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EDITORIAL COMMENT

Paclitaxel-Eluting Stents and Aneurysm Formation, A Worrisome Association*

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Even in mid-2018, there remain a few areas in vascular medicine with substantial discrepancies between guideline recommendations and routine clinical practice. Superficial femoral artery (SFA) management in symptomatic patients seems not to belong to this group. The recently published 2017 European Society of Cardiology/European Society for Vascular Surgery guidelines on peripheral arterial diseases suggest surgery as the first therapeutic option (Class I, Level of Evidence: B) in case of long lesions, whereas endovascular treatment should be preferred in case of <25-cm lesions (Class I, Level of Evidence: C). In this case, bare-metal stent implantation is given a Class IIa indication and drug-coated balloon (DCB) or drug-eluting stent (DES) a Class IIb indication. However, if the guidelines are examined closely, in the chapter "Gaps in Evidence," it is stated that "the role of drug-eluting stents and drug-coated balloons in superficial femoral artery and below-the-popliteal artery interventions has to be established" (1).

There is an acknowledged lack of adequately designed and powered clinical trials in this setting, but the gap between the epidemiological burden of SFA lesions and the investments made in their management must be underlined. Bearing this in mind, it must be recognized that small but well-designed studies may contribute to the topic.

The study by Bisdas et al. (2) published in this issue of *JACC: Cardiovascular Interventions* moves in this direction. Sixty-two patients with claudication or critical limb ischemia (48%) affected by relatively long SFA lesions, 79% of which were total occlusions, were treated with the fluoropolymer-based paclitaxel-eluting stent Eluvia (Boston Scientific, Natick, Massachusetts), which releases the drug over a period of 12 months. Both the primary study endpoint (primary patency) and freedom from target lesion revascularization were recorded in 87% of the patients after 12 months. The investigators concluded that this platform was associated with encouraging outcomes at 12 months.

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Although this was a single-center, retrospective study, and no comparison group was available (the question here is, What should be compared?), the investigators should be congratulated for the high level of technical skill that is evident in reading the paper and for the decision to include only patients with suboptimal angiographic results after simple balloon angioplasty. Moreover, the median follow-up period of 13.3 months (interquartile range: 12.0 to 16.5 months) seems adequate for this primary report, although longer follow-up should be carried out.

However, some limitations of this study should be mentioned. First of all, the lack of a core laboratory and of uniform methodology for clinical and instrumental assessment during follow-up does not allow a clear conclusion to be drawn regarding the performance of this device. Specifically, quantitative angiographic analysis would warrant data in terms of the performance and safety of a relatively new DES and would have been ethically and economically justified by the complexity of the patients and lesions treated and the small population enrolled.

Specific mention should be made of the device itself. After the removal from the market of the first-generation coronary DES, Taxus (Boston Scientific), manufacturers have invested in devices eluting limus drugs, which currently represent 100% of the coronary stents available in catheterization

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laboratories. One of the reasons for the decision to abandon the combination of paclitaxel plus stent was the relatively high rate of late adverse events, including thrombotic risk (3,4). Moreover, the addition of a bare-metal stent after DCB use has also been associated with impaired angiographic results and an increased risk for late thrombotic events (5).

One may wonder if this information can be translated into the peripheral field. The study by Bisdas et al. (2) may shed some light on this important argument. Despite the unstandardized follow-up methodology, and the absence of angiographic controls, a worrisome 8% of the patients developed aneurysms, which were detected on duplex sonography. The investigators hypothesize an increase in T-cell infiltration, positive remodeling, hypersensitivity reactions, and arteritis as possible explanations for this discovery, but the association between paclitaxel-eluting stent placement and aneurysm formation is not new (6,7). Yusuke et al. (8) analyzed 249 cross sections of the Zilver PTX DES using optical coherence tomography 12 months after implantation and discovered a high rate of extrastent new lumen (31%) and peristrut low-intensity areas (44%), showing probable delayed vascular healing and peristent inflammation.

Bisdas et al. (2) suggest some approaches to reduce the risk for thrombotic events related to new aneurysms or incomplete reendothelialization with DES, including prolongation of dual-antiplatelet treatment and strict post-operative surveillance, with inherent increased bleeding risk and higher costs. The point is, if safer and better performing devices are available, why should we proceed with a technology that has been associated with warning signs? DCBs for SFA lesions have been associated with short- and long-term good outcomes, with an excellent safety profile (9–11). In case of restenosis, often focal, this can be easily fixed with new angioplasty, with either a DCB or a stent. In contrast, managing iatrogenic aneurysms is not easy, because they are prone to thrombosis and a high rate of reocclusions (20% in this series), and usually they are not reversible (9).

Endovascular treatment of "short" (i.e., <25-cm) SFA lesions is still debatable and the subject of current and future research. Moreover, the peripheral field is not yet mature enough to warrant the same level of scientific evidence for coronary artery management, and local practice by experienced operators is often the leading mode of treatment. The present study brings an important piece to the puzzle of how to treat complex SFA lesions, although my conclusions are different from the ones outlined in this paper. Paclitaxel-eluting stents should have a limited role in this setting; in fact, it is undesirable to transform patients in stable condition into patients requiring closer surveillance and at higher thrombotic and bleeding risk because we have chosen one device instead of another. Complex SFA lesions, including total occlusions, should be treated with either surgery or endovascular treatment with older or newer therapeutic options with adequate safety profiles.

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