Long-term clinical outcome with titanium-nitride-oxide-coated stents and paclitaxel-eluting stents for coronary revascularization in an unselected population☆

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ARTICLE INFO

Article history:
Received 24 June 2008
Received in revised form 7 January 2009
Accepted 26 March 2009
Available online xxxx

Keywords:
Titanium-nitride-oxide-coated stent
Paclitaxel-eluting stent
Restenosis
Stent thrombosis

ABSTRACT

Background: The aim of this study was to evaluate long-term clinical events in patients treated with titanium-nitride-oxide-coated bio-active stents (BAS) and paclitaxel-eluting stents (PES) in routine clinical practice.

Methods: All patients undergoing percutaneous coronary intervention (PCI) were eligible for this single-centre registry between May 2003 and November 2004. The primary end point of the study was major adverse cardiac events (MACE) at 3 years including myocardial infarction (MI), cardiac death and target vessel revascularization (TVR).

Results: A total of 201 patients received BAS and 204 patients PES. In addition, during the same study period, 184 patients were treated with bare-metal stents (BMS) and 125 patients underwent CABG. Complete follow-up datasets were available in all patients. After 3 years of follow-up, the rate of MACE was 13.9% for BAS and 23.5% for PES (adjusted HR 2.0, 95% CI 1.2–3.2, p = 0.006). This difference was mainly driven by a higher incidence of MI in the PES group (19.1%) compared with the BAS (7.5%) group (adjusted HR 3.2, 95% CI 1.7–5.8, p < 0.001). The rate of MACE was 31.5% in the BMS group and 4% in the CABG group. At 3 years, stent thrombosis occurred in 15 patients in the PES (7.4%) group. There was no stent thrombosis in the BAS group.

Conclusions: After the 3 year follow-up, BAS resulted in better long-term outcome compared with PES with infrequent need for TVR.

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1. Introduction

The three major milestones in the evolution of interventional cardiology were the development of the balloon angioplasty, the introduction of coronary-artery stents and most recently, the development of drug eluting stents (DES). Although the implantation of coronary-artery stents has reduced the risk of periprocedural complications, in-stent restenosis (ISR) is still a clinical problem of metallic sheaths compared with stainless steel, gold, or other surface coatings [6]. Metallic sheaths coated with titanium nitride or titanium oxide exhibited higher cell density values on their surface compared to those without coating, supporting the view that deployment of stents with these coatings may achieve earlier complete endothelial coverage [7]. The safety of titanium-nitride-oxide-coated Titan-2® “bio-active-stent” (BAS) has been confirmed by several clinical studies in both unselected populations as well as in the most complex indications such as diabetics, small vessels and acute myocardial infarction (MI) [8–11]. Paclitaxel, a lipophilic molecule derived from the Pacific yew tree Taxus brevifolia, is capable of inhibiting cellular division, motility, activation, secretory processes, and signal transduction [12,13]. A polymer-based, paclitaxel-eluting stent (PES) reduced the rate of ISR as compared with BMS [2,4].

Previously, both the BAS and PES resulted in similar 12 month clinical outcome with infrequent need for repeat interventions in the real-world setting of high-risk patients and complex coronary lesions [9]. The aim of this study was to report long-term clinical outcome of this patient population with unrestricted use of BAS and PES(s).

2. Materials and methods

2.1. Patient population

The design of the original study has been previously reported [9]. Briefly, the main purpose of this prospective single-center registry was to evaluate the safety and efficacy of BAS and PES implantation for consecutive unselected patients treated in everyday
clinical practice. Between May 2003 and November 2004, all consecutive patients with symptoms or signs of myocardial ischemia and de novo coronary lesion(s) scheduled for stent implantation were considered for this registry. A total of 405 patients fulfilled the criteria and entered this study. A total of 201 patients received exclusively one or more BAS, and 204 received only one or more PES. This patient population comprised 63% of all patients who underwent percutaneous coronary intervention (PCI) during the study period.

In addition to original study population, we also gathered baseline data on patients receiving BMS(s) during the index study period in our centre, and these patients were also followed up to 3 years. The similar data from patients undergoing coronary-artery bypass grafting (CABG) were also collected. We also wanted to evaluate clinical events after clopidogrel discontinuation in all patients undergoing PCI with stent implantation. All patients who were MACE free at the time of the clopidogrel discontinuation were followed for an additional 12 months after the clopidogrel withdrawal.

The study was conducted according to the declaration of Helsinki and written informed consent was obtained from all patients. This protocol was approved by the Ethics Committee of Satakunta Central Hospital.

2.2. Study procedures

All patients were pre-treated with aspirin (100 mg daily) and received intravenous enoxaparine (1 mg/kg) during the procedure. Oral clopidogrel was administered as a loading dose of 300 mg before or immediately after the procedure. Patients treated with PES were prescribed for a minimum of 6 months of clopidogrel (75 mg/day), based on randomized controlled trials [2]. For patients treated with BAS, clopidogrel was prescribed for a minimum of 3 months. Lesions were treated according to current standard interventional techniques, with the final strategy (thrombectomy devices, direct stenting, postdilatation, periprocedural glycoprotein IIb/IIIa inhibitor, intravascular ultrasound) left entirely up to the operator’s discretion. Angiographic success was defined as a residual stenosis <30% by visual analysis in the presence of Thrombolysis in Myocardial Infarction (TIMI) flow grade 3.

The choice of an individual stent in BMS group was left at the discretion of the operator and these patients received at least 1 month duration of clopidogrel treatment after the index procedure. CABG was done according to current standard surgical techniques. After the CABG all patients were treated with aspirin indefinitely and the clopidogrel prescription was left to the decision of consulting surgeon.

2.3. Patients follow-up

All patients underwent clinical follow-up. Adverse events were monitored at hospital discharge and by office visits or telephone interviews by the cardiologist at 1 and 3 years. In addition, all data available from hospital records, the institutional electronic clinical database, and the referring physicians were checked at the end of the follow-up period (November 2007) and entered into the computer database. Follow-up angiography was clinically driven by symptoms or signs suggestive of myocardial ischemia. Indication for repeat revascularization was a significant luminal stenosis (>50% diameter stenosis) in the presence of anginal symptoms and/or proven myocardial ischemia in the target vessel territory.

2.4. End point definitions

The primary end point was major adverse cardiac events (MACE), defined as the first occurrence of any of the following during the follow-up: death from cardiac causes, Q-wave or non-Q-wave myocardial infarction (MI), or revascularization of the target vessel (emergency or elective coronary-artery bypass grafting or repeated coronary angioplasty). Q-wave MI was defined as either (1) the presence of chest pain or other acute symptoms consistent with myocardial ischemia and new pathologic Q waves in≥2 continuous electrocardiographic leads, or (2) elevated cardiac enzyme levels >2 times the upper limit of normal associated with any elevation above the upper limit of normal in creatine kinase-MB levels in the presence of new pathologic Q waves. Non-Q-wave MI was defined as an elevated creatine kinase >2 times the upper limit of normal associated with any elevation above the upper limit of normal in creatine kinase-MB levels. Target lesion revascularization (TLR) was defined as a repeat intervention to treat a stenosis within the stent or in the segments 5 mm distal or proximal to the stent. Target vessel revascularization (TVR) was defined as a reintervention driven by any lesion located in the stented vessel. ST per-protocol was diagnosed in the presence of an acute coronary syndrome with angiographic evidence of either vessel occlusion or thrombus within the studied stent, or in autopsy.

2.5. Statistical analysis

Continuous variables are presented as mean (SD) and groups were compared by Student’s unpaired t-test. Categorical variables are presented as counts and percentages and associations between categorical variables were compared by the chi-square or Fisher’s exact test. Variables significantly (p<0.05) associated with clinical events in univariate Cox proportional hazards regression models, were included in multivariable Cox regression analysis to identify independent predictors for clinical events during the 3 year follow-up.

Propensity scores were used to adjust for potential bias in the comparison between non-randomized BAS and PES groups. Propensity scores were calculated as the predicted probability that patient was treated by PES as opposed to BAS using logistic regression. The differences between BAS and PES groups in outcome variables were compared after adjustment for propensity score (linear term) by using Cox regression analysis. Propensity score was also included in multivariable models. Variables included in propensity score model and Cox regression models were age, gender, diabetes, current smoking, hypercholesterolemia, hypertension, previous MI, previous PCI, previous CABG, multivessel disease, acute ST-elevation MI, acute non-ST-elevation MI, unstable angina, stent diameter, stent length and glycoprotein IIb/IIIa inhibitors. A two-

Table 1

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Patient with any event</th>
<th>Cardiac death, n (%)</th>
<th>TLR, n (%)</th>
<th>MACE, n (%)</th>
<th>Stent thrombosis, n (%)</th>
<th>All cause death, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BAS (N=201)</td>
<td>15 (7.5)</td>
<td>9 (4.5)</td>
<td>28 (13.9)</td>
<td>11 (5.5)</td>
<td>22 (10.9)</td>
<td>11 (5.5)</td>
</tr>
<tr>
<td>PES (N=204)</td>
<td>39 (19.1)</td>
<td>21 (10.3)</td>
<td>48 (23.5)</td>
<td>19 (9.3)</td>
<td>28 (13.7)</td>
<td>15 (7.4)</td>
</tr>
<tr>
<td>HR (95%CI)</td>
<td>2.8 (1.5–5.0)</td>
<td>&lt;0.001</td>
<td>1.8 (1.1–2.8)</td>
<td>0.02</td>
<td>1.2 (0.5–2.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>p</td>
<td>3.5 (1.8–6.9)</td>
<td>&lt;0.001</td>
<td>2.1 (1.2–3.6)</td>
<td>0.001</td>
<td>3.8 (1.9–7.4)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Relative risk (HR) and 95% confidence intervals (95%CI) were calculated using the Cox proportional hazards regression model. All patients were pre-treated with aspirin (100 mg daily) and received intravenous enoxaparine (1 mg/kg) during the procedure. Clopidogrel was administered as a loading dose of 300 mg before or immediately after the procedure. Patients treated with PES were prescribed for a minimum of 6 months of clopidogrel (75 mg/day), based on randomized controlled trials [2]. For patients treated with BAS, clopidogrel was prescribed for a minimum of 3 months. Lesions were treated according to current standard interventional techniques, with the final strategy (thrombectomy devices, direct stenting, postdilatation, periprocedural glycoprotein IIb/IIIa inhibitor, intravascular ultrasound) left entirely up to the operator’s discretion. Angiographic success was defined as a residual stenosis <30% by visual analysis in the presence of TIMI flow grade 3.

Please cite this article as: Karjalainen PP, et al, Long-term clinical outcome with titanium-nitride-oxide-coated stents and paclitaxel-eluting stents for coronary revascularization in an unselected population, Int J Cardiol (2009), doi:10.1016/j.ijcard.2009.03.120.
sided p value < 0.05 was required for statistical significance. All cause death, TVR, MI and MACE were analyzed by means of Kaplan–Meier survival curves during the 3 years of follow-up and the differences between groups were compared using log-rank test. All data were analyzed with the use of SPSS version 11 [14] and SAS system for Windows version 9.1 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Clinical follow-up of the original study population

Between May 2003 and November 2004, 201 patients (218 lesions/221 stents) were treated with BAS, and 204 patients (244 lesions/247 stents) with PES. The baseline clinical characteristics of the study population and the main procedural characteristics have been described in detail previously [9]. Briefly, the BAS patients were older, and they had more often hypercholesterolemia and hypertension in their medical history. In addition, BAS patients had more often acute MI as their presenting symptom and more complex B and C-type lesions treated. The total stent length was, however, significantly longer (p < 0.001) in the PES group.

Outcome events during the 3 year follow-up are listed in Table 1. Complete follow-up was obtained in all 405 patients. MACE-free survival at 3 years was 86.1% in the BAS group, as compared with 76.5% in the PES group (p = 0.02, Table 1, Fig. 1). The rate of recurrent MI or cardiac death was significantly lower in the BAS group compared with the PES group (p < 0.001). In addition, a total of 15 patients (7.4%) suffered ST in the PES group, of which 8 cases occurred after 1 year from the index procedure (very late ST). There was no ST observed in the BAS group. Clinically driven control angiography was done in 28% of the patients in BAS group and 29% of the patients in PES group during the 3 year follow-up.

In multivariable analysis, MACE at 3 years was predicted by older age (HR 1.03, 95% CI 1.01–1.05, p = 0.02), previous MI (HR 1.7, 95% CI 1.0–2.8, p = 0.03), non-ST-elevation MI as presenting symptom (HR 1.8, 95% CI 1.1–3.0, p = 0.01) and the use of PES (HR 2.0, 95% CI 1.2–3.2, p = 0.006). MI or cardiac death was predicted by older age (HR 1.05, 95% CI 1.02–1.08, p < 0.001), previous PCI (HR 2.1, 95% CI 1.2–3.6, p = 0.009) and the use of PES (HR 3.2, 95% CI 1.7–5.8, p < 0.001). After multivariable models were adjusted for propensity score the differences in MACE (HR 2.2, 95% CI 1.2–3.8, p = 0.007) and MI or cardiac death (HR 4.1, 95% CI 2.1–8.1, p < 0.001) between groups remained significant.

3.2. Clinical follow-up of the patients receiving BMS or undergoing CABG

A total of 184 patients underwent PCI with BMS implantation during the same study period. Baseline and procedural characteristics in BMS group compared to original study population were comparable except that PES patients had more PCI’s in their medical history (24%...
in PES group vs. 7% in BMS group), and PES patients also received longer stents than BMS patients (21.2 mm vs. 16.4 mm, respectively). In BMS group, patients had more often acute non-ST-elevation MI as their presenting symptom before the procedure compared with PES group (39% in BMS group vs. 24% in PES group). When comparing to BAS group, BMS patients had less often previous MI in their medical history (44% in BAS group vs. 32% in BMS group) and also less complex C-type lesions treated (25% vs. 4%, respectively).

CABG was done in 124 patients during the study period (mean age 64 years [range 38–85], 86% male). Diabetes was present in 26%, hypercholesterolemia in 92% and hypertension in 62% of patients, and 18% of patients were current smokers. A total of 14 patients (11%) had revascularization (11 patients PCI and 3 CABG) and 33 patients (27%) MI in their medical history. Ten patients (8%) had single vessel disease, and 41 patients (9 patients had ST-elevation MI, 28 non-ST-elevation MI and 4 unstable angina) presented with acute coronary syndrome before the index angiography and subsequent CABG.

The overall rate of MACE in CABG patients during 3 years of follow-up was 4% including 3 events of sudden cardiac death (2.4%), 3 events of acute MI (2.4%) and 1 event of TVR (0.8%). Only 1 patient died during the index hospitalisation, and this event occurred 2 days after the CABG. In addition, 2 patients died for non-cardiac cause during the follow-up.

Fig. 1 illustrates the 3 year outcome events (MI, all cause death, TVR and MACE) in patients who received either BAS, PES or BMS, and in patients who underwent CABG. During the 3 year follow-up, per-protocol defined ST occurred in 2.7% of patients in BMS group (p = 0.4 vs. BAS group; p = 0.03 vs. PES group).

3.3. Late follow-up after the clopidogrel discontinuation

A consecutive series of 589 non-selected patients underwent PCI with stenting during the study period and 519 of them remained MACE free at the time of clopidogrel discontinuation (184 patients in BAS, 183 in PES and 152 in BMS groups). During the 12 month follow-up after the clopidogrel withdrawal, there was no difference in the incidence of MACE between the three groups, but the incidence of MI was higher in the PES group compared with the other two stent groups (Fig. 2). After the clopidogrel discontinuation, ST occurred more frequently in the PES group compared with the BAS group (3.8% vs. 0%, p = 0.009).

4. Discussion

4.1. Major findings

This study is the first long-term comparison of BAS with PES in routine clinical practice. The major finding of this study is that the unrestricted use of BAS in de novo lesions leads to a favourable long-term outcome compared with PES even in high-risk patients with complex coronary lesions. Secondly, although the overall risk of ST was fairly low, it was concentrated on the use of PES in the setting of acute MI. In addition, between 1 to 3 years, the use of PES resulted in significantly higher incidence of recurrent MI, ST and subsequent MACE compared with the use of BAS. The present study also showed that after clopidogrel discontinuation the rate of recurrent MI and very late ST was more common in PES group compared with other stent groups.

In patients undergoing CABG, we observed lower rates of MACE and repeated revascularization compared to other study groups. On the other hand, the similar incidence of all cause death was observed in CABG and PES patients.

4.2. Safety of DES

At present, the use of DES is the most effective way to reduce ISR according to randomized controlled trials in selected patient groups [1–3]. However, there is no evidence that DES or BMS could influence mortality or MI after stent implantation [2,3]. The benefit of the 1st generation and pioneer DES’s (Cypher® and Taxus®) is related to more powerful inhibition of neointimal hyperplasia compared with BMS but these devices may have some side effects as well, some of which only arose recently [4,15]. There have been some concerns that some patients develop ST, a life threatening complication, unusually late after the implantation of DES [4]. The overall rate of ST in PES group was higher in the present study than in previous studies and registries of DES [2,4,5,15–17]. The higher rate may have been due to the inclusion of patients with more complex conditions and lesions and a higher prevalence of acute coronary syndromes. Total stent length was significantly longer in the PES group compared with the other stent groups which may partly explain our findings.

It has been suggested that late ST has emerged as a distinct clinical entity with DES compared with BMS. Greater delay in arterial healing as manifested by poor endothelialization and persistence peristrit fibrin deposition associated with the implantation of DES may extend the risk of ST far beyond 30 days. Late ST is potentially due to a mismatch between the stent and the vessel and may be related to stent malapposition, overlapping stent placement, penetration of necrotic core, excessive stent length, bifurcation lesions, hypersensitivity to drug or polymer, or thrombogenic surface [18,19]. Premature discontinuation of antiplatelet therapy is recently recognised as the most important predisposing factor for late ST [20]. In the present study, 6 patients in the PES group and 4 patients in the BMS group suffered ST after the clopidogrel discontinuation. Most of the patients received dual antiplatelet treatment less than 12 months, and therefore the findings of the present work also underline the importance of proper and long-enough dual antiplatelet treatment.

Historically, diagnosis of ST has been based of angiographic and clinical criteria, but any measurements of ST were complicated by the lack of a standardized definition. The recently proposed Academic Research Consortium has developed definitions of ST for use in future trials [21]. For on-label use of DES, identical rates of ST were observed in both selected DES and BMS patients up to 4 years according to...
pooled analyses of randomized DES trials [4,5]. Recently presented data with the unrestricted use of first generation DES in routine clinical practice demonstrated that late ST occurred at a steady rate of 0.6% per year up to 4 years of follow-up [15].

In addition, despite the different incidence of ISR and ST, long-term death and MI rates appeared to be similar in pivotal DES trials in patients receiving either BMS or DES, including only relatively low-risk patients. The incidence of all cause death in our study was similar between the study groups whilst the rate of recurrent MI appeared to be higher in the PES group. Although DES’s seem to be safe and effective in on-label use, the long-term safety of off-label indications has not yet been properly evaluated.

4.3. Titanium-nitride-oxide-coating

The rate of TLR was moderately low in both BAS and PES groups. Surprisingly, there was no ST in the BAS group. Stent coating may contribute to these findings, since in vitro study has suggested that titanium-nitride-oxide reduces platelet adhesion and fibrinogen binding compared with stainless steel [6]. Titanium, a material commonly used for medical implants, features superior biocompatibility when compared with stainless steel, gold, or other surface coatings. Metallic sheaths coated with titanium nitride or titanium oxide exhibited higher cell density values on their surface compared to those without coating, supporting the view that deployment of stents with these coatings may achieve earlier complete endothelial coverage [7]. The safety of BAS has been confirmed by several clinical studies in both unselected populations as well as in the most complex indications such as diabetics, small vessels and acute MI [8–11].

4.4. Outcome of patients receiving BMS or undergoing CABG

At 3 years, the MACE rate in BMS group was higher compared to other stent groups and also to CABG group. This was mainly driven by a moderately high incidence of recurrent MI, TLR and cardiac death in the BMS group. It seems evident that when BMS are compared to DES [4,5] and also newer generation coated stents [11], the rate of TLR is high. In addition, the present study showed a favourable long-term outcome (MACE, MI and TVR) in patients undergoing CABG compared with patients undergoing PCI imitating the results of ARTS I and II trials [22,23]. The small sample size in CABG group may, however, limit the interpretation of these results.

4.5. Limitation

The strength of our single-center registry is the fact that Satakunta Central Hospital is the only centre with coronary angiography capacity in the referral area. In this rural area, population is stationary enabling trials [22,23]. The small sample size in CABG group may, however, give rise to unrecognised selection and performance bias. Angiographic control was performed in a minority of patients, and we may have underestimated the incidence of angiographic ISR and silent ST. On the other hand, by relying on clinical follow-up only, we avoided the chance of unnecessary TLR due to the oculostenotic reflex or patient’s unjustified anxiety.

5. Conclusions

In conclusion, BAS resulted in favourable clinical outcome during the 3-year follow-up with a reduced incidence of recurrent MI, MACCE and ST compared with PES. The present findings suggest that there is a place for these new-generation bare-metal, “bio-active”-stents with proper vascular healing in the present day interventional cardiology.

Acknowledgement

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology [24].

References