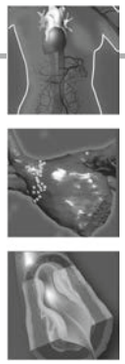

Bioactive stents for percutaneous coronary intervention: a new forerunner on the track

"Interestingly, some prospective trials showed an even better outcome with Titan2-BAS as compared with paclitaxel-eluting stents in high-risk patients..."

KEYWORDS: acute coronary syndrome ■ bioactive stents ■ clopidogrel ■ drug-eluting stents ■ in-stent restenosis ■ stent thrombosis ■ titanium

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Coronary artery stents were first introduced in the 1990s. Since then, in-stent restenosis has always been the 'Achilles' heel' of this advanced therapeutic technology, resulting in repeat target vessel revascularization (TVR) with increased total costs [1]. A major breakthrough coinciding with the birth of the third millennium was the invention of drug-eluting stents (DES). As a matter of fact, the arrival of DES has clearly revolutionized our practice of coronary intervention, resulting in a dramatic reduction of restenosis rates by one-half to two-thirds at 5 years follow-up, amounting to approximately 10% need for TVR following DES at long-term [2,3]. As such, following US FDA approval of first-generation DES in 2003, they were widely perceived as the long-waited solution to this classic problem of everyday practice. Healthcare systems, therefore, took an unprecedented initiative of assigning impressively high reimbursements to account for their extraordinary cost.

By the fall of 2006, alarming reports raised concerns about higher rates of very late (after 1 year) stent thrombosis associated with DES as compared with bare-metal stents. The media sounded the alarm, and a psychological turning point was heralded for the newly marketed 'smart' stent. Soon, an FDA-assigned expert panel announced in December 2006 that there was an evidence for a small, though insignificant, increase in stent thrombosis events following DES [4]. Evidence was far from clear and intuitively, further evidence was still needed, especially given the rare nature of the event that made all the available reports statistically underpowered. Nevertheless, from this point on, very late stent thrombosis has turned out to be the 'Sword of Damocles' of DES.

A late-breaking milestone of development was the introduction of a novel bioactive stent (BAS). The safety of titanium-nitride-oxide-coated BAS (Titan2, Hexacath, Paris, France) has been established in several reports from real-life unselected populations [5,6]. Interestingly, some prospective trials showed an even better outcome with Titan2-BAS as compared with paclitaxel-eluting stents in high-risk patients with complex (type B and C) coronary lesions [7], and in patients presenting with acute myocardial infarction [8].

Titan2-BAS

Titan2-BAS is a laser-cut slotted tube made of medical-grade 316L stainless steel coated with a thin atomic layer of titanium-nitride-oxide, which completely prevents discharge of nickel, chromium and molybdenum ions. The coating process is performed by plasma enhanced vapor deposition of titanium in a prespecified gas mixture of nitrogen and oxygen in a vacuum chamber. Chemical-elementary analysis confirmed the presence of nitride-oxide particles on the surface of the titanium coating. *In vitro* examinations have shown that titanium oxides were able to inhibit platelet aggregation and fibrin growth [9]. In addition, a preclinical study in a porcine restenosis model demonstrated an almost 50% reduction of neointimal hyperplasia at 6 weeks follow-up, as compared with an uncoated 316L stainless steel stent of otherwise identical design. Furthermore, the titanium-nitride-oxide-coated stent significantly reduced platelet adhesion and fibrinogen binding in that porcine model [10]. Amazingly, the antiproliferative effect obtained with titanium-nitride-oxide-coated stents was comparable with that reported by Suzuki *et al.* for sirolimus-eluting stents in pigs [11]. Thereafter, the achievement of the 'newborn' stent was confirmed in a small-scale multicenter randomized clinical trial against stainless steel stents [12].

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Percutaneous coronary intervention in acute coronary syndrome

One of the most challenging realms in interventional cardiology is emergency revascularization in the setting of an acute coronary syndrome (ACS). The presence of thrombus, the predilection for late stent malapposition, resistance to antiplatelet agents and the proinflammatory state would all contribute to a landscape hostile for the 'foreign device' to be deployed. Although randomized clinical trials demonstrated that the use of DES in patients with acute myocardial infarction was associated with no increased risk of stent thrombosis, reinfarction or overall mortality [13,14], registry data indicated that the early benefits of reduced TVR rates were diminished during long-term follow-up such that, total adverse cardiac events are similar between DES and bare-metal stents [15]. Although the newly introduced BAS have demonstrated a promising outcome in patients with ACS in a randomized comparison with a first-generation DES [8], its performance has yet to be proven in a well-designed randomized controlled trial, tested against a new-generation DES.

> "*The late-breaking prospective randomized BASE-ACS trial comparing Titan2-BAS with an EES in the setting of ACS demonstrated non-inferiority of the former in reducing the primary end point of major adverse cardiac events...*"

In this context, the presentation of the BASE-ACS trial during the late-breaking clinical-trials session, EuroPCR 2011, has been most timely [16]. The study randomized 827 patients with ACS to either a Titan2-BAS or an everolimus-eluting stent (EES; Xience-V™). Dual antiplatelet therapy was recommended for 6 months in both groups and ultimately received for 9 months in the Titan2-BAS group and 10.5 months in the EES group. At 12 months, major adverse cardiac events were similar between groups, at 9.6% for the BAS and 9.0% for the EES, a difference that easily met the predefined criteria for non-inferiority. When individual components were evaluated separately, rates of myocardial infarction were actually significantly different between the groups, favoring the BAS at 2.2% versus the EES at 5.9%, although the trial was not adequately powered to detect differences between secondary end points. Rates of stent thrombosis were low in both groups. "This is definitely going to shake the tree," was the comment by William Wijns (Aalst, Belgium), who moderated the morning press conference, appropriately alluding to the fact that larger trials with longer-term follow-up are needed for the interventional cardiology community to eventually vote for this new candidate.

Toxicity of the drug and polymer along with subsequent incomplete stent strut coverage has been associated with pathological vascular responses of DES with increased risk of late stent thrombosis [17,18]. The BASE-OCT, a substudy of the BASE-ACS trial has demonstrated a better vascular healing with the use of a BAS compared with the EES [101]. In this substudy, optical coherence tomography was performed at 9 months follow-up to examine stent strut coverage and stent malapposition. Although a small number of patients was included, the BAS was associated with a significantly greater percentage of covered struts (99.3 vs 88.9%, respectively; $p < 0.001$), and a significantly less percentage of malapposed struts (0.2 vs 4.7%, respectively; $p < 0.001$). These findings reveal additional insights that may portend a low rate of late adverse events with BAS. Altogether, the bioactive properties of BAS observed in previous studies may represent promoted vessel healing seen also in the BASE-OCT study.

Conclusion

The safety of Titan2-BAS has been established in several reports from real-life unselected populations. The late-breaking prospective randomized BASE-ACS trial comparing Titan2-BAS with an EES in the setting of ACS demonstrated non-inferiority of the former in reducing the primary end point of major adverse cardiac events, yet, with a favorable safety profile. Long-term follow-up from the BASE-ACS trial may guide us to decide how we should 'base' our opinion on treating ACS patients in the near future.

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The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

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