EuroIntervention
2024;20:e402-e404
published online e-edition April 2024
DOI: 10.4244/EIJ-E-24-00012

EDITORIAL

Improving carotid artery stenting to match carotid endarterectomy: a task accomplished

Piotr Musialek[1,2]*, MD, DPhil; Kosmas I. Paraskevas[3], MD, PhD; Gary S. Roubin[4], MD, PhD

**Corresponding author: Department of Cardiac & Vascular Diseases, Jagiellonian University, Stroke Thrombectomy-Capable Centre, St. John Paul II Hospital, ul. Pradnicka 80, 31-202, Krakow, Poland. E-mail: pmusialek@szpitaljp2.krakow.pl*

The authors' affiliations can be found at the end of this article.

Carotid artery stenting (CAS) was introduced 3 decades ago – in the absence (then) of dedicated stents and cerebral protection – as a treatment modality "to prevent strokes in thousands of patients, offering a number of potential advantages over surgical revascularisation"[1].

Carotid-related strokes are mechanistically linked to the thrombotic rupture or erosion of atherosclerotic plaque, resulting in cerebral embolism and/or carotid occlusion[2]. As pharmacotherapy, despite its progress, fails to universally guard against carotid-related stroke[1], surgical removal of plaque or mechanical plaque pacification – the objective of CAS – remain fundamental stroke prevention tools[2]. Multiple longitudinal studies in symptomatic and asymptomatic patients have convincingly demonstrated that CAS and carotid endarterectomy (CEA) are similarly effective in stroke prevention[2].

Despite the primary (powered) endpoint of the CREST Trial demonstrating the equivalence of CAS and CEA[2], CAS, employing a translesionally delivered filter and a single-layer metallic stent[2], had a relative "excess" of 30-day minor strokes – the vascular surgery community's key argument for the relative "inferiority" of CAS[3]. The 30-day "excess" strokes with 1st-generation CAS (≈40-80% of those occurring post-procedure)[2] are mechanistically linked to the intraluminal prolapse of atherothrombotic plaque material through single-layer stent cells[2,4]. Stent design innovation and improvements in intraprocedural cerebral protection evolved as two fundamental necessities for contemporary CAS, particularly in symptomatic and other increased-risk lesions[3].

Carotid stents with a protective micromesh layer ("mesh" stents) were developed to address the problem of plaque prolapse-related cerebral embolism during and after CAS[4]. Second-generation stents significantly reduce the incidence of embolic material in filters and filter load and profoundly reduce CAS-related cerebral embolic injury[2,5], translating – at least with some designs – into improved clinical outcomes[5-7]. In parallel, experimental imaging and clinical studies demonstrated the superiority of flow reversal/cessation cerebral protection in CAS over distal filters, in particular in increased-risk lesions[2]. A new paradigm[6] of competent CAS involves the routine use of antiembolic stents and a low threshold for proximal cerebral protection (vs filter) use[6].

With the progress in CAS technologies and their incorporation into routine practice, the time has come today to re-evaluate outcomes of CAS versus CEA using contemporary (rather than historic) data. In this issue of EuroIntervention, a consortium of vascular surgeons and interventionists provide a robust, real-life, matched analysis of current outcomes of CAS versus CEA[8]. From a prospective database of 1,110 patients, Bramucci and colleagues identified 269 distinct CEA-CAS treatment pairs[8]. The propensity-matched cohort (n=538) was well balanced for clinical (including symptomatic status) and lesion characteristics, except for more severely calcified lesions in patients who underwent CAS[8]. With 2nd-generation carotid stent (double metallic layer, RoadSaver/Casper [Terumo], or PET micronet-covered, CGuard [InspireMD]) use in nearly every second patient undergoing CAS and a dominant use of proximal cerebral protection[8], 30-day adverse clinical event rates were low and not statistically different between CAS and CEA patients[8]. Hospital stay was overall shorter with CAS[8]. Study limitations include the lack of power for separate comparisons in symptomatic patients (only 15% of the study population) and lack of correction for any potential unmeasured variables[8].

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These findings are consistent with other accumulating evidence. A large-scale (68,422 patients in 112 studies),

meta-analytic comparison of clinical outcomes with 2nd- versus 1st-generation carotid stents shows an overall significant improvement in short- and long-term clinical outcomes with antiembolic stent use[7]. Second-generation stent types, however, differ significantly in their individual outcomes (absence of a "mesh stent" class effect)[7], likely arising from marked differences in "mesh" stent designs[2,7]. A meta-analytic integration of 2nd-generation carotid stent outcomes versus contemporary CEA, using data from 103,642 patients, not only found (overall) "mesh" stent clinical outcomes to be not different from CEA at 30 days and 12 months[9], but also, the performance of some antiembolic stent designs was significantly superior to CEA[9]. Indeed, a comparison of outcomes in the most recent, rigorously monitored U.S. Food and Drug Administration (FDA) trial of the micronet-covered stent for CAS using proximal or distal protection (C-GUARDIANS, operators of different specialties involving vascular surgery, ClinicalTrials.gov: NCT04900844; presented at VIVA 2023) with contemporary CEA results in the ACST-2 trial[2] indicates, despite a clear population characteristics bias against C-GUARDIANS (24.3% symptomatic patients and 41.2% diabetics in C-GUARDIANS vs 0% symptomatic patients and 30.0% diabetics in ACST-2), a reduction by more than half in the 30-day stroke rate and a reduction in the 30-day composite endpoint of death/stroke/myocardial infarction by two-thirds for transfemoral CAS with the micronet-covered stent (0.95% vs 2.4% and 0.95% vs 3.2%; p=0.029, respectively).

Today, there is significant concern, due to the challenges of scope and logistics, as to whether large-scale randomised studies of 2nd-generation stents compared with CEA can be effectively executed. First, clinical event rates of ~0.5-1.5%[7] would require enrolment and monitoring of patient cohorts far larger than those in CREST, ACT-1 or ACST-2. Second, the magnitude of patients gravitating towards less-invasive treatment (surgical "operation" vs percutaneous "procedure") forced the stopping of, for instance, the SPACE-2 trial, far before it met its target (only 513/3,272 enrolled; i.e., 16% of the original target), leaving the investigation inconclusive. Objectively measured periprocedural cerebral embolism – an accepted index of revascularisation-related stroke risk[2,5] – and integration of data from multiple cohort studies[7,9], which optimally should involve external monitoring and independent adjudication of clinical events[6], are used increasingly to guide clinical decision-making. This is consistent with evidence-based medicine principles: "if no randomised trial powered for the clinical outcome of interest has been carried out with respect to the choice of the mode of treatment, the next best external evidence should be followed"[10].

There are no scientific reasons today that the carotid artery should remain the last artery in the body "reserved" for preferential open surgery. Today, physicians, and more importantly patients[2], do have a choice of treatment mode. Some specific lesion subtypes, such as those massively calcified, will remain, at least presently (and to some), an indication for CEA rather than CAS, serving as complementary modalities. However, endovascular techniques are progressing very rapidly (note, for instance, intravascular lithotripsy). Operator skills, including working knowledge of proximal and distal protection and the ability to choose optimal procedural strategy, play (and will continue to play) an important role in minimising the risk of complications and achieving optimal outcomes. Today, thrombus-containing and symptomatic carotid lesions can be safely and effectively treated with an antiembolic stent, resulting in the absence of plaque protrusion on routine endovascular imaging and optimal clinical outcomes (ClinicalTrials.gov: NCT04234854; CGuard-OPTIMA presented at TCT 2022 as Featured Research, 30-day ipsilateral stroke/death/MI rate of 0.57%).

Contemporary evidence shows excellent outcomes of competent CAS, employing a growing adoption of proximal protection and antiembolic stent(s). Competent CAS (transfemoral, transradial, and transcarotid) is here not only to stay, but its use will expand beyond its current role in elective patients – for instance, to address largely unmet needs in carotid-related stroke acute treatment[2]. The "case of CAS" is not dissimilar from treatments that are today, largely or increasingly endovascular, including abdominal aortic aneurysm treatment, lower-limb atherosclerotic occlusive disease management, and cardiac valve repair or implantation. They all represent progress in cardiovascular medicine!

Authors' affiliations

1. Department of Cardiac & Vascular Diseases, Jagiellonian University, Krakow, Poland; 2. St. John Paul II Hospital, Krakow, Poland; 3. Department of Vascular Surgery, Red Cross Hospital, Athens, Greece; 4. CREST2 Trial Interventional Management Committee, Jackson, WY, USA

Acknowledgements

We thank Dr Alberto Cremonesi for having introduced the concept of "competent CAS" that incorporates the cognitive and technical skills required to produce excellent outcomes.

Conflict of interest statement

P. Musialek has proctored and/or consulted for Abbott Vascular, Balton, Gore, InspireMD, and Medtronic.; he is the Polish Cardiac Society Board Representative for Stroke and Vascular Interventions; he serves as Global Co-PI in C-GUARDIANS FDA IDE Trial; and serves on the ESC Stroke Council Scientific Documents Task Force. G. Roubin has received honoraria from Cook Inc; owns equity in InspireMD; and serves as Chair of CREST2 Trial Interventional Management Committee. K. Paraskevas declares no conflicting interests.

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