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Editorial

Should we climb the next rung in the cerebral protection ladder?

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Power is no blessing in itself, except when it is used to protect the innocent. Jonathan Swift

Protected carotid artery stenting (CAS) has come a long way since the pioneering experience of Karl Mathias describing in 1981 the first case of carotid angioplasty. The main pillars for the success of CAS are indeed embolic protection and stent implantation itself, notwithstanding the important role of patient and lesion selection, adjunctive imaging, result optimization, and ancillary antithrombotic therapy [1,2]. Portraiting the current status of CAS as a half-full glass, we must recognize that asymptomatic carotid disease in general and complex lesions in symptomatic patients in particular remain areas where the risk-benefit balance of this intervention is still delicate [1]. Accordingly, ongoing research on improving the safety and effectiveness of CAS is warranted.

Quite expectedly, stents remain the cornerstone of endovascular carotid interventions. From the initial experiences with closed-cell devices, several new-generation stents have been developed, including open-cell devices or hybrid devices encompassing both open and closed cells [3,4]. In particular, open-cell devices boast increased flexibility in comparison to closed-cell devices, which however feature greater plaque coverage and support. Despite such interesting features, clear data in favor of closed- or open-cell devices are lacking, and individualized decision making is best applied for their choice in everyday's practice. Most recently, another round of innovation in the context of carotid stents has been the introduction of mesh-covered stents [3,4]. These devices consist of the combination of a traditional open-cell nitinol stent with an adjunctive mesh membrane capable of dramatically reducing eventual cell area. Accordingly, their use should purportedly improve acute outcomes of CAS by reducing acute thromboembolic events.

Despite favorable results from single arm registries or non-randomized trials, uncertainty persists on the comparative effectiveness of these novel-generation carotid stents. This issue of the Journal finally reports the first randomized trial comparing a mesh carotid stent versus a standard closed-cell device: the Peri-Procedural brain lesions Prevention in CAS (3PCAS) trial [5]. Specifically, Capoccia and colleagues randomized between 2015 and 2016 58 asymptomatic patients scheduled for CAS to receive CGuard Embolic Protection System (InspireMD, Tel Aviv, Israel) versus Wallstent (Boston Scientific, Natick, MA, USA), with a primary endpoint of 72-hour clinically significant neurologic events (neurologic death, stroke, transient ischemic attack or permanent focal retinal artery occlusion) or subclinical neurologic events detected by serial diffusion weighted-magnetic resonance imaging (DW-MRI). Additional outcomes included neurologic and cognitive scores, and blood levels of the β-subunit of protein S100 and neuron-specific enolase. Despite 100% technical success, no difference was found in the primary endpoint, with 1 (3%) stroke and 8 (28%) subclinical events (thus totalling 9 [31%]) in the CGuard Embolic Protection System group and 7 (24%) subclinical events (without any clinically relevant outcome) in the Wallstent group ($p > 0.05$). Notably, no significant difference in neurologic and cognitive scores or biomarkers was found between the two groups. Most importantly, out of the total of 15 subclinical events detected by DW-MRI, as many as 7 (47%) were not solely ipsilateral. Intriguingly, changes in neurologic and cognitive scores and biomarker levels correlated with DW-MRI findings, despite the fact that the clinical significance of these latter events remains debated [6].

The 3PCAS stands out as a bold and pioneering effort at comparing novel devices for CAS. The attentive collection of clinical, subclinical and surrogate outcomes provide a multidimensional perspective to the comparative effectiveness of CGuard Embolic Protection System versus Wallstent which at least partly overcomes the limitation inherent to any randomized trial conducted in a single center and on a

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small sample of patients. The main implications of this trial are twofold: first, the fact that almost half of neurologic events (clinical or subclinical) were not solely ipsilateral highlights the multifactorial etiology of periprocedural adverse events during CAS and the need for focusing not only on device features to improve CAS outcomes; second, despite the limited power of this trial, there is no evidence to date clearly favoring mesh devices for CAS.

Overall, we find support from the results reported by the 3PCAS investigators to our own strategy for CAS, which is based on a tailored approach for device selection, which encompasses, lesion, patient, operator, and center features [6–10]. Indeed, no single device is likely better than all others in all cases, but probably some devices are best used very selectively, notwithstanding that in complex anatomies an open-cell stent may be superior to other devices, whereas a hybrid one can offer in other cases the best of both worlds [8–10]. Moreover, operator experience and confidence is crucial, as favorable results can be achieved even with a single stent/embolic protection device combination, as long as devices are used smartly and proficiently. Finally, it could also be true that we have become veritable victims of our own successes with protected CAS, such that adverse events are so uncommon that any device comparison or improvement could be infeasible or futile unless thousands of patients are randomized [10].

In conclusion, whilst the armamentarium of endovascular specialists devoted to protected CAS continues to expand, an individualized approach to device choice is most likely to benefit patients. Whether new-generation mesh stent will be able to improve further the results of CAS remains uncertain, but clearly the evidence base remains to date in the clinical equipoise region.

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Conflicts of interest

Prof. Biondi-Zoccai has consulted for Abbott Vascular and Bayer.

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