Original article

Kardiologia Polska
2010; 68, 5: 503–509

ISSN 0022–9032

Novel biodegradable polymer-coated, paclitaxel-eluting stent inhibits neointimal formation in porcine coronary arteries

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Abstract

Background: Biodegradable polymer-coated stents may have positive effects on arterial healing, and reduce the need for prolonged antiplatelet therapy.

Aim: To assess the vascular effects of the biodegradable polymer proposed as a stent coating, as well as to evaluate inhibition of intimal hyperplasia by Biodegradable Polymer-Coated Paclitaxel-Eluting Stents (BP-PES, LUC-Chopin^{2TM}, Balton®) in porcine coronary arteries.

Methods: A total of 19 stents were implanted into the coronary arteries of 13 pigs: seven bare metal stents (BMS), six biodegradable polymer-coated stents (PCS) and six BP-PES. Animals were followed up for 28 days. Additionally, 11 BP-PES were implanted in four pigs which were followed for 90 days. Twenty eight and 90 days after stent implantation, the control coronary angiography was performed. Subsequently, the animals were sacrifised, their hearts were extracted and the coronary arteries were isolated for further histopathological analysis.

Results: After 28 days, BP-PES stents effectively limited neointimal hyperplasia in comparison to the control group (LL = 0.48 ± ± 0.06 for BMS *vs* 0.87 ± 0.16 for PCS *vs* 0.15 ± 0.05 mm for BP-PES; $p < 0.05$). However, at three months, a 'catch-up' effect in neointimal formation was observed. Histopathology demonstrated favourable safety, with complete endothelialisation and inflammation significantly decreased between one and three months.

Conclusions: It seems that the biodegradable polymer-coated, paclitaxel-eluting stent examined in the present study is both safe and feasible. This supports the first such study in humans being conducted.

Key words: biodegradable polymer, drug-eluting stents, neointimal hyperplasia, porcine

Kardiol Pol 2010; 68, 5: 503–509

INTRODUCTION

The efficacy of drug-eluting stents (DES) in preventing restenosis and reducing the risk of revascularisation has been proven in numerous clinical trials [1–5]. On the other hand, these stents simultaneously inhibit the physiological healing process of the vessel's wall, lengthen inflammatory reaction and adversely affect the restoration of correctly functioning endothelium [6–8]. It is believed that one possible cause of these adverse reactions might be the negative influence of the permanent presence of polymer used for stent coating and drug

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Received: 07.09.2009 **Accepted:** 06.01.2010

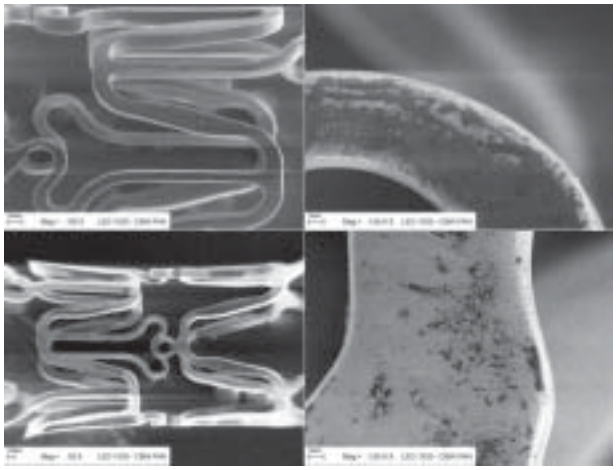

Figure 1. Polymer biodegradation in laboratory conditions. At the top polymer coating after a week in the system rinsing the stent with physiological salt solution. At the bottom stent area after eight weeks. Only little polymer focuses visible

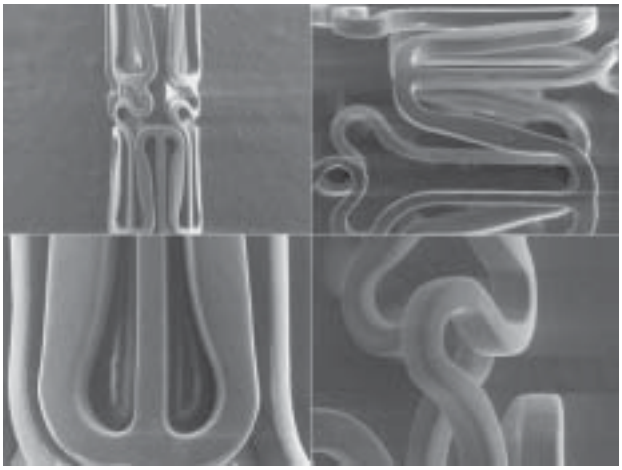

Figure 2. Microscopic pictures of BP-PES stent surface showed uniform biodegradable polymer coating without fractures or peeling [25]

elution. After the drug elution, polymer stays on the stent surface and may continue to incite local inflammatory reaction, impair healing, and eventually contribute to late and very late thrombosis [1, 6, 9–11]. This scenario could possibly be averted by the use of a biodegradable polymer. It would be absorbed from the stent surface following drug elution, leaving only a metal stent covered with neointima and endothelium without further irritation of the arterial wall. Theoretically, this may improve the arterial healing as well as reduce the need for prolonged antiplatelet therapy.

Recently, a novel stent was developed that elutes paclitaxel from a biodegradable coating (BP-PES, LUC-Chopin^{2TM}, Balton®) with a relatively short lifetime. The stainless steel Chopin^{2TM} stent (Balton®, Poland), widely used in clinical practice and well characterised clinically [12] was selected as the platform for a new DES. The purpose of the present study was to assess the vascular effects of the biodegradable polymer proposed as a stent coating, as well as to evaluate inhibition of intimal hyperplasia by Biodegradable Polymer-Coated Paclitaxel-Eluting Stents (BP-PES) in porcine coronary arteries.

METHODS

Stent characteristics

The BP-PES (LUC-Chopin^{2TM}) is covered with multi-layer structure containing copolymer of lactic and glycolic acid, paclitaxel and auxiliary substances. Total polymer mass on a 3.0 × × 15 mm stent does not exceed 360 μg. *In-vitro* evaluations suggest that the coating degrades almost entirely within eight weeks (Fig. 1). Analysis of BP-PES surface structure before and after expansion shows uniform coating without peeling or fractures (Fig. 2). Paclitaxel in a dose of 1.0 μg/mm^2 was chosen as a drug which inhibits neointimal proliferation.

Study design

Eighteen healthy domestic pigs, ranging between 35 and 40 kg body weight, were included in the study. A total of 19 stents were implanted into the coronary arteries of 13 animals for 28 day follow-up: seven bare metal stents (BMS), six biodegradable polymer-coated stents (PCS), and six BP-PES. Additionally, 11 BP-PES were implanted in four pigs for 90 day follow-up. Three days prior to stent implantation, the antiplatelet therapy was started, consisting of acetylsalicylic acid and ticlopidine which was continued until termination. Femoral artery access (using the Seldinger technique) was used for introduction and implantation of stents into three different coronary arteries. All stents were implanted under quantitative coronary angiography (QCA) guidance at the inflation pressure which ensured the balloon/artery diameter ratio of 1.15:1 to induce mechanical injury of the vessel. Twenty eight and 90 days after stent implantation, the control coronary angiography was performed. Subsequently, the animals were sacrificed and their coronary arteries were perfused with formaline at 100 mm Hg pressure and prepared for histopathological analysis. The QCA analysis was performed with the use of CMS-QCA software (Medis®). Two contralateral projections were chosen for stent assessment.

Intravascular ultrasound (IVUS) was recorded on GALAXY system (Boston Scientific®). Cross-sections were analysed at the proximal, distal and middle parts of the stents.

For histopathological analysis, resin-embedded arterial segments containing stents were cut into 10 μm slices using Leica microtome. The specimens were stained with hematoxylin-eosin. Based on the histomorphometric analysis, the following parameters were assessed: lumen cross-sectional area (lumen CSA); stent cross-sectional area (stent CSA), internal elastic lamina area (IEL area). Neointimal area (NA) was

defined as the difference between the internal elastic lamina area and the lumen cross-sectional area. The percentage of vascular lumen narrowing (% area stenosis) was calculated according to the following formula: 100 × (IEL area — lumen cross-sectional area)/IEL area. Each of the above mentioned parameters was measured in the proximal, medial and distal part of the stent. Subsequently, a mean value was calculated. The qualitative analysis to assess arterial wall integrity and the presence of endothelium, fibrin, thrombi or focal necrosis was carried out. Inflammatory response was evaluated using a four-grade scale (grades from 0 to 3) described by Kornowski et al. [13].

Statistical analysis

Results are expressed as mean ± standard deviation. Normal distribution of variables was verified by the Kolmogorov-Smirnov test. The variance uniformity was verified by using a Levene test. Angiographic, ultrasonographic and histomorphometric data were analysed using ANOVA and post-hoc (Newman-Keulus) tests. In the case of skewed distribution or non-uniformity of variance a nonparametric Kruskal-Wallis and U Mann-Whitney tests were used. A p-value < 0.05 was considered significant. The sample size of the groups studied was determined to give a power of 0.9 with standard deviation of 0.2 to detect a 0.5 mm difference in late lumen loss between the two groups.

RESULTS

One animal (5.6%) died after implantation of one BMS due to a dissection of the right coronary artery ostium with subsequent ventricular fibrillation. The remaining stents were implanted without any complications. During the entire follow-up period, no major adverse events were observed and all animals remained in good general condition. Autopsy did not reveal any macroscopic signs of myocardial infarction or inflammation.

Imaging outcomes at 28 days

There were no significant differences in the QCA results between all tested groups post-stent implantation (Table 1). At termination, all parameters of stenosis severity were significantly better in BP-PES stents with the lowest late lumen loss (LL) and percent diameter stenosis (%DS) (Table 1).

In-vivo IVUS analysis confirmed significantly better results in BP-PES stents (Table 2) with the lowest NA, late LL, and %DS.

Table 1. Quantitative angiography analysis

Parameter	BMS	PCS	BP-PES	P
Balloon diameter	3.2 ± 0.36	3.1 ± 0.14	3.1 ± 0.54	NS
Reference diameter	2.7 ± 0.28	2.9 ± 0.23	2.7 ± 0.17	NS
Stent-to-artery ratio	1.2 ± 0.11	1.1 ± 0.12	1.1 ± 0.13	NS
MLD after 28 days	2.4^{a} ± 0.09	$2.0^{a,b}$ ± 0.14	2.7^{b} ± 0.12	0.003
Lumen loss after 28 days	0.48^{c} ± 0.06	0.87^{b} ± 0.16	$0.15^{b,c}$ ± 0.05	0.002
%DS after 28 days	16.0^{c} ± 1.2	24.0^{b} ± 3.4	$7.3^{b,c}$ ± 1.1	0.002
MLD after 90 days	—	—	2.9 ± 0.5	—
Lumen loss after 90 days	—	—	0.52 ± 0.4	—
%DS after 90 days	—	—	11.2 ± 7.5	—

[a]significant difference between BMS and PCS stents; [b]significant difference between PCS and BP-PES stents; [c]significant difference between BMS and BP-PES stents; MLD — minimal lumen diameter; %DS — percent diameter stenosis

Table 2. Intravascular ultrasound examination

Parameter	BMS	PCS	BP-PES	P (ANOVA)
NI area mean after 28 days	2.1^{c} ± 0.1	2.7^{b} ± 0.3	$1.0^{b,c}$ ± 0.1	0.002
LL mean after 28 days	0.49^{c} ± 0.04	0.64^{b} ± 0.08	$0.19^{b,c}$ ± 0.02	0.002
%AS mean after 28 days	$24.5^{a,c}$ ± 1.8	$32.7^{a,b}$ ± 4.0	$11.7^{b,c}$ ± 0.7	0.003
NI area mean after 90 days	—	—	2.5 ± 0.8	—
LL mean after 90 days	—	—	0.45 ± 0.1	—
%AS mean after 90 days	—	—	22.5 ± 6.6	—

[a]significant difference between BMS and PCS stents; [b]significant difference between PCS and BP-PES stents; [c]significant difference between BMS and BP-PES stents; NI — neointima; LL — lumen loss; AS — area stenosis

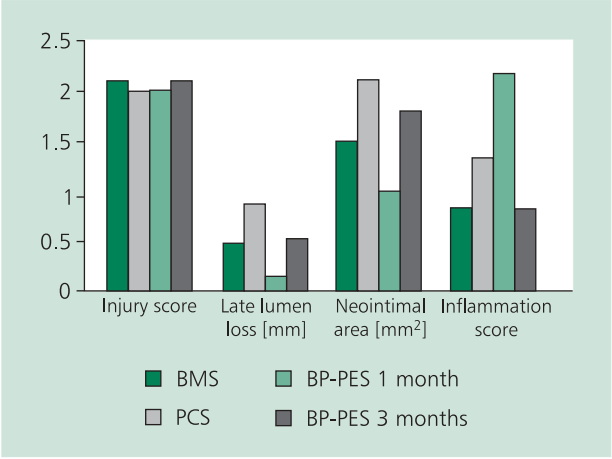

Figure 3. The configuration of injury, inflammation, late lumen loss and neointimal area in all examined groups

Histopathology at 28 days

The mean injury score (Fig. 3) was similar in all tested groups. The inflammation score in BP-PES stents assessed after 28 days was significantly higher than BMS and BP-PES stents evaluated after 90 days. There was no difference between PCS and BMS groups in terms of inflammation.

Although differences in histomorphometric parameters (Table 3) did not reach statistical significance between all tested groups, we observed a trend toward a smaller neointimal area and smaller percent area stenosis in BP-PES stents.

Qualitatively, in the BMS the endothelialisation process was finished. Vessel lumen was widely patent without evidence of thrombus. In one case, external elastic lamina (EEL) was disrupted. Inflammatory response consisted of isolated macrophages, rare eosinophilic granulocytes, and in some cases multinucleated foreign body giant cells surrounding the stents struts, probably as a foreign body response. Neither any changes in the perivascular tissue, nor the presence of fibrin, necrosis or vascular wall damage were observed.

In PCS, complete endothelialisation was also noted, although local disruption of the continuity of endothelium suggested mechanical injury probably due to endovascular manipulation. Small amounts of inflammatory infiltration, mainly near the struts, composed of macrophages, lymphocytes and eosinophilic granulocytes, were seen. In some cross-sections, near the stent struts multinucleated foreign body giant cells were also present. There was no evidence of thrombi, fibrin deposits or necrosis.

In BP-PES, endothelialisation process was not completed. In some cases, focal injuries with fibrin deposits were present. Occasionally, in these places also mild inflammatory infiltrations consisted of lypmphocytes, macrophages, granulocytes and eosinophiles as well as small amounts of thrombi were visible. The arteries were widely patent with thin neointima. The borders of muscular membrane were in one case blurred with homogenisation of muscle structure and loss of cellularity. Inflammatory infiltrations of moderate degree (Fig. 4), visible in all parts of the vessel, were found focally also in tunica adventitia and perivascular adipose tissue. In three cross-sections small focuses of necrosis were noticed. There were also multinucleated foreign body giant cells in some explants.

Imaging outcomes in BP-PES at 90 days

Lumen loss and %DS by QCA at 90 days were 0.52 ± 0.4 mm and 11.2 ± 7.5%, respectively, (Table 1) and comparable to BMS at 28 days. Accordingly, a 'catch-up' in the stenosis severity occurred in BP-PES between 28 and 90 days (Fig. 5). A similar trend as in angiographic analysis was also observed in IVUS and histomorphometric examination (Table 2, 3). For example, NA in BP-PES stents assessed after 28 days was 1.0 ± 0.2 mm^2, whereas after three months it was 1.8 ± 0.8 mm^2 ($p = 0.03$).

Histopathology of BP-PES at 90 days

In all specimens complete endothelium was visible. Only in two sections it was locally stimulated with proliferative

Table 3. Histomorphometry analysis

Parameter	BMS	PCS	BP-PES	P (ANOVA)
Lumen area after 28 days	4.1 ± 0.8	4.6 ± 0.6	5.1 ± 0.3	NS
Stent area after 28 days	7.4 ± 0.9	8.4 ± 1.0	8.1 ± 0.6	NS
IEL after 28 days	5.6 ± 1.0	6.7 ± 1.0	6.1 ± 0.5	NS
NA after 28 days	1.5 ± 0.3	2.1 ± 0.5	1.0 ± 0.2	0.1
%AS after 28 days	41.5 ± 7.2	48.2 ± 7.5	26.0 ± 3.7	0.1
Lumen area after 90 days	—	—	4.5 ± 2.1	—
Stent area after 90 days	—	—	9.6 ± 1.9	—
IEL after 90 days	—	—	6.2 ± 2.2	—
NA after 90 days	—	—	1.8 ± 0.8	—
%AS after 90 days	—	—	36.7 ± 6.7	—

IEL — internal elastic lamina area; NA — neointimal area; AS — area stenosis

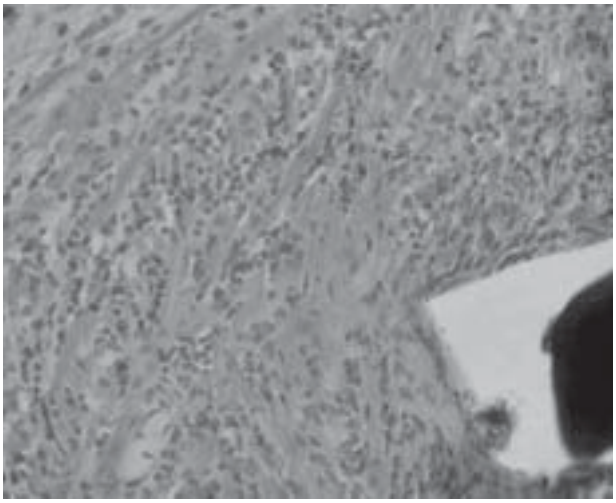

Figure 4. Inflammatory infiltrations around BP-PES's strut with lymphocytes, macrophages and eosinophiles (HE 200×)

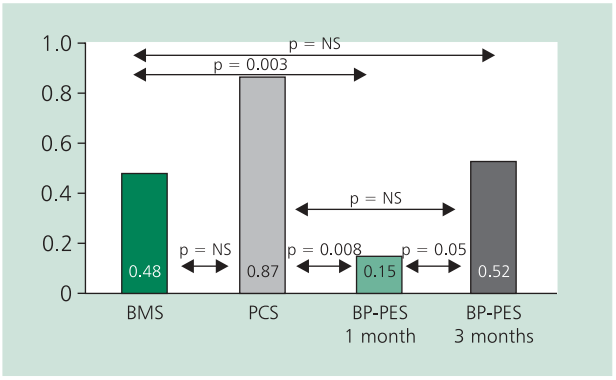

Figure 5. The configuration of late lumen loss value in the examined stents. Kruskal-Wallis ANOVA rang p = 0.006

features, in one case detached with infiltrations of granulocytes, macrophages and some lymphocytes. Neointima was generally deprived of any infiltrations, in rare cases lymphocytes and macrophages were present, and in three cross-sections eosinophiles were visible. In the areas of stent struts single lymphocytes and macrophages could be usually observed and only in three cross-sections the third degree infiltrations were seen. Consequently, the inflammatory score decreased in comparison to 28 days, while the NA got higher (Fig. 3). Moreover, in three stents small fibrin deposits were visible, and in one stent a lymphatic follicle was observed. Thrombi were present in two cross-sections around the stent struts. In tunica adventitia usually single lymphocytes were present, rarely eosinophiles and in two stents profuse infiltrations consisted of lymphocytes, macrophages and eosinophiles. The perivascular area showed no pathological changes.

DISCUSSION

A recent study of human pathology specimens confirmed that Taxus and Cypher stents delayed arterial healing in comparison to BMS [6]. It is believed that improved outcomes could be achieved if the stent coating was degradable shortly after drug elution and both would be no longer present in the artery wall once the anti-restenotic effect is accomplished.

To achieve this effect, a biodegradable polymer paclitaxel-eluting stent (BP-PES) was developed. The co-polymeric multi-layer absorbable coating is fully degrading in vitro in about eight weeks.

We decided to examine a fully biodegradable polymer composite because of presumed optimal drug elution kinetics and well-established physical and chemical characteristics. The indirect biodegradation product of the examined polymer is lactic acid, which is metabolised in the Krebs' cycle into carbon dioxide and water. The polymer is designed to degrade shortly after complete drug elution. Consequently, there is only a metal stent left which is covered with endothelium without tissue irritant coating. Stents coated only with the biodegradable polymer confirmed our expectations, demonstrating acceptable biocompatibility at 28 days. Although the neointima developed in PCS was slightly thicker than in BMS, endothelialisation appeared complete by light microscopy, neointima was mature without excessive residual inflammatory reaction or other adverse effects on the arterial wall.

Although developing a biocompatible stent coating is a success, striking an optimal balance between efficacy and toxicity in a paclitaxel-eluting stent remains a challenge. Paclitaxel was initially perceived as a universal inhibitor of neointimal proliferation, being effective in a variety of experimental settings, including intramural injections [14], intracoronary infusion with contrast agent and delivery off the angioplasty balloon surface [15, 16]; this was thought to be due to its highly lipophilic character and prolonged retention in the arterial tissue post-delivery. However, few of these favourable experimental reports have been translated into clinical success. More recent reports have suggested the paramount importance of precisely controlled pharmacokinetics of paclitaxel when eluted from the stent surface, with only select combinations of dose and duration rendering optimal results [17].

The overall safety and efficacy outcomes of this study align with previous reports of paclitaxel-eluting stents which were successfully translated into clinical practice. At 28 days, BP-PES stents effectively inhibited neointimal hyperplasia, as evidenced by imaging and histopathology. Typically for paclitaxel, this success came at the price of delayed endothelialisation. However, at 90 days the healing appeared to be adequate, with inflammatory reaction extinguished to the level seen in control stents at 28 days. This was accompanied by higher neointimal formation than previously noted at 28 days in BP-PES, although not exceeding the neointimal area in the

control stents. Such a 'catch-up' phenomenon was observed previously in preclinical studies evaluating the stents eluting paclitaxel, sirolimus and tacrolimus [18–20]. There is no complete explanation of this fact, but it is assumed that paclitaxel does not inhibit neointimal hyperplasia, but only delays its creation. The second probable explanation is related to drug kinetics optimisation during elution. It is possible that early and rapid elution causes only temporary inhibition of neointimal hyperplasia, with a later rebound. On the other hand, more prolonged and intense elution may ensure long-term neointimal inhibition but also a longer time to heal the stented site. The significance of optimal kinetics of paclitaxel elution was proved in the PISCES study, which showed that the best results for 30 days' observation (as well as for 90 days' observation) were seen in stents eluting the drug within 30 days, rather than the group eluting the drug for ten days. Moreover, in the latter group it was claimed that such quick drug eluting was associated with the 'catch-up' effect [21, 22] mostly visible after 90 days. However, the late loss of the initial inhibition of neointimal formation in pre-clinical studies with paclitaxel-eluting stents has not translated into a late increase in restenosis and revascularisation in clinical trials when examined out to 3––4 years [17, 23, 24]; as such, it has no impact on the durability of the anti-restenotic result in humans.

CONCLUSIONS

In summary, it seems that the bioabsorbable polymer of examined stent is safe and, together with paclitaxel, feasible in the prevention of neointimal hyperplasia. This supports a human investigation for the first time being conducted [25].

Acknowledgements

This study was supported by Balton, Warszawa, Poland by offering free products to the sites and financial support. The experiment was conducted with the consent of the Institutional Animal Review Committee of the Upper Silesian Medical School.

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Nowy stent pokryty biodegradowalnym polimerem, uwalniający paklitaksel, hamuje przerost neointimy w tętnicach wieńcowych świni

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Streszczenie

Wstęp: Stenty pokryte polimerem biodegradowalnym mogą pozytywnie wpływać na proces gojenia się tętnic wieńcowych po zabiegach przeskórnej rewaskularyzacji (PCI), jak również skracać okres przyjmowania podwójnej terapii przeciwpłytkowej.

Cel: Celem pracy było określenie efektów naczyniowych wywieranych przez biodegradowalny polimer zaproponowany jako pokrycie stentu, a także ocena zahamowania przerostu neointimy przez stent pokryty polimerem biodegradowalnym elutującym paklitaksel (BP-PES, LUC-Chopin^{2TM}, Balton®) na modelu przerostu neointimy tętnic wieńcowych świni.

Metody: Dziewiętnaście stentów wszczepiono przy zastosowaniu techniki 1:1,15 *oversize* do naczyń wieńcowych 13 świń: 7 stentów metalowych (BMS), 6 stentów pokrytych polimerem biodegradowalnym (PCS) oraz 6 BP-PES. Grupy te poddano 28-dniowej obserwacji. Dodatkowo, 11 BP-PES wszczepiono 4 zwierzętom, które poddano 90-dniowej obserwacji. Po okresie obserwacji wykonano kontrolną koronarografię oraz eutanazję. Serca oraz tętnice wieńcowe po wypreparowaniu poddano analizie histopatologicznej.

Wyniki: Po 28 dniach BP-PES ograniczyły przerost neointimy w porównaniu z grupą kontrolną (późna utrata światła [mm] = 0,48 ± 0,06 dla BMS *v.* 0,87 ± 0,16 dla PCS *v.* 0,15 ± 0,05 dla BP-PES; $p < 0,05$). Po 3 miesiącach od implantacji wystąpił efekt *catch-up*. Badania histopatologiczne potwierdziły bezpieczeństwo badanego stentu, ujawniając kompletne śródnabłonkowanie oraz istotne zmniejszenie stanu zapalnego między 1. a 3. miesiącem obserwacji.

Wnioski: Stent BP-PES (LUC-Chopin^{2TM}) jest bezpieczny oraz skutecznie hamuje przerost neointimy na modelu tętnic wieńcowych świni domowej. Niniejsze wyniki stały się podstawą do przeprowadzenia pierwszego badania klinicznego.

Słowa kluczowe: polimer biodegradowalny, stent elutujący lek, przerost neointimy, świnia

Kardiol Pol 2010; 68, 5: 503–509

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Praca wpłynęła: 07.09.2009 r. **Zaakceptowana do druku:** 06.01.2010 r.