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EDITORIAL COMMENT

Blurred Lines

Assessing the Stent as Provocateur in Carotid Intervention*

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Carotid artery stenting with embolic protection (CAS) has been extensively studied over the past 2 decades, largely in comparison with the established standard of care, carotid endarterectomy. We have witnessed double-digit rates of 30-day death and stroke in patients at high surgical risk in the initial CAS experience (1) progress to rates that are statistically indistinguishable from standard-risk carotid endarterectomy in 2 large trials (2,3). This is likely due to improvements in patient selection, operator technique, pharmacology, and technology, all the result of careful analysis of the continuously emerging data. Nevertheless, despite these rapid advances, there continue to be nagging excesses, albeit small, in minor stroke (2,3) and in the frequency of asymptomatic abnormalities on diffusion-weighted magnetic resonance imaging (DW-MRI) when transfemoral CAS is compared with carotid endarterectomy (4), the 2 observations almost certainly being linked. In addition, the majority of strokes that occur in CAS are not noted intraprocedurally but rather in the following 24 to 48 h, raising questions as to whether they originate from the stent itself after the removal of embolic protection device (5).

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In this issue of *JACC: Cardiovascular Interventions*, Kotsugi et al. (6) set out to better understand the stent as a potential provocateur of complications. From a roughly 10-year retrospective Japanese multicenter consecutive experience of CAS in 354 (mostly male) patients, intravascular ultrasound (IVUS) was performed in nearly all, and magnetic resonance angiography before and DW-MRI (on either 1.5- or 3-T scanners) within 48 h in most. Although in this study the interventional techniques used were modern (e.g., a minimalist approach to post-stent balloon dilation) and standardized, there were multiple embolic protection devices and stents (left to the discretion of the operators) and variable antiplatelet (the use of cilostazol being more common in Japan) and statin regimens. Rather surprisingly, the investigators found that the rates of new DW-MRI findings in plaques defined as stable and unstable were similar. But new DW-MRI findings were more common when open-cell stents were used and in cases in which plaque protrusion (PP; defined as seen on both IVUS and angiography) was evident. Although PP was noted in only a small number of cases (2.6%), it was highly associated with ischemic stroke in the majority within 24 h. In 2 patients with late symptoms, PP was seen only days later and not during the procedure. PP was seen exclusively in cases with open-cell stents and predominantly with unstable plaque.

Although the investigators are to be congratulated on their work here in the largest assessment of some of the proximate causes of stroke in CAS to date, there are several caveats about the study beyond its retrospective nature that may affect its ultimate interpretation. First, the sensitivity of PP is likely to be much higher with IVUS and much less so with angiography. The investigators pre-defined PP as having to occur in both modalities, which cut by two-thirds the incidence of IVUS PP and which will clearly affect many of the subsequent associations and conclusions.

Second, IVUS, magnetic resonance angiography, and DW-MRI were not core laboratory controlled, and although some definitions were offered that might help standardize the assessments, these were not uniformly described across all modalities. The lack of a core laboratory likely also limited a more nuanced appraisal of DW-MRI findings, such as lesion volumes, and not just lesion number.

Third, it does not appear that DW-MRI was routinely performed before and after the procedure, so that

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lesions described may have antedated the procedure, thus potentially limiting their association with procedural events, devices, or other imaging findings.

Fourth, the assessors were not blinded, and unintentional bias in image interpretation may be present given their knowledge of the clinical or other imaging outcomes.

Fifth, stent use was not programmatically directed by the protocol, so the operators may have had a predisposition to use certain stents in specific anatomies (e.g., open-cell stents in angulated or tortuous anatomy), which are highly likely to affect the presence or absence of PP.

Sixth, routine independent neurological assessment of the clinical outcomes was not performed, resulting in a lower the stroke event rate (7,8), and could affect the analysis of predictors.

Seventh, the investigators, wearing their clinician hats, understandably treated plaque prolapse with second stent placement in approximately one-half the PP cases, thus potentially changing the clinical as well as imaging outcomes.

And last, the distinction between PP and thrombus by ultrasound is difficult at best, and digital subtraction angiographic confirmation not likely to add further clarity, with optical coherence tomography being much more definitive. Acute stent thrombosis in CAS, although unusual, occurs presumably as a result of iatrogenic plaque rupture in the process of lesion dilation and stent placement, with exposure of the necrotic lipid core to the bloodstream and an exuberant activation and aggregation of platelets. Such thrombosis is not likely affected by stent type but will be associated with unstable plaque. This type of biological dynamism may explain the 2 cases of presumed late PP (mechanistically otherwise difficult to understand) that were associated with symptoms; they may in fact been subacute thrombosis.

With these provisos in mind, what can be reasonably concluded from the data presented? It appears true that in well-performed CAS such as this (i.e., in which stroke related to operator error is limited), PP findings (true PP or thrombosis) occur infrequently but are associated with clinical events and unstable plaques, though it would have been helpful to have an analysis of clinical events and magnetic resonance imaging on the IVUS-only PP group as well. But absent routine neurological evaluation, the presence of subtler stroke events not detected in this study could further dilute this association. It also seems that the use of open-cell stents is likely to be associated with PP findings, though possibly not as strongly as noted here given the aforementioned selection bias, and therefore the investigators' recommendations on closed-cell stents or cell size are not fully supported by these data.

However, when the findings from this study are paired with the emerging data on apparent reductions in both PP on optical coherence tomography and new DW-MRI abnormalities with the use of mesh-covered stents (9), the case begins to grow for such improvements in stent design. Toward that end, a U.S. trial evaluating a mesh-covered open-cell stent in patients at high surgical risk has already completed enrollment (SCAFFOLD, WL Gore), and 2 other similar trials using different mesh technologies are imminent. Inherent in these technologies is the hope is that the stent can be transformed from a potential offender into a reliable protector during CAS. This advance, once proved, along with others such as direct carotid access for flow reversal and double-filtration strategies, will thereby continue to chisel away at the causes of stroke in CAS to patients' benefit.

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