting and angioplasty with protection in patients at high-risk for endarterectomy: SAPPHIRE Worldwide Registry first 2,001 patients. *Catheter Cardiovasc Interv* 2009;**73**:129–136.

35. Sidawy AN, Zwolak RM, White RA, Siami FS, Schermerhorn ML, Sicard GA. Risk-adjusted 30-day outcomes of carotid stenting and endarterectomy: results from the SVS Vascular Registry. *J Vasc Surg* 2009;**49**:71–79.

36. Gray WA, Chaturvedi S, Verta P. Thirty-day outcomes for carotid artery stenting in 6320 patients from 2 prospective, multicenter, high-surgical-risk registries. *Circ Cardiovasc Interv* 2009;**2**:159–166.

37. Stabile E, Salemme L, Sorropago G, Tesorio T, Nammas W, Miranda M, Popusoi G, Cioppa A, Ambrosini V, Cota L, Petroni G, Della Pietra G, Ausania A, Fontanelli A, Biamino G, Rubino P. Proximal endovascular occlusion for carotid artery stenting: results from a prospective registry of 1,300 patients. *J Am Coll Cardiol* 2010;**55**:1661–1667.

38. Pieniazek P, Tekieli L, Musialek P, Kablak Ziembicka A, Przewlocki T, Motyl R, Dzierwa K, Paluszek P, Hlawaty M, Zmudka K, Podolec P. Carotid artery stenting according to the tailored-CAS algorithm is associated with a low complication rate at 30 days: data from the TARGET-CAS study. *Kardiol Pol* 2012;**70**:378–386.

39. Hopkins LN, White CJ, Foster MT, Powell RJ, Zemel G, Diaz-Cartelle J. Carotid artery stenting and patient outcomes: the CABANA surveillance study. *Catheter Cardiovasc Interv* 2014;**84**:997–1004.