

Short- and long-term outcomes of the titanium-NO stent registry

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Abstract

Background: Five to 15% of the population have allergy to nickel, chromium, or molybdenum, which is a potential cause for in-stent restenosis. The Titan stent is made of stainless steel and is coated with titanium-nitride oxide (TiNOX), which completely prevents the discharge of metal elements. We performed a real-life multicenter registry to assess the short- and long-term characteristics of the Titan stent.

Methods and results: A total of 103 Titan stents was implanted in 100 patients. Patients were 61.4 ± 12.6 years old (81 men). Risk factors included hypercholesterolemia (63%), hypertension (53%), diabetes mellitus (DM; 35%), and current smoking (23%). Indications for PCI (percutaneous coronary intervention) were acute coronary syndromes (ACS) in 68% [acute ST elevation myocardial infarction (MI) in 8%], stable AP (angina pectoris) in 25%, and silent ischemia in 7% of the patients. Fifty-two percent of the treated lesions were of Type B2 or C. Lesion length was 14.3 ± 2.9 mm and stent diameter was 3.06 ± 0.36 mm. Indications for stenting were prevention of restenosis in 66%, residual stenosis in 33%, dissection in 13%, acute MI in 13%, and in-stent restenosis in 7% of the patients.

Procedural success was 100%, with no complications. At 30 days, there were no major adverse cardiac events (MACE), including death, MI, and revascularization. At 180 days, only three patients had TVR (target vessel revascularization); two had TLR (target lesion revascularization) (one PCI and one CABG [coronary artery bypass grafting]), and one patient had a new narrowing proximal to the stent and underwent CABG due to multivessel disease.

Conclusions: The Titan stent has a remarkable safety profile in high-risk patients and complex coronary lesions and excellent short- and long-term outcome with a very low clinical TLR rate.

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1. Introduction

Most stents have been made from stainless steel, which is known to be contaminated from other elements and agents during foundry production. Recently, the use of other alloys,

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such as cobalt–chromium, enabled the construction of more flexible stents with thinner struts.

Inflammation plays a major role in restenosis. Inflammatory cells react differently to different chemical domains and metals and are often stimulated by ionic charges. Five to 15% of the population have an allergy to nickel, chromium, or molybdenum, which has been held responsible for inducing restenosis.

The Titan stent is a balloon expandable stent made of stainless steel and coated with titanium-nitride oxide (TiNOX), which completely prevents discharge of nickel, chromium and molybdenum. Windecker et al. [1] have shown that TiNOX coating decreases tissue reaction and diminishes cell reaction in a pig model. In vitro experiments implied that the electromechanical properties of TiNOX were more important for the prevention of neointimal hyperplasia than was the difference in platelet adhesion or fibrinogen binding [1].

We report here the results of a multicenter registry that was performed to assess the short- and long-term characteristics of the Titan stent in patients.

2. Methods

This multicenter (nine hospitals) registry was performed as a part of the requirements of the Israeli Ministry of Health for the approval of new stents.

2.1. Patients and lesions

Included were all patients who were candidates for stent implantation. Choosing the Titan stent was at the operator discretion, with no exclusion criteria.

Treated lesions included de novo and restenotic lesions of native coronary arteries and SVGs. Thirty-day and 6-month phone call follow-up was performed by an independent research nurse.

2.2. Stents

Titan stents were available in diameters of 2.5, 3.0, and 3.5 mm and lengths of 10, 13, 16, and 19 mm.

2.3. Data analysis and statistics

Clinical data included gender, age, risk factors, cardiac history, and clinical presentation. PCI data included lesion location, type and characteristics, delivery data, stent size, and deployment pressure. Outcome data included immediate technical and clinical success and complications and major adverse cardiac events (MACE), including subacute thrombosis, myocardial infarction (MI), TLR, TVR, and death, at 30 days and 6 months.

The χ^2 test was used to compare the TVR and death rate of the Titan stent with previous Israeli national stent registries (pooled data of 15 bare stents and 1 drug-eluting stent).

3. Results

3.1. Patients

The mean patient age was 61.4 ± 12.6 (42–86) years, and 81% of them were men. Risk factors for ischemic heart disease included hypercholesterolemia in 63%, hypertension in 53%, diabetes mellitus (DM) in 35%, current smoking in 23%, past smoking in 19%, and family history in 12% of the patients. Fifty-seven of the patients had single vessel, 19% had double vessel, and 24% had triple vessel disease. Previous cardiac history included MI in 21%, PCI in 14%, and CABG in 7% of the patients.

The indications for PCI were acute coronary syndromes (ACS) in 68%, including acute ST elevation MI in 8% (six were treated with primary angioplasty and two with thrombolysis), non-ST elevation MI in 26%, and unstable AP in 34% of the patients. Other indications for PCI were stable AP in 25% and silent ischemia in 7% of the patients. During PCI, all patients were treated with heparin, and 20% were treated with IIb–IIIa antagonists. All patients were treated with Aspirin 100 mg for life and Clopidogrel 75 mg for 1 month.

3.2. Lesion anatomy and morphology

A total of 103 Titan stents was implanted in 100 patients. Stented arteries included 34 LAD coronary arteries, 29 RCA, 20 Cx, 15 marginal branches, 12 diagonal branches, 2 LM coronary arteries, and 1 SVG. The stented segment was proximal in 37, mid in 46, distal in 10, and ostial in 7 of the lesions. Sixteen percent of the treated lesions was of Type A, 32% of Type B1, 38% Type B2, and 14% Type C. Stent diameter was 3.06 ± 0.36 mm (2.5 mm in 22%, 3 mm in 46%, and 3.5 mm in 35% of the stents). Stent length was 14.31 ± 2.90 mm. Forty seven of 100 patients had a lesion length of ≥ 15 mm. Fourteen lesions had a bend of $>45^\circ$, and 35 were calcified.

The indication for stenting as recorded by the operators was prevention of restenosis in 66% of the patients, residual stenosis in 33%, dissection in 13%, and acute MI in 13%.

Table 1
The 180-day follow-up results of 15 stent registries in Israel

	Bare stent	Titan	Cypher
Total number	1434	100	408
TVR (CABG)	124 (29)	3 (2)	5 (5)
Death	19	0	3

The data are given in absolute numbers. See Results and Fig. 1 for percent data and statistics.

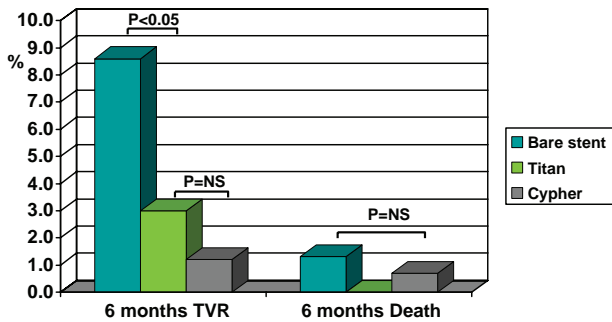


Fig. 1. One hundred eighty-days follow-up results of 17 stent (including Titan and Cypher) registries in Israel.

Notably, in 7% of the patients, a Titan stent was implanted within an in-stent restenosis.

3.3. Stent deployment

In 71% of the patients, dilation of the lesion with a balloon catheter was performed prior to stent implantation, and in 29%, direct stenting was performed. The pressure used for deployment was <12 bar in 42% and \geq 12 bars in 58% of the patients. Twenty patients underwent an implantation of additional 26 non-Titan stents to other lesions (3 of them Cypher stents).

3.4. Outcome

Procedural success was 100%, with no complications. At 30 days, there was no MACE. At 180 days, 95% of the patients had angina class grade I. Eight patients underwent repeat angiography for chest pain and five of them had patent stents. Only three patients (3%) had TVR; two had TLR (one PCI and one CABG), and one had a new narrowing proximal to the stent and underwent CABG due to multivessel disease.

A comparison of 180-day TVR rate of the Titan stent with pooled data of 15 Israeli national bare-stent registries (which had 8.6% TVR, Table 1 and Fig. 1) showed that the Titan stent was superior ($P<0.05$). A comparison of 180-day TVR of the Titan stent with The Israeli Cypher registry (which had 1.2% TVR, Table 1 and Fig. 1) showed that the Titan stent was not statistically inferior to the Cypher. The number of deaths in all three groups was small and with no statistical difference.

4. Discussion

In-stent restenosis is observed in 20–30% of patients undergoing stent implantation and is caused by neointimal proliferation [2,3]. Drug-eluting stents have not abolished restenosis and still have 8–9% angiographic restenosis and 1–2% TVR. Factors such as diabetes mellitus, vessel

morphology (e.g., vessel diameter, lesion length, and amount of residual plaque burden; [4,5]), stent characteristics (the use of multiple stents and their length), and extent of arterial trauma during angioplasty may all contribute to the increased rate of in-stent restenosis.

In this manuscript, we present, for the first time, clinical experience with the Titan, a TiNOX-coated stent. The results of this real-life multicenter registry of high-risk patients with complex coronary lesions were exceptionally good. There were no immediate complications and only 3% 6-month TVR (2% TLR), with no other MACE.

4.1. Biologic interactions of metallic implants

Metallic implants can interact with living tissues in three ways: electron exchange (redox reaction), proton exchange (hydrolysis), and complex formation (metal ion-organic molecule binding). These reactions are responsible for protein (e.g., fibrinogen) activation, cell toxicity, fibroblast growth stimulation, platelet, monocyte/macrophage and endothelial cells adhesion, and endothelial cell migration.

Stainless steel is made of iron fortified with carbon. Stainless steel used to produce stents (316L) contains significant amounts of other elements, mainly nickel (12%), chromium (as chromate; 17%), and molybdenum (2%). This combination renders the alloy even more resistant to corrosion (rust) while in contact with blood, but ions of these elements are eluted from the stents. Iron and carbon are major constituents of cell structure and metabolism and are unlikely to cause any hypersensitivity reaction. The biological behavior of stainless steel is dominated principally by its nickel component, which induces all three reactions mentioned above [6]. Clinically, nickel has been shown to cause skin contact allergic reaction in 5% of male and 15% of female population. Inflammatory and allergic reactions associated with the formation of new tissue around metallic alloys that include nickel are well known in patients with orthopedic and dental implants [7]. To date, there are only two clinical studies that examined the association between metal allergy and coronary in-stent restenosis. Koster et al. [7] studied 131 patients prior to angiography for suspected coronary in-stent restenosis of a stainless-steel stent. All patients underwent allergy patch testing for nickel, chromate, molybdenum, manganese, and stainless steel. Eighty-nine patients had restenosis (>50% angiographic narrowing), and 10 of them (11%) had positive patch test results (4 to molybdenum and 7 to nickel) and underwent repeat angioplasty. Forty-two patients did not have restenosis and none of them had a positive patch test ($P=.03$). Thus, all 10 patients with a positive patch test had in-stent restenosis. There was no positive reaction to chromate, manganese, or 316L. Following this publication, Hillen et al. [8] performed a patch test in a small group of 20 patients after angioplasty and another 7 patients before angioplasty (another 7 patients in the prospective group did not get a stent or were lost to follow up). Nickel sensitivity did not correlate with

restenosis, but these groups were far too small to expect a measurable restenosis rate or draw any conclusion.

4.2. Stent coatings for the prevention of thrombosis and restenosis

Stent coatings are made to create a biologically inert barrier between the stent surface and circulating blood. Heparin-coated stents have been shown to reduce subacute stent thrombosis [9,10], but no reduction in neointimal proliferation was observed in animal models or in clinical studies. Silicon carbide, a semiconductor ceramic, deposited on the surface of coronary artery stents reduces the electrochemical surface potential of stainless-steel stents. However, stent thrombosis and in-stent restenosis rates in one clinical study were 2% and 27%, respectively [11], similar to uncoated stents. Gold-coated stents have been used in two coronary artery stents (InFlow and NIR Royal, Boston Scientific). A randomized clinical trial demonstrated a significantly increased (50%) in-stent restenosis in the gold-coated inflow stents compared with 38% restenosis in identical uncoated stainless-steel stents [12]. Several polymers have been investigated as a platform for drug-eluting stents. An investigation of eight different biodegradable and nondegradable polymers showed marked inflammatory reactions with subsequent neointimal hyperplasia [13]. Nevertheless, the polymers included in the drug-eluting stents presently in use (Cypher and Taxus) did not impede with the favorable results of these stents.

Titanium, with its low electrochemical surface potential, is biologically inert and has excellent biocompatibility, exemplified by the lack of a redox and hydrolysis reaction, as well as an absent complex formation. Biologically, this is translated to no fibroblast growth, protein, or platelet adhesion observed with titanium [14]. TiNOX is a titanium alloy suitable for the coating of stainless-steel stents. TiNOX does not release nickel, chromium, molybdenum, or other metals. Windecker et al. [1] have shown that, in a pig model, stents coated with TiNOX had decreased tissue reaction and diminished cell reaction. In vitro experiments showed reduced platelet adhesion and fibrinogen binding after the incubation of TiNOX-coated stents with human plasma for 48 h [1]. The results of these experiments implied that the electromechanical properties of TiNOX were more important than the reduced platelet and fibrinogen effects for the prevention of neointimal hyperplasia. It is important to emphasize that nitride oxide was used as a part of the TiNOX coating in the Titan stent because it rendered titanium suitable for coating stainless steel stents. The TiNOX does not release NO, and it is not known whether it obtains biological characteristics similar to those of free NO molecules released from endothelial cells.

Inflammation is an important factor in restenosis. The inflammation burden prior and after angioplasty depends on individual systemic and local (arterial) factors and on procedural factors such as the degree of trauma to the

vessel wall and disruption of the basement membrane. Bare stents add iatrogenic contribution by enhancing neointimal hyperplasia—a so-called “response to foreign material”. It is imperative to diminish any inflammatory stimulus that may exist before, during, or after percutaneous vascular intervention. Our study is the first to summarize clinical experience with the TiNOX-coated stent. While keeping in mind that it is a registry and not a randomized study, the results are remarkably good, especially when compared with our database stent registries performed in the same fashion. We propose that this outcome is due to the prevention of discharge of elements such as nickel and chromium, thereby eliminating one important cause for inflammation and restenosis. The possible contribution of the low electrochemical surface potential of titanium and of nitride oxide to the outstanding results in this study has to be elucidated.

In summary, nickel and other elements eluted from stainless steel stents may provoke inflammatory reaction. The Titan stent is coated with TiNOX, which eliminates the discharge of such elements. In this real-life multicenter registry, the Titan stent had a remarkable safety profile in high-risk patients with complex coronary lesions, as well as excellent short- and long-term outcome with a very low clinical TLR rate.

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