Interventional Cardiology

One-Year Follow-Up after Percutaneous Coronary Intervention with Titanium-Nitride-Oxide-Coated Stents versus Paclitaxel-Eluting Stents in Patients from Real-World Clinical Practice

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Background: Drug-eluting stents significantly decreased intimal hyperplasia in comparison with bare metal stents; however, safety issues have been reported by recent studies. In this study, titanium-nitride-oxide-coated stents, which exhibit less thrombogenicity, were compared to paclitaxel-eluting stents with respect to the rate of major adverse cardiovascular events (MACE).

Methods: One hundred and fourteen patients [65 in titanium-nitride-oxide-coated (Titan®) stent group and 49 in paclitaxel-eluting (TAXUS®) stent group] were enrolled in a single teaching hospital in northern Taiwan between November 2005 and October 2008. Patients with acute coronary syndrome or chronic stable angina with a positive myocardial thallium scan were eligible for the study, and patients who underwent percutaneous coronary intervention (PCI) with either Titan stents or TAXUS stents were enrolled. We evaluated the MACE rate in the two groups during the first year after stent placement.

Results: The MACE rates of the Titan and TAXUS groups were 10.8% (7/65) and 6.1% (3/49), respectively, but the difference was not statistically significant (p = 0.3). In addition, the 12-month clinical outcomes were not statistically different between the groups. In a comparison of the risk factors of diabetes mellitus, acute myocardial infarction, hypertension, smoking, and dyslipidemia between the two groups, there was no significant difference in the rates of MACE.

Conclusion: There was no difference in MACE or all-cause mortality at 12 months after stent implantation in patients who received the TAXUS or Titan stents.

Key Words: Major adverse cardiovascular event • Paclitaxel-eluting stent • Titanium-nitride-oxide-coated stent

INTRODUCTION

Patients with coronary artery disease (CAD) who received percutaneous coronary intervention (PCI) with bare metal stents (BMS) have a lower rate of restenosis than patients who receive plain balloon angioplasty alone.[1] In-stent restenosis (ISRS) occurs in 20-30% of patients undergoing BMS implantation, and is caused by neointimal proliferation.[2-4] Inflammation is a critical factor in the restenosis process, and the inflammation burden depends on the individual's systemic and local arterial factors. Diabetes mellitus (DM), vessel morphology, including vessel diameter, lesion length, and amount of residual plaque burden,[5,6] and procedural factors such as

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vessel wall trauma and basement membrane disruption may all amplify ISRS. Drug-eluting stents (DES) have been shown to reduce ISRS after PCI compared to BMS.[7,8] However, safety issues of stent thrombosis with DES have arisen.[9-12]

Titanium-nitride-oxide (TiNOX) is a titanium alloy suitable for coating stainless steel stents. TiNOX coated (Titan®; Hexacath, France) stents have been shown to reduce adhesion of platelets and fibrinogens in comparison to BMS.[13] In addition, neointimal hyperplasia was reduced by almost 50% with Titan stents as compared to BMS in a porcine restenosis model at 6-week follow-up.[13] Additionally, the safety and lower restenosis rate of Titan stents have been proven by several studies.[14-17] Therefore, our aim was to report the first series of Titan stent utilization in Taiwan and compare the outcomes with those of DES.

MATERIALS AND METHODS

Study patients

This was an observational study in which all patients were enrolled from a single teaching hospital in northern Taiwan between November 2005 and October 2008. One hundred and fourteen subjects with acute coronary syndrome or chronic stable angina with a positive myocardial thallium scan were eligible for the study, and patients who underwent PCI with either Titan stents or paclitaxel-eluting stents (TAXUS®; Boston Scientific Corp., Natick, MA, USA) were enrolled. Among these 114 subjects, 65 had Titan stents and 49 had TAXUS stent implantation.

Coronary-stent procedure

All patients were pretreated with intravenous heparin at a dose of 70-100 U/kg to keep the activated clotting time > 250 seconds. Aspirin, 100 mg once daily, was administered to those patients without contraindications and was continued indefinitely. Oral clopidogrel was administered as a loading dose of 300 mg before or immediately after the procedure, and was continued at a daily dose of 75 mg for 3 months in the Titan stent group and for at least 9 months in the TAXUS stent group. Lesions were treated according to current standard interventional techniques, with the final strategy (including the thrombectomy procedure, direct stenting, post-dilatation, and periprocedural glycoprotein IIb/IIIa inhibitor) left entirely up to the operator's discretion. The choice between Titan and TAXUS stents was decided by the patient and their family according to individual economic considerations. If more than one stent was needed, stents of the same type as the assigned stent were recommended. Stent length was carefully judged in order to cover the full length of the lesion without any gap between stents if more than one stent was placed. Angiographic stenting success was defined as a residual stenosis < 10% by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3. The medical treatment of CAD was optimized according to contemporary guidelines.

Patients follow-up

All enrolled patients were followed up at the outpatient department. Stress tests such as treadmill exercise ECG or myocardial perfusion scan would be arranged if patients had experienced the symptoms suspecting angina. Coronary angiogram would be performed with scheduled PCI for other coronary lesions. Some patients had cardiac catheterization directly if there had been attack of acute coronary syndrome. Coronary angiogram follow-up rate in this study was around 30.8% (20/65) in the Titan stent group and 26.5% (13/49) in the TAXUS stent group (Table 1).

Definitions of endpoint

The primary endpoint of the study was major adverse cardiac event (MACE) occurrence within 12 months after the index procedure. MACE was defined as death from cardiac causes, myocardial infarction (MI), or target vessel revascularization (TVR) with either PCI or coronary artery bypass graft (CABG) surgery. MI during follow-up was diagnosed by symptoms suggestive of acute myocardial ischemia along with a troponin I level above the upper reference limit. Death from cardiac causes was defined as any death due to any cardiac related causes, unwitnessed death, or death of unknown causes. TVR was defined as a reintervention driven by any lesion located in the stented vessel.

Statistical analysis

Continuous variables were presented as mean ±

standard deviation (SD) and compared by Student's *t* test. Categorical variables were presented as counts and percentages and compared by chi-square test. All statistical tests were two-tailed. Kaplan-Meier curves were plotted to represent the cumulative incidence of adverse events.

RESULTS

Patient profiles

Between November 2005 and October 2008, a total of 114 patients (88 men, 26 women; mean age 62 ± 14 years) were enrolled. There were 93 Titan stents implanted in 65 patients (mean, 1.43 stents/patient) and 76 TAXUS stents implanted in 49 patients (mean, 1.55 stents/patient). Twelve-month clinical follow-up was completed by all patients. Baseline patient characteristics are presented in Table 1. Among the patients, 44.7% (51/114) had been diagnosed with diabetes mellitus (DM), and 44.7% (51/114) had a diagnosis of acute MI (AMI). A total of 138 native coronary artery lesions were treated. Locations of the lesions and numbers of diseased vessels treated are presented in Table 2. Most of the lesions were located in the left anterior descending (LAD) coronary artery. There was no difference in treated target vessels between these two groups. However, there was a lower prevalence of type C lesions (18% versus 37%, $p < 0.05$) in the Titan stent group compared with the TAXUS stent group, but higher incidence of type B lesions was seen in the Titan stent group than in the TAXUS stent group (81% versus 62%, $p < 0.05$). (Table 2). The result also showed that there were no differences between groups with respect to lesion length (18.9 ± 7.5 versus 17.9 ± 6.5 mm, $p = 0.38$). But reference vessel diameter was larger in the Titan stent group compared with the TAXUS stent group (3.1 ± 0.6 versus 2.7 ± 0.3 mm, $p < 0.001$) (Table 3). Table 4 shows the differences of stent diameter between these two groups. The largest diameter of TAXUS stent was 3.5 mm, Therefore, in this study, Titan stent was the only option for bigger vessels (> 3.5 mm). Overall, during the 12-month follow-up period, the clinical outcomes were not statistically different between the two groups (Table 5). The patients who received stents with diameters bigger than 3.5 mm and smaller than 2.5 mm in the Titan stent group were excluded. Then we compared the MACE rate, stroke and all cause mortality rate between the Titan and TAXUS

Table 1. Patient clinical characteristics

	Titan® stent	TAXUS® stent	p value
Number of patients	65 (20 f/u)	49 (13 f/u)	
Number of stents	93	76	
Numbers of average stent	1.43	1.55	0.28*
Age (yrs)	64.6 ± 13.5	59.2 ± 13.9	0.04
Male	50 (76.9)	38 (77.6)	0.56
Diabetes mellitus	29 (44.6)	22 (44.9)	0.56
Hypertension	53 (81.5)	33 (67.3)	0.06
Dyslipidemia	37 (56.9)	27 (55.1)	0.50
History of smoking	34 (52.3)	21 (42.8)	0.21
LVEF	0.6 ± 0.16	0.57 ± 0.14	0.28
Acute MI	29 (44.6)	22 (44.9)	0.53
Prior MI	4 (6.2)	8 (16.3)	0.08
Prior CABG	1 (1.5)	1 (2)	0.69
Prior PCI	5 (7.7)	10 (20)	0.05
Clopidogrel (months)	5.4 ± 3.5	9.5 ± 3.6	< 0.001

* Kendall's tau.

Data are presented as mean ± standard deviation or number (%). LVEF, left ventricular ejection fraction; MI, myocardial infarction; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

Table 2. Location of target lesions, number of diseased vessels and lesion characteristics

	Titan® stent	TAXUS® stent	p value
Location of lesion			
LM	3	2	0.63
LAD	50	31	0.08
LCX	9	12	0.11
RCA	16	15	0.25
Number of diseased vessels			
1	24	20	0.50
2	23	17	0.55
3	18	12	0.44
LM	6	2	0.25
Number of lesions	89	73	
ACC/AHA class, number			0.011
Type A	1 (1)	1 (1)	0.700
Type B	72 (81)	45 (62)	0.006
Type C	16 (18)	27 (37)	0.006

LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery.

Data are presented as number (%).

Table 3. Quantitative coronary angiography

	Titan® stent	TAXUS® stent	p value
Lesion length, mm	18.9 ± 7.5	17.9 ± 6.5	0.38
Reference vessel diameter, mm	3.1 ± 0.6	2.7 ± 0.3	< 0.001
Before procedure, diameter stenosis, %	81 ± 14.4	82 ± 12.7	0.64
After procedure, residual stenosis, %	5.6 ± 3.8	8.3 ± 3.4	< 0.001

Data are presented as mean ± standard deviation.

Table 4. Differences of stent size and number

Stent diameter	Titan® stent	TAXUS® stent
5 mm	2	
4.5 mm	1	
4 mm	9	
3.5 mm	19	11
3 mm	24	26
2.75 mm	25	24
2.5 mm	10	15
2.25 mm	1	
2 mm	2	

Table 5. Clinical outcomes at 12 months after procedure

	Titan® stent	TAXUS® stent	p value
MACE	7 (10.8)	3 (6.1)	0.3
TVR	6 (9.2)	3 (6.1)	0.40
Re-MI	0 (0)	0 (0)	1.0
Cardiac death	1 (1.5)	0 (0)	0.38
Stroke	1 (1.5)	1 (2)	0.68
All-cause mortality	3 (4.6)	1 (2)	0.42

Data are presented as number (%).
MACE, major cardiovascular event; TVR, target vessel revascularization; MI, myocardial infarction.

groups. Still, no statistical difference was shown between the two groups (Table 6). The MACE rates of the Titan and TAXUS stent groups were 10.8% (7/65) and 6.1% (3/49), respectively (p = 0.3). There was no difference in MACE rate between the groups when the risk factors of DM, AMI, hypertension (HTN), smoking, and dyslipidemia were examined (Table 7). The MACE-free survival Kaplan-Meier curves are shown in Figure 1. The MACE-free survival rates of the Titan and TAXUS stent groups at one year were 89.2% and 93.9%, respectively (p = 0.3).

One patient in the Titan stent group died in-hospital due to cardiogenic shock, and one patient in the same group with chronic atrial fibrillation had an embolic

Table 6. Clinical outcomes at 12 months after procedure (subgroup analysis of comparable stent diameters)

	Titan® stent	TAXUS® stent	p value
MACE	6 (12)	3 (6.1)	0.49
TVR	5 (10)	3 (6.1)	0.72
Re-MI	0 (0)	0 (0)	-
Cardiac death	1 (2)	0 (0)	1.00
Stroke	1 (2)	1 (2)	1.00
All-cause mortality	3 (6)	1 (2)	0.62

Data are presented as number (%).
MACE, major cardiovascular event; TVR, target vessel revascularization; MI, myocardial infarction.
*Stent diameters ≥ 4.0 and ≤ 2.25 mm were excluded.

Table 7. MACE incidence by risk factors

	MACE rate (%)		p value
DM vs. non-DM	5.9	11.1	0.26
AMI vs. non-AMI	13.7	4.8	0.89
Hypertension vs. non-hypertension	8.1	10.7	0.46
Smoking vs. non-smoking	9.1	8.5	0.58
Dyslipidemia vs. non-dyslipidemia	10	12	0.47

MACE, major cardiovascular event; DM, diabetes mellitus; AMI, acute myocardial infarction.

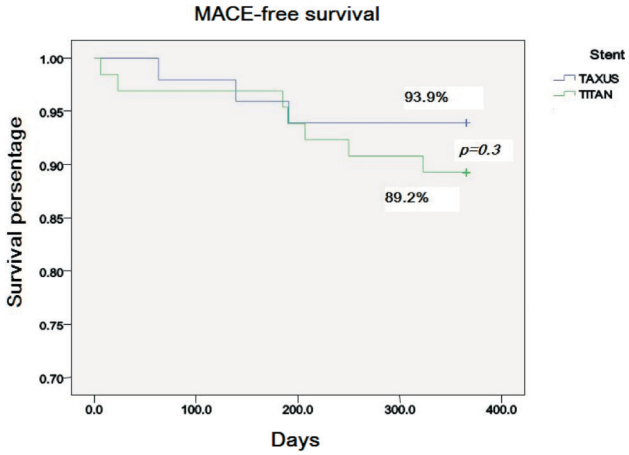

Figure 1. *The MACE-free survival rates of the Titan and TAXUS groups at one year.*

stroke 5 days after the procedure. There were 4 patients who died during the 12-month follow-up period. A patient in the TAXUS stent group died from gastrointestinal (GI) bleeding, and 3 patients in the Titan stent group were dead due to cardiogenic shock, pneumonia, and sepsis. There was one case of subacute stent thrombosis that happened 23 days after PCI in the Titan group. This special case did not discontinue his dual antiplatelet agents. And we couldn't find the reason why this event would have occurred. No patient in either group experienced a new non-Q-wave MI or Q-wave MI within 12 months after the index day.

DISCUSSION

This study has presented the first series of Titan stent utilization in Taiwan. The main finding of this study is that there was no statistically significant difference with respect to MACE rate and all-cause mortality during the 12 months after stent placement between patients who received Titan or TAXUS stent implantation.

Titanium is biologically inert due to its low electrochemical surface potential. The titanium alloy coating of the Titan stent prevents the release of nickel, chromium, molybdenum, and other metals. The hypothesis is that TiNOX renders the stent surface biologically inert, and by reducing platelet and fibrinogen binding attenuates neointimal hyperplasia. In vitro examinations of TiNOX show diminished platelet adhesion and fibrinogen binding compared with stainless steel.[18] TiNOX also reduced inflammation and promoted endothelial healing in the other studies.[19,20] In addition, neointimal hyperplasia was reduced by almost 50% with TiNOX coated stents compared with stainless steel stents in a porcine restenosis model at 6 weeks after stenting.[13] Moreover, the TiNOX trial demonstrated a reduced restenosis and MACE rate with Titan stents as compared with BMS at 6 months (7% vs. 27%, p = 0.02).[21]

Mosseri et al.[22] presented an observational study of the safety profile of Titan stents used in high-risk patients and complex coronary lesions and showed excellent short- and long-term outcomes with very low clinical TVR (3%) and TLR (2%) rates. In our current study, the duration of follow-up was 12 months and the MACE rate of the Titan group was 10.7%, as compared to the MACE rates observed in previous studies of 10.3% to 10.4% during 9 to 12 months of follow-up.[15,23]

DES have been shown to reduce in-stent restenosis after PCI as compared to BMS.[7,8] As is well known, both sirolimus-eluting stents and paclitaxel-eluting stents have demonstrated dramatic decreases in binary restenosis (8.9% and 7.9%, respectively) and late loss (sirolimus 0.24 mm versus paclitaxel 0.39 mm) compared with BMS over a wide range of lesions and patients.[24] The binary restenosis rate of 15% and the mean late loss of 0.55 mm for Titan stents are favorable, but clearly not sufficiently superior to that seen with DES.[8,24-26] On the other hand, coating stents with compounds like TiNOX appears to decrease acute surface thrombogenicity,[14,17,21,23] and reduce in-stent restenosis when compared with conventional stainless steel stents.[21]

Most previous stent trials have been performed with restrictive patient selection criteria, and patients with conditions such as MI, left main coronary artery disease, ostial or bifurcated lesions, and depressed left ventricular function were excluded. In our study, a high proportion of patients had AMI (44.6% of Titan group and 44.9% of TAXUS group). Analyzing only those subjects with AMI, 17% of the Titan group (5 of 29) and 14% of the TAXUS group (3 of 22) were found to have had MACE, thus there was no significant difference between the Titan and TAXUS groups. Karjalainen et al. also demonstrated the result in an unselected population of similar MACE rate in both Titan and TAXUS groups during 12 months follow-up (10.9% vs. 13.7%).[14]

In this study, we found clinical outcomes as measured by MACE (10.8% vs. 6.1%, p = 0.3) and all-cause mortality (4.6% vs. 2%, p = 0.42) to be equivalent in patients who received Titan and TAXUS stents, results similar to these of the TITAX AMI trial.[15] In the TITAX AMI trial, the rate of MACE among Titan stent treated patients was 10.3% and among TAXUS stent treated patients was 12.8%.[15] In our study, there was a high prevalence of DM (44.7%), one of the most important clinical risk factors for restenosis. After subgrouping for subjects with DM, 3.4% of the Titan group (1 of 29) and 9.1% of the TAXUS® group (2 of 22) had MACE. In the balloon angioplasty era, the restenosis rate after angioplasty in patients with DM reached 62%. After BMS implantation was introduced, the restenosis rate decreased to 27%.[27,28] In the SIRIUS trial, DES were shown to be

associated with a significant reduction of MACE and TVR in diabetic patients as compared with BMS at 9 months (9.2% vs. 25%, respectively).[29]

Research regarding the use of Titan stents in DM populations is limited. In the Titan PORI Registry, which enrolled patients in routine practice, only 17% of the subjects had DM.[23] Mosseri et al.[17] reported that 36.6% of the subjects in the multicenter registry of Titan stents had DM, but no subgroup analysis of diabetic patients was performed. The TIBET registry demonstrated an acceptable rate (15.5%) of angiographic restenosis in DM patients treated with the Titan stent.[30]

Patients who are implanted with the TAXUS stent are recommended to take dual antiplatelet agents including clopidogrel for at least 9 months, and some researchers believe a prolonged duration of clopidogrel administration is necessary to prevent late stent thrombosis.[31] In comparison, clopidogrel is only required for 1 month following Titan stent implantation.[21] This has an obvious economic advantage, as well as decreasing the potential bleeding risk.

Study limitation

This was an observational study from a single hospital, thus the study population was relatively small and had selection bias. Therefore, larger, multicenter, long-term and randomized control study is necessary.

CONCLUSION

In summary, there was no difference in MACE or all-cause mortality at 12 months after stent implantation in patients who received the TAXUS or Titan stents. However, the longer duration of MACE rate of both groups should be followed.

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