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Editorial

Nitric-oxide Coated Bioactive Titanium Stents: Safer and More Effective Than Second-generation Drug-eluting Stents?

Stent bioactivo de titanio y óxido nítrico, ¿más seguro y eficaz que los *stents* farmacoactivos de segunda generación?

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Polymer-coated drug-eluting stents (DESs) have become the treatment of choice in most patients undergoing percutaneous coronary interventions.[1] Although these stents are effective in the sense that they reduce the restenosis rate and the need for repeat intervention by 70% compared with bare-metal stents, concerns have been raised about a series of risks closely related to the metal mesh of the stent and the polymer coating.[2] Thus, in recent years, interest has been renewed in alternative strategies and technologies to promote repair mechanisms after stent implantation. In general, a DES consists of a platform (made from different alloys) that acts as a scaffold for the vessel, a polymer coating (hardwearing and bioabsorbable) that includes certain copolymers to confer the desired degree of thromboresistance and hemocompatibility on the stent, and the drug which is released to provide the antiproliferative properties of the device. Guided by the above general considerations, a nitric-oxide coated bioactive stent (NO-BAS, Titan-2, Hexacath; Paris, France) was developed. Although not a DES, NO-BASs have been presented as a safe and feasible alternative to bare-metal stents.[3]

Articles by López-Mínguez et al[4] and Tuomainen et al[5] published in *Revista Española de Cardiología* describe the results of 3 studies and a meta-analysis[4–7] that assessed the efficacy and safety of NO-BASs compared with DESs in 2 different clinical settings: acute coronary syndrome with ST-segment elevation (STEACS) (TITAX-AMI[6] and BASE-ACS[7]) and diabetes mellitus (TITANIC XV[4]). Tuomainen et al[5] report a pooled analysis of patients with STEACS from the TITAX-AMI and BASE-ACS studies. Specifically, in the TITAX-AMI study, the safety and efficacy of NO-BASs were compared with those of first-generation paclitaxel DESs (TAXUS Liberte, Boston Scientific; Natick, Massachusetts, United States).[6] In the BASE–ACS and TITANIC XV trials, in contrast, NO-BASs were compared with second-generation DESs comprising a cobalt-chromium scaffold that elutes everolimus from the coating (XIENCE V, Abbott Vascular; Santa Clara, California, United States). In general, the 3 studies confirm the safety of NO-BASs. Rates of thrombosis and myocardial infarction were very low during follow-up, which lasted 2 years in the STEACS studies and 12 months in the study of patients with diabetes.

Assessment of the efficacy of NO-BASs compared with that of DESs, however, merits further discussion. In the TITAX-AMI study, the superiority of NO-BASs compared with TAXUS DESs was demonstrated in terms of lower cardiac mortality, reinfarction, and definite stent thrombosis at 2 years.[6] This study served to confirm the long-term risks of first-generation DESs.[2] These DESs are thus no longer on the market and have been superseded by new safer and more effective devices. The results of NO-BASs in comparison with second-generation everolimus DESs are more open to debate. In the BASE-ACS study, NO-BASs was not inferior to XIENCE DESs in terms of the incidence of major adverse cardiac events.[7] The reinfarction rate was lower with NO-BASs (2.2% vs 5.9%; $P = .007$), a finding that was further supported by the pooled analysis presented in *Revista Española de Cardiología*.[5] However, a number of caveats should be considered before accepting these results.

First, in the BASE-ACS study, the number of patients with ST-elevation myocardial infarction treated with second-generation DESs (XIENCE) was very small (n = 159) and in the pooled analysis, the results were combined with those of 97 patients treated with first-generation DESs (TAXUS). We are therefore facing a problem, on the one hand, of confounding variables (first-generation DESs combined with second-generation DESs) and, on the other, of a lack of statistical power with a high risk of a beta error (results occurring by chance). Moreover, these results should be interpreted alongside the results of the EXAMINATION study[8] and a recently published network meta-analysis of patients with ST-elevation myocardial infarction.[9] In the EXAMINATION study, more than 1500 patients with STEACS were randomly assigned to receive bare-metal stents or DESs (XIENCE). Although the patient-oriented outcome (combined endpoint of all-cause death, any recurrent myocardial infarction, and any revascularization) was not reduced at 1 year, the rate of revascularization of the culprit vessel and, more interestingly, the rate of stent thrombosis were significantly lower among patients in the DES arm. Furthermore, the overall infarction recurrence rate in the DES group was only 1.1%. As published recently, these outcomes were maintained after 2 years of follow-up.[10] Likewise, a network meta-analysis of 22 randomized studies with 12 453 patients concluded that DESs

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(everolimus-eluting with cobalt-chromium scaffold) were associated with significantly lower rates of cardiac death or myocardial infarction and stent thrombosis than bare-metal stents.[9] The differences were already apparent after 30 days and were maintained throughout 2 years of follow-up. Moreover, these second-generation DESs showed a lower rate of stent thrombosis than the first-generation paclitaxel DESs. Recently, a comparative analysis of 117 762 patient-years showed that the safest stent (probability > 86%) is one with an everolimus-eluting cobalt-chromium scaffold compared with other DESs and bare-metal stents.[11] In view of these findings, the high rates of recurrent infarction and stent thrombosis reported in the BASE-ACS study (5.9% and 2.7%, respectively) with the use of everolimus DESs are striking. In addition to the aforementioned issue of small sample size, each trial uses a different definition of myocardial infarction. Thus, while the EXAMINATION trial used the extended definition of the World Health Organization (WHO),[12] the BASE-ACS study used a previous WHO classification that probably tended to overestimate the rate of myocardial infarction, particularly in patients with STEACS. Another aspect to bear in mind is that the myocardial infarction rates in these 2 studies diverged soon after stent placement. The authors of the BASE-ACS study reported several factors related to the appearance of definite stent thrombosis.[7] First, the use of bivalirudin as the only anticoagulant was associated with stent thrombosis in up to 30% of events in the DES arm, thereby confirming previous findings in the HORIZONS-AMI study regarding the increase in stent thrombosis with bivalirudin in monotherapy.[13] In addition, a series of technical issues (distal dissection, underexpanded stents, etc) were also associated with the development of thrombosis in DESs. Thus, in a small cohort of patients, firm conclusions about the safety or efficacy of one type of stent compared with another cannot be made when technical issues or suboptimal pharmacological therapy are present in a substantial percentage of the patients.

Finally, the TITANIC XV study demonstrated that stents with an everolimus-eluting cobalt-chromium scaffold were superior to NO-BASs in patients with diabetes after 1 year of follow-up in terms of major cardiac events and clinical restenosis and angiography.[4] This benefit was greater in patients with insulin-dependent diabetes. The NO-BAS restenosis rates were similar to those of other bare-metal stents in randomized studies in patients with similar characteristics[14] (Figure). Diabetes mellitus is probably one of the situations in which DESs still have the most important role to play in view of their greater ability to inhibit neointimal proliferation after damage caused during revascularization.

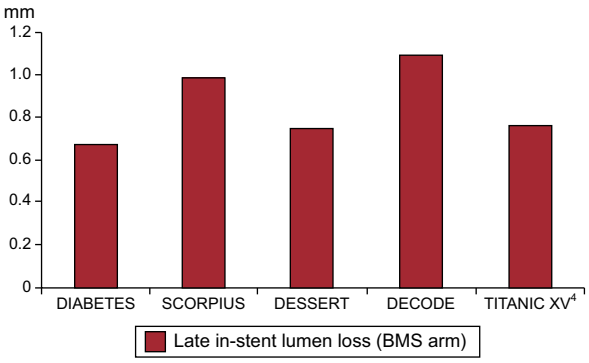

Figure. Late in-stent lumen loss in groups treated with bare-metal stents in randomized trials in patients with diabetes. BMS, bare-metal stent; DECODE, A Randomized Study With the Sirolimus-eluting BX-Velocity™ Balloon Expandable Stent in the Treatment of Diabetic Patients With Native Coronary Artery Lesions; DESSERT, The Diabetes Drug Eluting Sirolimus Stent Experience in Restenosis Trial; DIABETES, The Diabetes and Sirolimus-eluting Stent Trial; SCORPIUS, German Multicenter Randomized Single Blind Study of the CYPHER Sirolimus-eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions.

When thrombotic lesions are associated with STEACS, the everolimus-eluting stent is surely the current standard of care. However, one may wonder whether a metal mesh is really necessary for the treatment of normally soft lesions with little underlying atherosclerotic content but with a large thrombotic component. Fully bioresorbable vascular devices would seem to be a promising alternative, as they allow the vasomotor response and pulsatility of the coronary artery segment to be restored after reabsorption (at approximately 2 years) once the vulnerable or ruptured plaque has been sealed.[15–17] The ongoing ABSORB STEMI: the TROFI II Study, which compares the bioresorbable vascular device with the everolimus DES, should shed some light on the percutaneous treatment of this type of lesion.[18]

CONFLICTS OF INTEREST

None declared.

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