Titanium-nitride-oxide-coated Titan-2 bioactive coronary stent: a new breakthrough in interventional cardiology

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The introduction of drug-eluting stents (DES) has revolutionized the field of interventional cardiology, since it has reduced the incidence of restenosis by 50% to 70%. However, recent worrisome data from registries and meta-analyses emphasized higher rates of late and very late stent thrombosis associated with DES. The recently introduced titanium-nitride-oxide-coated stent bioactive stent (Titan-2) was manufactured by a proprietary process to coat titanium-nitride-oxide on the surface of the stainless steel stent, based on a plasma technology using the nano-synthesis of gas and metal. This late-breaking stent has demonstrated an excellent biocompatibility, as reflected by lower rates of platelet aggregation and fibrin deposition, and better endothelialization. Preclinical and clinical trials and registries involving real-life unselected populations have shown a low rate of major adverse cardiac events at long-term follow-up. Restenosis rates were comparable with those of DES, with very rare stent thrombosis. Equally favorable results have been obtained in patients at high-risk of in-stent restenosis, such as diabetics and those with small coronary arteries. Results in patients presenting with acute coronary syndrome have been again comparable to those of DES, with tendency to lower rates of myocardial infarction and stent thrombosis. Comparisons with second generation drug-eluting stents have also been promising.

Key words: **Titanium - Stents - Coronary restenosis.**

Conflicts of interest.—None.

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It has come a long way since the first introduction of coronary stents for percutaneous coronary interventions (PCI) providing a safer approach of coronary angioplasty and endorsing a better short- and long-term outcome as compared to *solo* balloon angioplasty.[1, 2] Nevertheless, since their first-in-man use, in-stent restenosis (ISR) has always been the "Achilles heel" of this advanced technology, frequently resulting in repeat target vessel revascularization (TVR) with increased healthcare costs.[3, 4] ISR results from neointimal hyperplasia, an exaggerated healing response of the vessel wall to trauma resulting from the PCI procedure. ISR occurs at a frequency of 15% to 25% following bare metal stent (BMS) implantation, and probably up to 30% in specific subgroups, in particular, diabetic patients and those with small coronary vessels, or long lesions.[5, 6]

A major breakthrough coming with the birth of the third millennium was the invention of drug-eluting stents (DES). As a mat-

ter of fact, the arrival of DES in arena has clearly revolutionized our practice of coronary intervention, resulting in a dramatic reduction of ISR rates by one-half to two-thirds at five-year follow-up, amounting to roughly 10-15% need for TVR following DES at long-term.[7, 8] With the fall of 2006, however, alarming reports raised concerns about higher rates of very late (after one year) stent thrombosis associated with DES as compared with BMS.[9-11]

Ultimately, the late-breaking invention of bioactive stents (BAS) has been one further step forward in the natural evolution of stent technology. In fact, the safety of titanium-nitride-oxide-coated BAS (Titan-2) has been established in several reports from real-life unselected populations.[12-16] Interestingly, some non-randomized comparisons have demonstrated an even "better" outcome with BAS as compared to paclitaxel-eluting stents (PES) in high-risk patients with complex (type B and C) coronary lesions,[17, 18] and in patients presenting with acute myocardial infarction (MI).[19, 20]

Titan-2 BAS

The titanium-nitride-oxide-coated BAS (Titan-2, Hexacath, Paris, France) is a laser-cut slotted-tube stent made of medical-grade 316L stainless steel coated with a thin atomic layer of titanium-nitride-oxide. The stent is mounted over a 140 cm long rapid-exchange balloon carrier made of a semi-compliant material, compatible with 0.014" guide wires. The catheter has a hydrophilic coating, and its surface properties enable kissing procedures in 6F guiding catheters. The stent platform is the bare metal Helistent™ with a unique helicoidal design providing excellent flexibility and conformability (Figure 1). These features enable stent navigation inside curved arteries, with minimal stent-induced trauma and inflammation. Moreover, the design of the stent provides ultra-low recoil, while maintaining a collapse pressure of 1.2 bars, 50% higher than other tubular stent structures known to have an excellent radial force. In addition, this platform enables treatment of lesions located at bifurcations and allows side-branch access. Titan-2 BAS is available in various diameters and lengths, and provides extra-small and extra-large designs, with a strut thickness ranging from 70 to 91 microns.

Figure 1.—The helicoidal design of the stent platform of the Titan-2 bioactive stent (Helistent™, Hexacath, Paris, France).

A proprietary process has been developed to coat titanium-nitride-oxide on the surface of the stainless steel stent, based on a plasma technology using the nano-synthesis of gas and metal. The combination of magnetic fields, vacuum, and simultaneous injection of nitrogen and oxygen are necessary to create ionization and plasma formation of titanium-nitride-oxide. Titanium-nitride-oxide is then coated on all the surfaces of the stent, both inside and outside, through a patented process which results in nitride-oxide particles on the stent surface. This coating is extremely dense and hard, making the titanium-nitride-oxide-coated stent well adapted for direct stenting, where the most calcified lesions cannot damage, at all, the external layers of the coating. In addition, the titanium-nitride-oxide coating adds strength to the stainless steel substrate, making possible the use of thinner struts. Fatigue tests simulating 10 years of stent implantation with scanning electron microscope analysis have proven the integrity of the titanium-nitride-oxide coating. This was shown to remain intact after stent implantation without any signs of microfractures, thus ensuring all the demonstrated benefits of the titanium-nitride-oxide coating, which is particularly active against both thrombosis

and restenosis, as well as being an accelerator of reendothelialization. Titan-2 BAS are available in lengths of 7, 10, 13, 16, 19, 22 and 28 mm for stents with diameters of 2.5, 2.75, 3.0, 3.5, 4.0 and 4.5 mm. For stents with diameters of 2 and 2.25 mm (Titan-2 X-Small), only the lengths of 7, 10 and 13 mm are available.

Experimental and preclinical studies

Titanium has a better biocompatibility as compared to stainless steel, gold, or other surface coating materials, since it offers minimal toxic ion release, a fact that would reduce tissue reaction and inflammation.[21] *In vitro* examination has shown that titanium oxides were able to inhibit platelet aggregation and fibrin growth.[22] On the other hand, *in vivo* investigation of titanium films was performed by implanting titanium-coated and uncoated carbon cylinders (used as a reference material) in the ventral aorta of the same dog (5 in total). After 14 days, examination by scanning electron microscopy revealed the absence of platelet aggregation and fibrin deposition over the titanium-coated cylinders, in contrast to a large amount of platelets and fibrin over the uncoated ones.[23] Moreover, in an interesting experiment by Yeh HI *et al.*, endothelial cells from human umbilical vein were seeded on different metallic sheets, including nitinol, 316L stainless steel, and 316L stainless steel coated with titanium oxide and nitride. Forty eight hours later, metallic sheets coated with titanium oxide and nitride demonstrated higher cell density values on their surfaces in comparison with those without these coatings, suggesting that the use of stents covered with these coatings may accomplish earlier complete endothelialization.[24]

The blood compatibility of titanium oxide concerning platelet adhesion and fibrinogen adsorption can be improved by the addition of nitrogen. Platelet adhesion and fibrinogen adsorption are lower for titanium-nitride-oxide than for titanium oxide.[25, 26] Chemical elementary analysis confirmed the presence

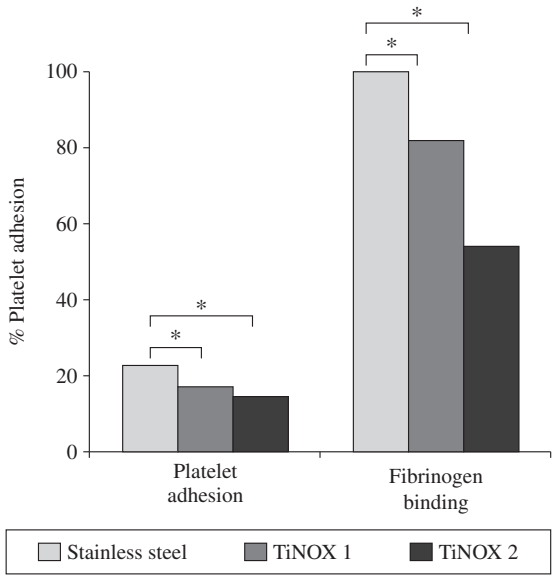

Figure 2.—Platelet adhesion and fibrinogen binding with the titanium-nitride-oxide-coated bioactive stent *versus* a 316L stainless steel stent of a similar design in a porcine model. * means P<0.05.

of nitride-oxide particles on the surface of the titanium coating. These observations indicate that stent coating with titanium-nitride-oxide is associated with nitride-oxide particles on the stent surface. The ion release characteristics have not been studied yet, however, the presence of nitride-oxide on the stent surface may be beneficial regarding intimal proliferation and platelet aggregation.[27]

A preclinical study in a porcine restenosis model investigated the outcome of a titanium-nitride-oxide-coated stent, and showed an almost 50% reduction of neointimal hyperplasia at six-week follow-up (P<0.05), as compared to an uncoated 316L stainless steel stent of otherwise identical design.[28] Furthermore, the titanium-nitride-oxide-coated stent significantly reduced platelet adhesion and fibrinogen binding in that porcine model (P<0.05) (Figure 2).[28] The antiproliferative effect obtained with titanium-nitride-oxide-coated stents was comparable to that reported by Suzuki *et al.* for sirolimus-eluting stents in pigs.[29]

Clinical studies employing bioactive stents

Surrogate endpoint studies

A robust body of evidence supports the efficacy and safety of the titanium-nitride-oxide-coated stent both in unselected patient populations, and in populations with the most challenging patient and lesion characteristics. In a prospective randomized comparison in an unselected population, titanium-nitride-oxide-coated stents significantly reduced late lumen loss by 40% (P=0.03) *versus* 316L stainless steel stent of the same design, at six-month follow-up.[12] Besides, in patients with acute coronary syndrome, Titan-2 BAS reduced binary restenosis rate by 71% (P<0.05), in comparison with BMS of other designs, with no stent thrombosis at six-month follow-up.[30]

Hard endpoint studies

Yet, stronger evidence always stems from studies employing the "hard" clinical endpoints rather than the "surrogate" ones. In a randomized comparison, involving a real-life population without exclusion criteria, Titan-2 BAS reduced the rate of overall major adverse cardiac events (MACE) by 88% (P=0.013) as compared to BMS, at six-month follow-up.[31] Additionally, in a prospective multi-center registry involving 296 patients with high-risk clinical characteristics (36% diabetics, 81% presenting with acute coronary syndrome) and a high prevalence of complex lesions (62% type B2 and C), implantation of Titan-2 BAS was associated with a target lesion revascularization (TLR) rate of 5.4%, and a total MACE toll of 7.6%, at six-month follow-up.[14] More interestingly, in a prospective non-randomized study by Karjalainen P *et al.*, Titan-2 BAS were compared to PES in 405 unselected patients. At 12-month follow-up, the former achieved a significant reduction of the incidence of MI as compared to the later (4.5% versus 10.3% respectively, P=0.025) mainly driven by a significant reduction of the rate of stent thrombosis (0% *versus* 3.4%, respectively, P=0.008).[17] At five years, titan-2 BAS demonstrated a significant reduction of the rate of total MACE as compared to PES (16.9% *versus* 26% respectively, P=0.03) mainly driven by a significant reduction of the rate of MI (9.5% *versus* 20.6%, respectively, P=0.002) and stent thrombosis (0% *versus* 7.8% respectively, P<0.001).[18] Similarly, in a propensity-score matched analysis from a prospective single-center registry, Limacher A *et al.*, compared the long-term outcome of BAS (558 patients, 882 stents) with that of both sirolimus-eluting stent (542 patients, 916 stents) and PES (507 patients, 891 stents) in a population with rather complex clinical characteristics. At three years, BAS achieved a similar outcome of the total MACE when compared to either sirolimus-eluting stent or the PES.[32] The primary composite endpoint of death, MI and TVR occurred in 20% of patients with BAS, 19% of patients with sirolimus-eluting stents, and 23% of patients with PES. The hazard ratio for BAS was 1.0 as compared with the sirolimus-eluting stents (95% CI 0.69-1.45, P=1.0), and was 0.95 as compared with the PES (95% CI 0.66-1.36, P=0.78).

Bioactive stents in high-risk groups

In the meantime, the performance of the titan-2 BAS was interestingly superior in several specific high-risk groups, as well. In a prospective multi-center registry involving 156 diabetic patients with high-risk clinical characteristics (59.6% hypertensive, 57.1% dyslipidemic, 63.9% presenting with unstable angina) and rather complex lesion characteristics (74.6% type B), Titan-2 BAS was associated with a TLR rate of 7.1%, and a total MACE toll of 10.3%, at six months.[33] In the same registry, follow-up coronary angiography with quantitative coronary analysis and intravascular ultrasonography was performed in 45 patients (with 72 stents) at 9 months. Late lumen loss was 0.56 mm by quantitative coronary analysis, and 0.5 mm by intravascular ultrasonography.[33] Furthermore, in a prospective multi-center registry employing Titan-2 BAS in 311 patients (356 stents) with small vessel disease,

the incidence of death was 0.7%, MI 2.1%, TLR 4.2%, and the cumulative incidence of MACE was 8.7% at an average follow-up period of 8 ± 2 months. Of great interest is that only one patient suffered subacute stent thrombosis, but no one suffred late thrombosis over the period of follow-up.[34]

Bioactive stents in acute myocardial infarction

Moreover, another prospective multicenter registry employing the titan-2 BAS in 226 patients presenting with acute ST elevation MI, demonstrated a TLR rate of 2.4%, and a cumulative MACE of 5.7% at the end of 12 months. Surprisingly, no patient suffered stent thrombosis during follow-up, according to the per-protocol definition.[35] Ultimately, Karjalainen P *et al*. randomized 425 patients presenting with acute MI to receive either titan-2 BAS or PES, in a prospective study design. At 30 days, they observed a significant reduction of the primary composite endpoint of death, MI and TLR in the group which received the former *versus* the later stent (1.4% *versus* 5.7% respectively, P=0.018) chiefly driven by a significant reduction of MI (0.9% *versus* 4.3% respectively, P=0.031).[19] Eventually, at two years, the titan-2 BAS achieved a significant reduction of the rates of cardiac death (0.9% *versus* 4.7% respectively, P=0.02), MI (5.1% *versus* 15.6% respectively, P<0.001), total MACE (11.2% *versus* 21.8%, respectively, P=0.004), and stent thrombosis (0.5% *versus* 6.2%, respectively, P=0.001) as compared to the PES.[20] A late-breaking multicenter large registry performed in 2137 patients presenting with acute MI (1452 ST elevation MI and 685 non-ST elevation MI), total MACE occurred in 3.6% of patients at 30 days (cardiac death, MI, urgent target lesion revascularization and stent thrombosis), and in 9.8% of patients at one year (cardiac death, MI, target lesion revascularization and stent thrombosis) follow-up.[36] Individual components of MACE at one year follow-up were also favorable. Total death occurred in 4.4% of patients, cardiac death in 3.1%, MI in 2.7%, definite or probable stent thrombosis in 1.8%, target lesion revascularization in 5.7%. It is worthmentioning that the one-year rate of stent thrombosis (definite or probable) in this registry was lower than its counterparts in recntly reported studies of DES. It is relevant also that the rate of mid-term (6-12 months) TLR was comparable to those reported from other registries of BAS.[12, 14, 17]

Bioactive stents versus second generation drug-eluting stents

Comparison with second generation DES has been equally satisfactory. In a late-breaking multicenter randomized controlled trial in patients presenting with acute coronary syndrome, BAS proved non-inferior to an everolimus-eluting stent regarding the composite efficacy and safety outcome of cardiac death, non-fatal MI and ischemia-driven TLR at 12 months.[37] The primary composite endpoint occurred in 9.6% of patients in the BAS group as compared to 9% of patients in the everolimus-eluting stent group (P=0.81, p=0.001 for non-inferiority). Interestingly, among the individual components of the primary endpoint, MI occurred significantly less frequently in the BAS group as compared with the everolimus-eluting stent group (2.2% *versus* 5.9%, respectively, P<0.007). Further interestingly, definite stent thrombosis trended higher in the group who received the everolimus-eluting stent as compared with those who received the BAS (2.2% *versus* 0.7%, respectively, P<0.07).[37] Figure 3 shows the composite endpoint of total MACE at 12 months follow-up in 2 large randomized controlled trials and a large registry of the titan-2 BAS in acute coronary syndrome. In a substudy of this trial, optimal coherence tomography was performed in 13 non-diabetic patients who received the BAS and 15 who received the everolimus-eluting stent at an average of 8-9 months follow-up.[38] Essentially, all the subgroup of 28 patients had a stent in the proximal left anterior descending artery, and angiography at follow-up ruled out restenosis. Findings were of immense clinical interest. Binary stent strut coverage

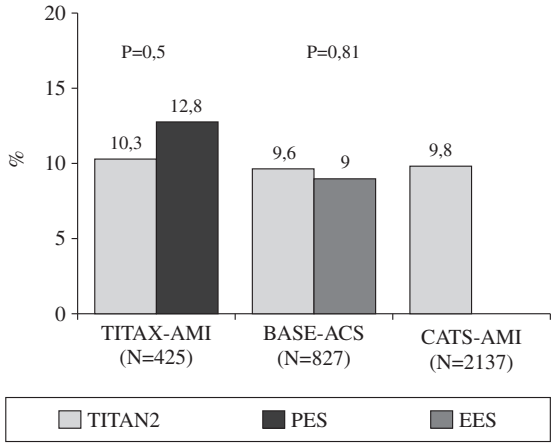

Figure 3.—The composite endpoint of total major adverse cardiac events at 12 month follow-up in 2 large randomized controlled trials and a large registry of the Titan-2 BAS in acute coronary syndrome.

was significantly better and the percentage of malapposed stent struts was significantly lower with the BAS as compared with the everolimus-eluting stent (99.3% *versus* 87.3%, and 0.2% *versus* 5.3%, respectively, P<0.001 for both). In contrast, minimal lumen area was significantly lower, and mean neointimal hyperplasia thickness and area significantly greater in the BAS group (4.7±1.6 *versus* 6.2±2.5 mm^2, 274.2±168.3 *versus* 100.1±101.0 μm, and 2±1.1 *versus* 0.6±0.8 mm^2, respectively, P<0.001 for all).[38] In this same substudy, patients underwent transthoracic echocardiography to measure the diastolic coronary flow velocity, and hence calculate the coronary flow reserve (CFR).[39] Surprisingly, CFR was significantly lower in the patients who received the everolimus-eluting stent as compared with those who received the BAS (2.2±0.8 *versus* 3±0.5, P<0.001). Furthermore, abnormal CFR values below 2.5 were detected more frequently in the patients who received the everolimus-eluting stent as compared with those who received the BAS. Interestingly, uncovered (apposed) stent struts were associated with decreasing CFR (P=0.02). In a logistic regression analysis, stent type was an independent predictor of abnormal CFR. Uncovered stent struts (both apposed and malapposed) were significantly more frequent in patients with abnormal than in those with normal CFR (8.3% *versus* 3.1%, and 3.6% *versus* 1.6%, respectively, P<0.001 for both). Yet, neointimal thickness was significantly lower in those with abnormal CFR (118.2±124.9 *versus* 211.3±168.5, P<0.001).[39]

Another recently published report compared BAS with zotarolimus-eluting stents, another member of second generation DES at mid-term follow-up. In this somewhat small randomized trial, BAS achieved a similar clinical outcome at 6-8 month follow-up in comparison with the zotarolimus-eluting stent in term of the total MACE (21.1% *versus* 18%, respectively, P=0.5), death (0.7% *versus* 0.7%, respectively, P=1.0), MI (5.3% *versus* 6.7%, respectively, P=0.6).[40] In-stent late loss, however, was better in patients who received the zotarolimus-eluting stent when compared with the BAS (0.64±0.61 mm *versus* 0.47±0.48 mm, respectively, P=0.02).[40]

Pooled analysis

Finally, in a pooled analysis of three trials comparing the outcome of BAS with PES in 1774 patients, Karjalainen P *et al.*, demonstrated that BAS significantly reduced the risk of recurrent MI (2.7% *vs.* 5.6%; risk ratio 0.50, 95% CI 0.31-0.81, P=0.004) and total MACE (8.9% *vs.* 12.6%; risk ratio 0.71, 95% CI 0.54-0.94, P=0.02) at 12 months.[41]

BAS in perspective

A cost-effectiveness analysis of DES based on the BASKET trial justified the use of DES only in high-risk groups.[42] Moreover, new-generation DES demonstrated a different vascular response as compared with earlier Food and Drug Administration (FDA) approved ones, even when implanted side-by-side in the same vessel. Achievement of the goal of reducing TLR following PCI without taking the risk to develop the life-threatening "hard" endpoints of late and very late stent thrombosis, and at an almost similar cost, would be an attractive strategy in combating ISR. Furthermore, unlike DES which need maintenance dual antiplatelet therapy

for at least 12 months (sometimes even for more extended periods), this therapy is required for no more than one month with Titan® BAS. In the modern era of mounting healthcare costs, physicians will do both patients and "the Healthcare System" a great favor by resorting to safer and less costly means of maintaining coronary patency. These data would ignite enthusiasm that BAS will be at the forefront as a contender in the "arena" of revascularization strategies in patients with atherosclerotic coronary disease.

Riassunto

Stent coronarico bioattivo con rivestimento in titanio-ossido nitrico Titan-2: un nuovo passo in avanti nella cardiologia interventistica

L'introduzione degli stent medicati ha rivoluzionato il settore della cardiologia interventistica, riducendo l'incidenza della restenosi dal 50% al 70%. Tuttavia, recenti dati preoccupanti derivanti da registri e meta-analisi hanno evidenziato maggiori tassi di trombosi tardiva e molto tardiva da stent associate a stent medicati. Lo stent bioattivo con rivestimento in titanio-ossido nitrico (Titan-2) è stato prodotto tramite un processo brevettato di rivestimento della superficie di uno stent d'acciaio inossidabile con titanio-ossido nitrico basato sulla tecnologia al plasma utilizzando la nano-sintesi tra gas e metallo. Questo recente tipo di stent ha dimostrato un'eccellente biocompatibilità, come illustrato dai minori tassi di aggregazione piastrinica e deposizione di fibrina e dalla migliore endotelizzazione. Studi clinici, preclinici e registri che interessano popolazioni "real life" non selezionate hanno mostrato un basso tasso di eventi cardiaci avversi gravi in un follow-up a lungo termine. I tassi di restenosi sono paragonabili a quelli degli stent medicati con la trombosi da stent molto rara. Risultati egualmente favorevoli sono stati ottenuti in pazienti a elevato rischio di restenosi intra-stent, come pazienti diabetici e piccoli vasi. I risultati in pazienti con sindrome coronarica acuta sono stati paragonabili a quelli degli stent medicati, con una tendenza di minor incidenza di infarto miocardico e stent trombosi. Anche i confronti con gli stent medicati di seconda generazione sono stati promettenti.

Parole chiave: Titanio - Stent - Restenosi coronarica.

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