Pooled Analysis of Trials Comparing Titanium-Nitride-Oxide-Coated Stents with Paclitaxel-Eluting Stents in Patients Undergoing Coronary Stenting..............................................................P.P. KARJALAINEN, ET AL.
Pooled Analysis of Trials Comparing Titanium-Nitride-Oxide-Coated Stents with Paclitaxel-Eluting Stents in Patients Undergoing Coronary Stenting

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ABSTRACT: We performed a pooled analysis of three trials comparing titanium-nitride-oxide-coated bioactive stents (BAS) with paclitaxel-eluting stents (PES) in 1,774 patients. All patients were followed for 12 months. The primary outcomes of interest were recurrent myocardial infarction (MI), death and target lesion revascularization (TLR). Secondary endpoints were stent thrombosis (ST) and major adverse cardiac events (MACE) including MI, death and TLR. There were 922 patients in the BAS group and 852 in the PES group. 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 MACE (8.9% vs. 12.6%; risk ratio 0.71, 95% CI 0.54–0.94; \( p = 0.02 \)) during the 12 months of follow up. In contrast, the differences between BAS and PES were not statistically significant with respect to TLR (risk ratio 0.98, 95% CI 0.68–1.41), death (risk ratio 0.96, 95% CI 0.61–1.51) and definite ST (risk ratio 0.28, 95% CI 0.05–1.47). In conclusion, the results of this analysis suggest that BAS is effective in reducing TLR and improves clinical outcomes by reducing MI and MACE compared with PES.


Standalone balloon angioplasty has been replaced with the use of coronary stents because of the near-elimination of abrupt closure and emergency coronary artery bypass graft surgery (CABG).1,2 Drug-eluting stents (DES), including paclitaxel-eluting stents (PES), have been shown to improve early and late outcomes as compared with bare-metal stents (BMS), predominantly as a result of a reduction in in-stent restenosis (ISR) and subsequent target lesion revascularization (TLR).3,4 Recently, there have been concerns about the safety of DES, e.g., most notably late or very late stent thrombosis (ST).5,6 On the other hand, stent coatings with compounds like titanium-nitride-oxide seem to decrease acute surface thrombogenicity7–11 and reduce ISR when compared with conventional stainless-steel stents.8 Results from several trials comparing titanium-nitride-oxide coated bioactive stent (BAS) and PES have been previously reported.9,12–14 BAS have been shown to result in comparable clinical outcomes compared with PES in the real-world clinical practice involving high-risk patients and patients presenting with acute myocardial infarction (MI). Since these studies had insufficient power to assess the incidence of rare outcome events such as ST, we decided to perform a pooled analysis based on data from studies comparing BAS and PES.

Methods

Search strategy. The reference search was performed through PubMed, Science Direct, and the Cochrane Library up to November 2009 for studies comparing BAS versus PES in myocardial revascularization and reporting on at least 1-year outcomes. Tangential electronic exploration of related articles and hand searches of bibliographies and related journals were also performed. The key words employed in the search were: titanium, paclitaxel, eluting, titanium-nitride-oxide-coated, Titan, BAS, PES and stent. Studies evaluating any other coronary stents other than BAS and PES were not included in this study. Two review authors (PPK, FB) independently assessed the titles and abstracts of references identified by the search strategy according to the selection criteria. Full versions of the identified articles were obtained if, from the initial assessment, they appeared to satisfy the inclusion criteria. Full papers were checked independently to identify those that matched the inclusion criteria. Any disagreement was resolved by consensus. Reference lists of all retrieved studies were screened to identify further studies which were then reviewed. Studies were included if they met each of the following criteria: prospective studies with randomization as well as with control groups comparing BAS with PES in coronary revascularization reporting at least two pertinent clinical outcome endpoints among the following: death, MI, revascularization of the target vessel (CABG or repeat percutaneous coronary intervention [PCI] to treat ISR or a stenosis immediately adjacent to the stent). Clinical endpoints are reported as originally defined by the authors.

Statistical analysis. This analysis was performed using Review Manager (RevMan) Version 5.0 for Windows (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2008). The outcome endpoints were analyzed as dichotomous and continuous variables. Continuous outcome endpoints were expressed as weighted mean difference with a 95% confidence interval (95% CI). Dichotomous outcome endpoints were expressed as risk ratio (RR) with 95% CI. Heterogeneity was explored by calculating the
Table 1. Characteristics of three prospective studies included in the present pooled analysis comparing titanium-nitride-oxide bioactive stents (BAS) and paclitaxel-eluting stents (PES) in coronary revascularization.

<table>
<thead>
<tr>
<th>Data are mean (SD) or numbers (%)</th>
<th>BAS, 922 Patients (%)</th>
<th>PES, 852 Patients (%)</th>
<th>( p )-Value, Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>Bern Registry 67 ± 12</td>
<td>PES, 852 Patients 65 ± 11</td>
<td>0.03, 1.73* (0.18–3.29)</td>
</tr>
<tr>
<td>Male</td>
<td>Bern Registry 700 (75.9%)</td>
<td>PES, 852 Patients 636 (74.6%)</td>
<td>0.58, 1.02 (0.96–1.07)</td>
</tr>
<tr>
<td>Sex</td>
<td>Bern Registry 395</td>
<td>PES, 852 Patients 332</td>
<td>0.0001, 1.20 (1.11–1.129)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>PES, 852 Patients 199 (21.6%)</td>
<td>PES, 852 Patients 171 (20.1%)</td>
<td>0.49, 1.07 (0.89–1.28)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>PES, 852 Patients 629 (68.2%)</td>
<td>PES, 852 Patients 483 (56.7%)</td>
<td>&lt; 0.0001, 1.20 (1.11–1.129)</td>
</tr>
<tr>
<td>Smoking</td>
<td>Bern Registry 404 (43.8%)</td>
<td>PES, 852 Patients 316 (37.1%)</td>
<td>0.005, 1.18 (1.05–1.32)</td>
</tr>
<tr>
<td>History of MI</td>
<td>Bern Registry 560 (60.7%)</td>
<td>PES, 852 Patients 545 (64.0%)</td>
<td>0.77, 0.98 (0.84–1.14)</td>
</tr>
<tr>
<td>Previous PCI</td>
<td>Bern Registry 112 (12.1%)</td>
<td>PES, 852 Patients 124 (14.6%)</td>
<td>0.07, 1.27 (0.98–1.66)</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>Bern Registry 87 (9.4%)</td>
<td>PES, 852 Patients 72 (8.5%)</td>
<td>0.46, 1.12 (0.83–1.50)</td>
</tr>
<tr>
<td>Acute STEMI</td>
<td>Bern Registry 312 (33.8%)</td>
<td>PES, 852 Patients 291 (34.2%)</td>
<td>0.82, 0.94 (0.53–1.65)</td>
</tr>
<tr>
<td>Acute NSTEMI</td>
<td>Bern Registry 264 (28.6%)</td>
<td>PES, 852 Patients 233 (27.3%)</td>
<td>0.28, 1.08 (0.94–1.24)</td>
</tr>
<tr>
<td>GP IIb/IIIa inhibitor</td>
<td>Bern Registry 236 (25.6%)</td>
<td>PES, 852 Patients 158 (18.5%)</td>
<td>0.10, 1.69 (0.91–3.16)</td>
</tr>
</tbody>
</table>

\( I^2 \) statistic to quantify the degree of heterogeneity across the trials that could not be attributed to chance alone. If there was a significant heterogeneity (\( I^2 < 40\% \)), a random-effect model was chosen, otherwise a fixed-effect model was used.

**Results**

We identified seven studies comparing BAS with either BMS or DES. Three of those studies compared exclusively BAS with BMS and were therefore excluded from the analysis. The study by Grenadier et al has been excluded for the analysis because they reported unpublished results on the use of BAS compared with PES or sirolimus-eluting stents. Altogether, three trials with 1,774 patients were included in the present analysis: two prospective, nonrandomized reports (Pori registry, Bern registry) and one prospective, randomized multicenter trial (TITAX-AMI). Baseline clinical characteristics of these reports are summarized in Table 1. A total of 922 patients (Pori, n = 201; Bern, n = 507; TITAX-AMI, n = 214) were treated with BAS, and 852 patients (Pori, n = 204; Bern, n = 437; TITAX-AMI, n = 211) with PES. The patients in the BAS group were older and were more likely to undergo treatment for hypertension. Lesion and procedural characteristics are listed in Table 2. Lesion and stent lengths, as well as diameters, were comparable between the study groups. All trials reported results from 12-month clinical follow up. The mean length of clopidogrel therapy in BAS and PES groups was 7.7 and 8.2 months in the Pori registry and 7.6 and 10.0 months in the TITAX-AMI trial, respectively. In the Bern registry, clopidogrel was prescribed for 1 month in the BAS group and for 12 months in the PES group.

Figure 1 shows forest plots on the absolute rate of MI and MACE during the 12-month clinical follow up in the BAS versus PES groups, with the risk ratio for each of these trials. Across the trials, no evidence of heterogeneity was observed (\( I^2 = 0\% \)). With respect to recurrent MI, the use of BAS was associated with a risk ratio of 0.50 (95% CI 0.31–0.81; \( p = 0.004 \)) compared with PES. Similarly, BAS were associated with a risk ratio of 0.71 (95% CI 0.54–0.94; \( p = 0.02 \)) for MACE. Twelve-month probability of MACE was 8.9% in the BAS group and 12.6% in the PES group (\( p = 0.014 \)). The number of patients who suffered TLR, death and definite ST are shown in Figure 2. Overall, the use of BAS was associated with a...
risk ratio of 0.98 (95% CI 0.68–1.41; p = 0.90) for TLR, 0.96 (95% CI 0.61–1.51; p = 0.85) for death, and 0.28 (95% CI 0.05–1.47; p = 0.13) for definite ST when compared with PES.

**Discussion**

To our knowledge, this is the first pooled analysis comparing BAS with PES in patients undergoing PCI. With respect to stent efficacy as measured by the device-specific, ischemia-driven TLR, we found no significant difference between patients treated with either BAS or PES. On the other hand, the safety data of the present analysis showed that treatment with BAS was associated with a 52% decrease in the risk of MI and a 29% decrease in MACE compared with PES. However, no significant difference was found in the risk of definite ST or death between the study groups.

Previous studies and meta-analysis have demonstrated a drastic reduction of neointimal hyperplasia and subsequent TLR with DES when compared with BMS in patients with various clinical and angiographic characteristics. The data from the present analysis is intriguing because it includes MI patients (TITAX-AMI) and all-comers (Pori, Bern), and therefore this cohort of patients reflects our everyday clinical practice. Although the present pooled analysis shows imprecise estimates of TLR, the findings are of a similar magnitude as presented with the use of DES in previous randomized trials. Interestingly, the rate of TLR was moderately low in both BAS and PES groups.

The safety of DES has been scrutinized in depth and there have been concerns that some patients develop ST, a life-threatening complication, unusually late after stent implantation. However, in randomized trials and large-scale registries, mortality and MI rates were found to be similar or even lower with use of DES. In our analysis, the incidence of definite ST was comparable among patients treated with BAS or PES (0.7% vs. 2.2%), which substantiates the safety of these devices. Nevertheless, the MI rate was found to be significantly higher with the use of PES compared with BAS.

The literature is rich with data regarding the advantages of titanium (-oxides) used for implantable medical devices. In our analysis, the incidence of MI and MACE was lower in patients receiving BAS. Titanium-nitride-oxide coating may contribute to these findings, since in vitro examinations showed that titanium oxides were able to inhibit platelet aggregation and fibrin growth. In addition, a recent report demonstrated that titanium-nitride-oxide was able to promote and accelerate endothelial cell growth when compared with other materials such as stainless steel or nitinol, supporting the hypothesis that a stent with titanium-nitride-oxide coating could achieve earlier reendothelialization compared with BMS or DES.

Our analysis included trials with follow up of 12 months. Recently, longer-term follow-up data were published from the Pori registry (36 months) and the TITAX-AMI trial (24 months). Both of these trials exhibited an increase in ST, cardiac death and MI in the PES group between 12- to 24-month follow up, which was mainly seen after clopidogrel discontinuation. An alternative
explanation for the lower incidence of late ST and MIs with BAS is the stent coating and its ability to enhance vascular healing at the site of stent implantation. In addition, polymers used on current DES may trigger an immune reaction and induce chronic inflammation, explaining some of the late events after PES use.

**Study limitations.** The findings of our pooled analysis should be interpreted with caution. Regardless of the benefit of a pooled analysis to increase the statistical power, the rare occurrence of adverse events might limit the capacity of our analysis to detect differences between the treatment strategies. One limitation of the present study is that only three trials were available for the analysis. Two of them were prospective registries, hence our analysis is liable to reflect a selection bias.

**Conclusions**

In conclusion, we observed comparable efficacy with BAS and PES in patients undergoing PCI during 12 months of clinical follow up. On the other hand, the use of BAS reduced the risk of recurrent MI and MACE compared with PES.

**References**

Figure 2. Risk of target lesion revascularization, cardiac death and definite stent thrombosis during 12-month clinical follow up in the BAS versus PES groups. BAS = bioactive stents; PES = paclitaxel-eluting stents.