Long-term outcomes after treatment of bare-metal stent restenosis with seal-wing or iopromide-coated paclitaxel-eluting balloon catheters.

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Research article

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Abstract

**Background:**

The efficacy of paclitaxel-eluting balloon catheters (PEB) is affected by the method of binding paclitaxel to the balloon catheter surface.

The aim of this study was to compare the long-term efficacy of seal-wing and iopromide-coated PEB for bare-metal stent restenosis (BMS-ISR) treatment.

**Methods:**

We analyzed 3-year clinical follow-up data of 132 patients with BMS-ISR. 64 of them were treated with seal-wing PEB, the control group comprised 68 patients from the iopromide-coated PEB arm of the previous TIS clinical study.

Primary end-points included the occurrence of major adverse cardiac events (MACE; cardiovascular [CV] death, myocardial infarction [MI], or target vessel revascularization [TVR])

**Results:**

At 3 year clinical follow-up, the incidence of MACE was significantly higher in the seal-wing PEB than in the iopromide-coated PEB group (40.6 % vs. 19.1%; \( p=0.008 \)); the same can be said about TVR (26.9% vs. 8.8%; \( p=0.011 \)). Similarly, the event-free survival was significantly longer in the iopromide-coated PEB than in the seal-wing PEB group (\( p=0.021 \)). No significant differences were found between the groups where CV mortality (4.7% vs. 5.9%; \( p=1.000 \)), MI (6.3% vs. 4.4%; \( p=0.712 \)), definite stent thrombosis (0% vs. 2.9%; \( p=0.497 \)) or the second MACE (4.7% vs. 1.5%; \( p=0.354 \)) are concerned.

**Conclusions:**

Compared to iopromide-coated PEB, the use of seal-wing PEB for BMS-ISR treatment led to a significantly higher 3-year occurrence of MACE and TVR.

**Trial registration:**

ClinicalTrials.gov; [https://clinicaltrials.gov](https://clinicaltrials.gov); NCT01735825 (Registered 7 Nov 2012).

**Background**

The method of binding paclitaxel to the balloon catheter surface represents the principal factor affecting the efficacy of paclitaxel-eluting balloon catheters (PEB). We previously demonstrated that in bare-metal stent restenosis (BMS-ISR) treatment, the use of iopromide-coated PEB resulted in significantly better 12-month angiographic and clinical outcomes in comparison with seal-wing PEB [1].
In our present study, we aimed to compare the long-term efficacy of BMS-ISR treatment using these PEBs with different methods of paclitaxel binding to their surface.

**Methods**

**Patients and Study Design**

The methods of our study have been previously described in detail [1, 2]. Briefly, two groups of patients were compared; the first (hereinafter treatment group) comprised consecutive adult patients (> 18 years of age) with BMS-ISR (≥ 50% diameter stenosis; DS) treated with seal-wing PEB (Protége) in the Cathlab of the University Hospital Ostrava over the period of three years (2013–2015). Patients with BMS-ISR who were treated using iopromide-coated PEB (Sequent Please) in the previous randomized part of the TIS study [2] formed the other group, hereinafter referred to as the control group. The principal exclusion criteria were as follows: concomitant diseases carrying expected survival of < 12 months or limiting the possibility of follow-up coronary angiography.

In this study, we extended the clinical follow-up to 3 years. Primary end-point included the incidence of major adverse cardiac events (MACE; cardiovascular [CV] death, myocardial infarction [MI], or target vessel revascularization [TVR]). In addition, the occurrence of stent thrombosis [ST] and the second MACE was also followed.

**Interventions**

The PCI was performed on standard condition [1, 2]. After appropriate lesion preparation, the PEB was inflated for 30 s at the recommended pressure. In the seal-wing PEB Protége (Blue Medical, Helmond, the Netherlands), paclitaxel (3 µg/mm²) is firmly bound directly to the balloon catheter surface prior to folding (between the wings and the hydrophilic coating, which prevents releasing particles while bending the balloon or during its transition to the stenosis). In effect, only paclitaxel, not the coating, is released into the vessel wall [3, 4]. On the other hand, in the iopromide-coated PEB Sequent Please (B. Braun AG, Melsungen, Germany) paclitaxel (also 3 µg/mm²) was bound via the hydrophilic contrast agent iopromide (Paccocath®,), which increased its solubility and vascular wall penetration. The implantation of an additional bailout stent was allowed in case of edge dissection. The patients received aspirin 100 mg and clopidogrel 75 mg per day for 6 months.

**Follow-Up**

After the first year, patients were followed up every 12 months (+/-2 months) through an office visit or at least a phone call with the aim to assess very long-term outcomes, as per study protocol. At 3 years (+/-0.5 year), the final clinical follow-up was performed, which included a full clinical evaluation and recording of all MACE.

The adjudication of events was blinded and performed by an independent investigator. Any death that was not clearly due to non-cardiac causes was considered cardiac related. The third universal definition
of myocardial infarction by the European Society of Cardiology [5] was used as a definition of MI; stent thrombosis was defined according to the Academic Research Consortium criteria [6].

**Statistical Analysis**

Continuous variables were tested for normality using the Shapiro-Wilk test. Depending on the results of that test, the values were either tested using the independent-sample Student’s t-test and are presented as mean and standard deviation (SD) where the distribution was normal, or tested using Mann-Whitney/Wilcoxon U test and presented as median and 25%-75% interquartile range where the distribution was not normal. Categorical variables are presented as counts and percentages and were compared using the χ² or Fisher’s exact test as appropriate. A P value of < 0.05 was considered significant. Kaplan-Meier analysis with Log-rank test was used to analyze time-to-event data. Cox proportional hazard regression was performed to evaluate hazard ratio with or without adjustment for significantly different baseline variables. All statistical analyses were performed using IBM SPSS Statistics version 22.

**Results**

The course of the study is shown in the CONSORT flow diagram (Figure 1). We analyzed 3-year clinical follow-up data of 132 patients with BMS-ISR. 64 of them were treated with seal-wing PEB and the control group comprised 68 patients from the iopromide-coated PEB arm of the previous TIS clinical study. Table 1 presents the baseline demographic, clinical, angiographic, and ISR characteristics of both groups.

At the 3-year follow-up, clinical data of all patients were collected. The mean time to the 3-year follow-up was 1170 days (±176; median 1260) in the seal-wing PEB and 1210 days (±167; median 1270) in the iopromide-coated PEB group (p=0.089).

Table 2 shows the MACE incidence within 12 months from the intervention, between months 13-36, and over the entire follow-up period. At the 3-year clinical follow-up, the seal-wing PEB was associated with significantly higher incidence of MACE (p=0.008) and TVR (p=0.011) compared to the iopromide-coated PEB. However, no significant differences were found between the groups regarding CV mortality (p=1.000), MI (p=0.712), definite ST (p=0.497) or the second MACE (p=0.354). The greatest difference in the incidences of MACE and TVR between the groups was observed in the first year of the follow-up (p=0.003 and 0.009, respectively).

Figures 2 and 3 present estimates of event-free survival (EFS). EFS (time-to-MACE and time-to-TV) was significantly longer in the iopromide-coated PEB compared to the seal-wing PEB group (p=0.021 and 0.006, respectively).

Cox proportional hazards regression analysis revealed significantly higher risk of MACE (including TVR) in the seal-wing PEB group, even after the adjustment for significantly different baseline variables (e.g. postdilatation) [Table 3].
Discussion

In clinical practice, paclitaxel is used in DEB as an effective antiproliferative agent. The drug is highly lipophilic, with rapid penetration into the tissue. The method of paclitaxel binding to the balloon catheter surface is probably the single most significant factor influencing the PEB efficacy. Originally, as described by Scheller et al., paclitaxel was bound via a hydrophilic contrast agent iopromide increasing its solubility and vascular wall penetration [7]. It has been established that 3 µg/mm² is the optimum drug concentration [7], which is the case also in both compared PEBs.

Multiple studies with follow-up times of 9 to 12 months demonstrated the efficacy of iopromide-coated PEB treatment for BMS-ISR in comparison with POBA or paclitaxel-eluting stents (PES); however, the comparison of PEB with the 2nd generation DES with everolimus (everolimus-eluting stents; EES) still remains unclear. Moreover, the long-term results of these studies are now also available.

In the long-term follow-up (5.4+/−1.2 years) of Paccocath I and II studies, the PEB group confirmed the sustained significant reduction of MACE (p = 0.009) compared to POBA, which was largely driven by the TVR incidence reduction from 38.9–9.3% (p = 0.004) [8, 9].

In the PEPCAD II study, despite the trends toward reduced 12-month incidences of binary restenosis (p = 0.06) and MACE (p = 0.08) [10], at 3-year follow-up, the differences in incidences of MACE (p = 0.14) and TVR (p = 0.10) between PEB and PES groups did not reach statistical significance [11].

Contrary to different 12-month angiographic results between the TIS and RIBS V studies comparing the PEB and EES [2, 12] in the long-term clinical follow-up, the only significant difference was a lower incidence of target lesion revascularisation in the EES group of the RIBS V study (p = 0.04). The overall incidence of 3-year MACE did not differ between the groups in both studies (p = 0.230 and p = 0.64, respectively) [13, 14].

Many other PEBs with different coating are currently used in clinical practice, including the DIOR II (shellac-coated; Eurocor, Bonn, Germany), the IN.PACT Falcon (urea-coated; Medtronic, Minneapolis, USA), the Pantera Lux (butyryl-tri-hexyl citrate [BTHC]-coated; Biotronik, Berlin, Germany), etc. Nevertheless, among several registries, the most favourable results were achieved with the use of iopromide-coated PEB.

In a subanalysis of the SCAAR registry, iopromide-coated PEB (paclitaxel 3 µg/mm2) was used for treating ISR lesions. Compared to uncoated PEB (paclitaxel 2 µg/mm2), iopromide-coated PEB was associated with a lower risk of binary restenosis (adjusted HR: 0.48; 95%CI: 0.23–0.98 [15].

Benezet et al. found that patients with BMS or DES-ISR treated with iopromide-coated PEB displayed a significantly lower TLR rate at 36 months (p = 0.03) compared to shellac-coated PEB [16].

In contrast, in the Düsseldorf DCB registry, patients treated for ISR with BTHC-coated PEB had significantly longer event-free survival rates (p = 0.405) than those treated with the iopromide-coated PEB
In a non-randomised study, Nijhoff et al. compared the efficacy of urea-coated and shellac-coated PEB in patients with BMS or DES-ISR. The urea-coated PEB group showed significantly lower 6-month LLL \((p = 0.014)\), a higher FFR value distally \((p = 0.029)\), and a reduced volume percentage of neointimal hyperplasia \((p = 0.006)\). The incidence of repeated binary restenosis was not significantly different between groups \((p = 0.16)\) and a trend was observed towards lower TLR \((p = 0.057)\) in the urea-coated PEB group [18].

Our results confirm that iopromide coating influenced the efficacy of PEB in ISR treatment. We previously demonstrated that patients with BMS-ISR showed significantly higher 12-month LLL \((p < 0.0001)\), incidence of repeated binary restenosis \((p = 0.012)\), 12-month MACE \((p = 0.003)\) and TVR \((p = 0.009)\) rates following treatment with seal-wing PEB compared to iopromide-coated PEB [1].

The difference in the overall MACE incidence was predominantly caused by the significantly higher incidence of TVR in the seal-wing PEB group due to a higher rate of repeated binary restenosis. No significant differences were found between the groups where CV mortality, MI, definite ST or the second MACE are concerned. These differences in the clinical outcomes (MACE and TVR) occurred mainly during the first year, however they also persisted after 3 years of follow-up. The use of the seal-wing PEB for BMS-ISR treatment was associated with a significantly higher risk of MACE (including TVR), even after the adjustment for significantly different baseline variables.

**Limitations**

Our study has several limitations. In particular, it was a non-randomized study comparing patients who underwent one type of treatment (seal-wing PEB) with patients from the control arm of the previous TIS study.

Nevertheless, the baseline parameters of both patient cohorts did not differ with respect to main baseline parameters and hence, it is unlikely that the selection bias would have played a major role. Similarly, the further clinical follow-up and medical therapy, including duration of dual antiplatelet treatment, were also the same.

**Conclusions**

Treatment of BMS-ISR using seal-wing PEB led to a significantly higher 3-year TVR and overall MACE incidences compared to iopromide-coated PEB.

**Abbreviations**

BMS-ISR - bare-metal stent restenosis

CV - cardiovascular
Declaration Section

Ethics approval and consent to participate

The study protocol complied with the Declaration of Helsinki and was approved by the Ethics Committee of University Hospital Ostrava, Czech Republic.

The study was registered at ClinicalTrials.gov (NCT01735825) on the 7th November 2012.

Written informed consent was obtained from each patient before enrollment in the study.

Consent for publication

Written informed consent for publication was obtained from each patient before enrollment in the study.

Availability of data and materials

The data sets supporting the results of this article are available in the LabArchives repository [http://dx.doi.org/10.25833/2pxh-1q10].
Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

LP: study design; PK, OH: literature search; LP, PK: data collection; LP, PK, OH: data analysis; JZ: statistical analysis; LP, OH: data interpretation; All authors: manuscript revision. All authors read and approved the final manuscript.

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CONSORT guidelines statement

We hereby declare that our study adheres to CONSORT guidelines and include a completed CONSORT checklist as an additional file.

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Tables

Table 1. Baseline parameters
| Demographic parameters | seal-wing PEB | iopromide-coated PEB | p  |
|-------------------------|--------------|----------------------|----|
| Patients/ISR lesions, n | 64/69        | 68/74                |    |
| Male/female             | 49(76.56%)/ 43(63.24%) |
|                        | 15(23.44%)/ 25(36.74%) | 0.288c |
| Age, years              | 65.25 ± 11.01a | 65.6 ± 10.9a         | 1.00d |
| Body mass index, kg/m²  | 28.38 ± 4.93a/21.19b | 28.7 ± 4.0a/19.23b   | 1.000e |
| Ejection fraction, %    | 52.31 ± 10.01a/55.00b | 49.74 ± 11.95a/50.00b | 0.732e |
| Diabetes mellitus       | 18 (28.12%)  | 17 (25.00%)          | 1.000c |
| Renal insufficiency     | 2 (3.12%)    | 2 (2.94%)            | 1.000f |
| CABG                    | 6 (9.38%)    | 3 (4.41%)            | 1.000f |
| Ever smoked             | 31 (48.44%)  | 31 (45.59%)          | 1.000f |
| Previous MI             | 31 (48.44%)  | 43 (63.24%)          | 0.117c |
| 2VD/3VD                 | 43 (67.19%)  | 38 (55.88%)          | 1.000c |
| Multi ISR               | 5 (7.81%)    | 4 (5.88%)            | 1.000f |
| Baseline PCI            |              |                      |    |
| ACSy (STEMI/NSTEMI)     | 37 (57.81%)  | 45 (66.18%)          | 0.966c |
| stable AP               | 27 (42.19%)  | 23 (33.82%)          |    |
| Type of lesion          |              |                      |    |
| B2/C                    | 47 (68.12%)  | 51 (68.92%)          | 1.000c |
| Lesion localization     |              |                      |    |
| LAD/RD                  | 34 (49.28%)  | 35 (47.30%)          | 1.000f |
| RCx/OM                  | 15 (21.74%)  | 16 (21.62%)          |    |
| RCA                     | 18 (26.09%)  | 22 (29.73%)          |    |
| SVG                     | 2 (2.9%)     | 1 (1.35%)            |    |
| Diameter of the previous stent, mm | 3.09 ± 0.48a/3.00b | 3.18 ± 0.43a/3.0b | 0.390e |
| Length of the previous stent, mm | 25.67 ± 15.48a/20.00b | 22.65 ± 11.70a/19.0b | 0.720e |
| In-stent restenosis     |              |                      |    |
| ACSy, STEMI/NSTEMI      | 19 (29.69%)  | 24 (35.29%)          | 1.000f |
| Stable AP               | 42 (65.62%)  | 41 (60.29%)          |    |
| Other, silent ischemia | 4 (6.25%) | 3 (4.41%) | 1.000\textsuperscript{e} |
|------------------------|-----------|-----------|------------------------|
| Time to ISR, months    | 12.49± 11.06\textsuperscript{a}/7.00\textsuperscript{b} | 12.10± 8.47\textsuperscript{a}/9.0\textsuperscript{b} | |
| **Type of ISR**         |           |           |                        |
| I (focal; all)          | 25 (36.23%) | 30 (40.54%) | 1.000\textsuperscript{f}       |
| II (diffuse)           | 33 (47.83%) | 34 (45.95%) |                        |
| III (proliferative)    | 6 (8.7%)   | 5 (6.76%)  |                        |
| IV (occlusion)         | 5 (7.25%)  | 5 (6.76%)  |                        |

**Periprocedural parameters**

| Cutting predilatation | 20 (28.99%) | 16 (21.62%) | 0.933\textsuperscript{c} |
|-----------------------|-------------|-------------|------------------------|
| ISR; PEB/EES diameter, mm | 3.27± 0.47\textsuperscript{a}/3.17\textsuperscript{b} | 3.32± 0.39\textsuperscript{a}/3.5\textsuperscript{b} | |
| ISR; PEB/EES length, mm | 23.19± 12.98\textsuperscript{a}/20.00\textsuperscript{b} | 22.53± 8.13\textsuperscript{a}/20.0\textsuperscript{b} | |
| Postdilatation, atm   | 13.48± 2.34\textsuperscript{a}/12.00\textsuperscript{b} | 14.84± 2.77\textsuperscript{a}/16.0\textsuperscript{b} | 0.009\textsuperscript{e} |
| Second stent implantation | 8 (11.59%) | 11 (14.86%) | 1.000\textsuperscript{c} |
| Crossover to DES      | 2 (2.9%)   | 2 (2.7%)   | 1.000\textsuperscript{c} |

Qualitative data are given as n (%); quantitative data as a mean (± standard deviation) and b median;
\textsuperscript{c} chi-square test; \textsuperscript{d} Student T-test; \textsuperscript{e} Mann-Whitney U test; \textsuperscript{f} Fisher's exact test.

**Table 2.** Incidence of MACE within 12 months, 1 to 3 years and for the entire follow-up period
|                  | Seal-wing PEB | Iopromide PEB | p<sup>a</sup> |
|------------------|---------------|---------------|--------------|
| patients, n      | 64            | 68            |              |
| **0-12 month**   |               |               |              |
| MACE all         | 17 (26.9%)    | 7 (10.3%)     | 0.003        |
| CV death         | 0 (0%)        | 1 (1.5%)      | 1.000        |
| MI               | 4 (6.3%)      | 1 (1.5%)      | 0.468        |
| TVR              | 13 (20.6%)    | 5 (7.4%)      | 0.009        |
| Definite ST      | 0 (0%)        | 1 (1.4%)      | 1            |
| **1-3 years**    |               |               |              |
| MACE all         | 9 (14.1%)     | 6 (8.8%)      | 0.343        |
| CV death         | 3 (4.7%)      | 3 (4.4%)      | 1.000        |
| MI               | 0 (0%)        | 2 (2.9%)      | 0.497        |
| TVR              | 4 (6.3%)      | 1 (1.5%)      | 0.198        |
| Definite ST      | 0 (0%)        | 1 (1.5%)      | 1.000        |
| 2nd MACE/TVR     | 3 (4.7%)      | 1 (1.5%)      | 0.354        |
| non CV death     | 6 (9.4%)      | 2 (2.9%)      | 0.156        |
| all cause of death | 9 (14.1%) | 5 (7.4%)      | 0.264        |
| **0-3 years**    |               |               |              |
| MACE all         | 26 (40.6%)    | 13 (19.1%)    | 0.008        |
| CV death         | 3 (4.7%)      | 4 (5.9%)      | 1.000        |
| MI               | 4 (6.3%)      | 3 (4.4%)      | 0.712        |
| TVR              | 17 (26.9%)    | 6 (8.8%)      | 0.011        |
| Definite ST      | 0 (0%)        | 2 (2.9%)      | 0.497        |
| 2nd MACE/TVR     | 3 (4.7%)      | 1 (1.5%)      | 0.354        |
| non CV death     | 6 (9.4%)      | 2 (2.9%)      | 0.156        |
| all cause of death | 9 (14.1%) | 6 (8.8%)      | 0.416        |
| Event-free survivals | 43 (67.2%) | 57 (83.2%)    | **0.026**    |

<sup>a</sup> Fisher's exact test

**Table 3.** Cox regression analysis
| Event                  | Predictor                        | Unadjusted estimates                                      | Adjusted estimates                                       |
|-----------------------|----------------------------------|------------------------------------------------------------|----------------------------------------------------------|
|                       |                                  | Sig. | HR | 95% CI for HR | Sig. | HR | 95% CI for HR |
|                       |                                  |      |    | Lower | Upper |      |    | Lower | Upper |
| MAC E                 | Group (1= Seal-wing PEB)         | 0.025 | 2.265 | 1.111 | 4.619 | 0.026 | 2.325 | 1.107 | 4.881 |
| CV death              | Group (1= Seal-wing PEB)         | 0.981 | 0.982 | 0.215 | 4.477 | 0.848 | 0.856 | 0.174 | 4.209 |
| Acute MI              | Group (1= Seal-wing PEB)         | 0.367 | 2.184 | 0.400 | 11.93 | 0.287 | 2.648 | 0.441 | 15.89 |
| TVR                   | Group (1= Seal-wing PEB)         | 0.010 | 3.162 | 1.320 | 7.573 | 0.009 | 3.387 | 1.363 | 8.420 |
| All course of death   | Group (1= Seal-wing PEB)         | 0.198 | 1.987 | 0.698 | 5.653 | 0.202 | 2.034 | 0.683 | 6.059 |
| Definite ST           | Group (1= Seal-wing PEB)         | 0.475 | 0.016 | 0     | 1383  | -     | -     | -     | -     |
| 2nd MAC E             | Group (1= Seal-wing PEB)         | 0.164 | 5.078 | 0.514 | 50.16 | 0.204 | 4.578 | 0.439 | 47.84 |

**Figures**
Figure 1

the CONSORT flow diagram
Figure 2

Event-free survival_time-to MACE
Figure 3

Event-free survival_time-to TVR

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- CONSORT2010Checklist.docx