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Drug release kinetics from a drug-eluting stent with asymmetrical coat

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1. ABSTRACT

The aim of this study was to investigate the drug release profiles of biodegradable polymer sirolimus- or paclitaxel-eluting stents with asymmetrical coating (BPSES-A or BPPES-A) both *in vitro* and *in vivo*. *In vitro*, the drug release profile was characterized by measuring the drug concentration by HPLC over a time-course. *In vivo*, a porcine aorta stenting model was employed. The results showed that the drug release rates of BPSES-A and BPPES-A were slower, more stable and less burst releasing than those of conventionally coated stents (BPSES-C and BPPES-C respectively), both *in vitro* and *in vivo*. Based on the *in vivo* results, the sirolimus and paclitaxel content of the local coronary wall was maintained at a higher and more effective level with BPSES-A and BPPES-A than with BPSES-C and BPPES-C, respectively. The drug levels in peripheral tissue samples were below detection levels. These data demonstrated the effectiveness of both sirolimus and paclitaxel as stent coating agents, and revealed the favorable drug release kinetics and pharmacokinetics of asymmetrical coated stents compared with conventional coated stents.

2. INTRODUCTION

Intravascular drug delivery has revolutionized the practice of cardiovascular medicine, and drug-eluting stents (DES) have made stenting a successful treatment modality. DES are now the primary choice for percutaneous coronary interventions (PCI), being implanted into millions of patients (1) at a cost of billions of dollars (2). Restenosis, a condition characterized by arterial intimal thickening as a result of vascular remodeling, cellular proliferation and neointimal formation, is frequently found to be a negative consequence of PCI. The introduction of DES during PCI has resulted in a reduction in coronary restenosis rates to 10 percent, diminishing the need for subsequent

revascularization procedures (3–5) and confirming the effectiveness of DES compared with conventional bare-metal stents.

The application of a polymer coating to a stent is necessary to secure the drug during delivery and to control its release following implantation. The recent introduction of biodegradable polymer coated DES has shown promising results in reducing the adverse effects associated with permanent polymer coatings, which include inflammatory reactions and thrombosis (6–9). Poly (D, L-lactide-co-glycolide) (PLGA) is a commonly employed biomaterial approved for use in a variety of drug delivery systems (10–13). The coating of DES with such biocompatible, biodegradable polymers allows for release of the immunosuppressive drug into the target tissue, alongside complete metabolism of the polymer into the body after it has fulfilled its purpose, theoretically leaving a bare metal stent in place. Degradation of the polymer component of the stent helps reduce inflammation, eliminate potential problems from remnant drug inside the coating, and thereby improve reendothelialization. This advance has reportedly had a positive impact on the safety of DES (7–9).

Sirolimus and paclitaxel are the predominant pharmacologic agents used in DES to modulate cellular proliferation, believed to be the major cause of coronary restenosis. Both sirolimus- and paclitaxel-eluting stents have been shown in randomized trials to reduce restenosis compared with conventional metallic stents (3, 14–17). Sirolimus (also known as rapamycin) is a macrocyclic lactone isolated from *Streptomyces hygroscopicus* that displays potent immunosuppressive activity and antiproliferative effects (18). Sirolimus functions by inhibiting the interleukin-2-mediated signal transduction pathway, reducing T-lymphocyte activation (19). Sirolimus has been shown to effectively inhibit growth factor-mediated cellular proliferation by preventing cell-cycle progression from G1 to S phase to prevent restenosis after DES implantation (20–22).

There are many variables that can influence how the drug is released and transported from the stent coating into the surrounding arterial wall. One of these variables is the method by which the polymeric coating is applied to the stent. Stents with an asymmetric coating elute the drug to the abluminal surface, whereas stents with a conventional coating elute the drug in all directions including to the luminal side potentially harming reendothelialization. It has been reported that stents with an asymmetric coating, eluting the drug to the vessel wall, confer improved reendothelialization after PCI, thereby potentially decreasing in-stent thrombosis and late restenosis. This was confirmed by our previous study, in which we reported that a biodegradable polymer sirolimus-eluting stent with an asymmetrical coat showed better reendothelialization than conventional coated stents (23).

Drug release by diffusion from the DES polymer coating should ideally occur at a constant therapeutic dose thereby allowing for reendothelialization whilst limiting intimal hyperplasia. The process of drug release is controlled by the rate of water imbibition into the polymer coating, subsequent dissolution of the drug and diffusion of the soluble drug out of the polymer matrix (24). An initial burst phase is therefore observed that corresponds to the rapid dissolution of the outermost drug molecules (25). This sudden influx of drug after stent implantation may saturate the artery resulting in measurable systemic drug levels (26) and potential endothelial damage (27). In effect, the period of optimal drug dosing may be short, occurring at a brief time point between the initial drug burst and the steady decline in drug levels. A detailed understanding of the drug release kinetics and pharmacokinetics is therefore crucial in the design of effective stent-based drug delivery systems to ensure optimal therapeutic outcomes.

The aim of the current study was to investigate the release kinetics of sirolimus and paclitaxel on a biodegradable polymer stent with an asymmetrical coat, compared with a conventional coat, both *in vitro* and *in vivo*. For our *in vivo* study, a porcine aorta stenting model was employed since pigs have been shown to display similarities to humans with regard to their cardiovascular profile (28) and their cellular proliferation rates (29).

3. METHODS

3.1. Stent preparation

The stent platform comprised 316L stainless steel. The stents were spray-coated with the polymer/drug coating matrix using a MediCoat YM II Stent Coating System (Sono-Tek Corp., Milton, NY, USA). The polymer used was poly (D, L-lactide-co-glycolide) (PLGA, LA: GA=70:30) and the drugs were sirolimus or paclitaxel. To prepare the biodegradable polymer sirolimus-eluting stent with an asymmetrical coat (BPSES-A) and the biodegradable polymer paclitaxel-eluting stent with an asymmetrical coat (BPPES-A), the polymer-drug complex was asymmetrically sprayed onto the abluminal surface of the stent. To prepare the equivalent sirolimus-eluting or paclitaxel-eluting stents with a conventional coat (BPSES-C or BPPES-C, respectively), the polymer-drug complex was symmetrically sprayed onto both the luminal and abluminal surfaces of the stent. Both BPSES-A and BPSES-C were coated at 1.40 μg/mm^2 (30) on the stent surface of 108.29 mm^2, giving an average sirolimus content of 151 μg per stent. BPPES-A and BPPES-C were coated with 1 μg/mm^2 paclitaxel on the stent surface.

3.2. Analysis of *in vitro* drug release kinetics

Three drug-eluting stents were placed individually in tubes with 5 ml PBS and incubated at

37°C. The drug release rates were tested on days 1, 3, 7, 14, 21 and 28 by high pressure liquid chromatography (HPLC) to obtain the release curve. After each analysis, the supernatant solution was placed back in the tube to maintain the volume of the medium.

3.3. Analysis of *in vivo* pharmacokinetics

3.3.1. Stent implantation

Animal experiments were approved by the Institutional Animal Care and Use Committee and conformed to AHA guidelines. Stent implantation was performed as previously described with slight modifications (23). Briefly, castrated male minis pigs of 20–30 kg, received 81 mg acetylsalicylic acid and 75 mg clopidogrel daily for 3 days before stent implantation. All pigs were fasted overnight before the stent implant procedure. Pigs were sedated by intramuscular injection of ketamine 20 mg/kg, xylazine 2 mg/kg, and atropine 0.05 mg/kg. After intubation, general anesthesia was induced and maintained with isoflurane (2.5 percent). Electrocardiogram and blood pressure were monitored continuously. With systemic heparin (200 U/kg) administration, activated clotting time measurements were performed. Stents were implanted in the pig coronary arteries using quantitative coronary angiography (GE Inn via 2000 C-arm), to obtain a stent/artery ratio of 1:1. Additional inflations were performed based on the target site diameter. Stents (BPSES-A, BPSES-C, BPPES-A or BPPES-C) were randomly implanted into either the left anterior descending coronary artery or the left circumflex artery of each pig. During follow-up, the animals received 300 mg acetylsalicylic acid and 75 mg clopidogrel daily.

3.3.2. Pharmacokinetic analysis

For pharmacokinetic analysis, animals were euthanized at 1, 3, 7, 14, 21, 28 days. After the stent was explanted, the drug residue in the stent was tested using HPLC. Drug release rates were calculated at different time points (as percentages). Release rate = (the original drug content − residue)/original drug content × 100 percent.

3.3.3. Drug distribution *in vivo*

Local coronary and peripheral venous blood samples were taken 60 min after stent implantation. Additionally, 1, 3, 7, 14, 21 and 28 days after stent implantation, local coronary blood samples were extracted from 1 cm of the local artery using a 6F guiding catheter, 0.014 guiding wire and a 2F micro catheter, peripheral venous blood samples were extracted from the jugular before the pigs were euthanized, and tissue samples were taken from the stented artery, as well as the liver, spleen, lung, kidney, skin and small intestine.

To prepare the blood samples for drug analysis, 100 µl of the whole blood sample was mixed with 10 µl of an internal standard and 200 µl of precipitating agent (prepared by solubilizing 2.3 g $ZnSO_4$ ($7H_2O$, molecular weight 287.54) in 150 ml water, 125 ml methanol and 125 ml acetonitrile). This mixture was vortexed for 1 min, incubated for 5 min at room temperature, centrifuged at 9,300 ×*g* for 5 min, then the supernatant was retained for testing. To prepare the tissue samples for drug analysis, the samples were homogenized then subjected to the same extraction method.

The drug contents of the blood samples and tissue extracts were determined using a liquid chromatograph-mass spectrometer (LC-MS) (3200 QTRAP tandem mass spectrometry, Applied Biosystems, Foster City, CA, USA) and HPLC (Shimadzu Corporation, Kyoto, Japan). For LC-MS, the operating conditions were: mobile phase A, 1 mm NH_4Ac + 0.1 percent FA/H_2O; mobile phase B, 0.1 percent FA/ACN; mobile phase C, H_2O-ACN (50/50). HPLC analysis was performed using a Xbridge RP18 analytical column (Waters Corporation, Milford, MA, USA; 3.5 µm, 2.1×100 mm), according to the following parameters: injection volume of 10 µl, flow rate: 0.35 ml/min, A: B ratio=40:60.

3.4. Statistical analysis

Group means were calculated and compared by Student's *t*-tests. Results were reported as the mean±SD. Correlations between the release kinetics *in vitro* and *in vivo* were analyzed using the statistics package SPSS 19.0. (SPSS, Chicago, IL, USA). Differences were considered significant at $P < 0.05$.

4. RESULTS

4.1. *In vitro* drug release kinetics

To compare the *in vitro* drug release profiles of the asymmetrically-coated stents with the conventionally-coated stents, coated with either sirolimus or paclitaxel, the stents were incubated in PBS at 37°C and the drug release rates were measured over a time-course of 28 days by HPLC. The drug release curves for each of the DES are shown in Figure 1. For both drugs, sirolimus (Figure 1A) and paclitaxel (Figure 1B), the drug release kinetics were similar, with the drug release rates steadily increasing over the 28-day time-course, reaching just under 100 percent between 21 and 28 days. In the case of both the sirolimus-eluting and the paclitaxel-eluting stents, the rates of drug release were lower for the asymmetrically-coated stents than for the conventionally-coated stents by approximately 10 percent throughout the time-course, indicating a slightly steadier rate of drug release from asymmetrically-coated stents.

4.2. *In vivo* drug release pharmacokinetics

To determine whether the *in vitro* drug release kinetics for the DES coated conventionally or asymmetrically were replicated *in vivo*, a porcine model was employed (Figure 2). DES was implanted into the coronary arteries of pigs and the animals were euthanized at 1, 3, 7, 14, 21 and 28 days. The drug residue in the

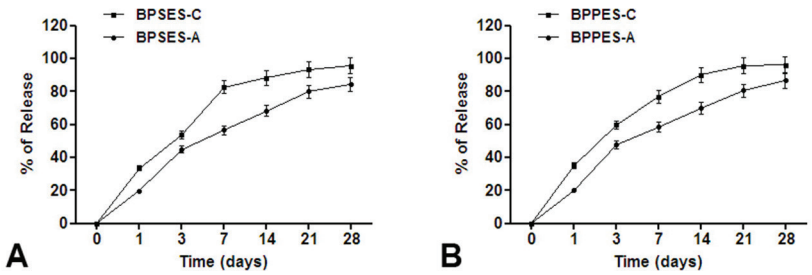

Figure 1. Comparison of the drug release profiles *in vitro* for the biodegradable polymer drug-eluting stents with an asymmetrical or conventional coat in PBS. A. *In vitro* release profile of sirolimus from BPSES-A and BPSES-C. B. *In vitro* release profile of paclitaxel from BPPES-A and BPPES-C. Values represent the mean ± SD of three stents at each time piont.

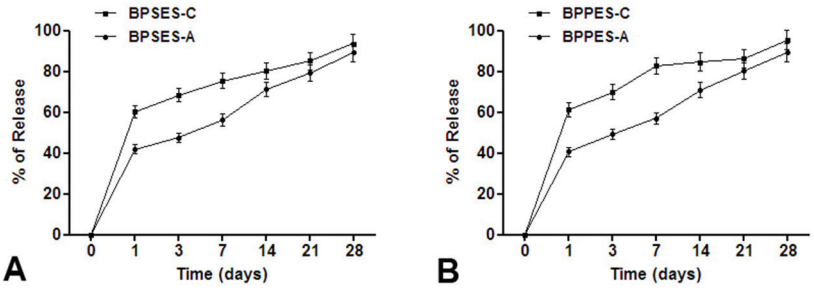

Figure 2. Comparison of the drug release profiles *in vivo* for the biodegradable polymer drug-eluting stents with an asymmetrical or conventional coat in a porcine model. A. *In vivo* release profile of sirolimus from BPSES-A and BPSES-C. B. *In vivo* release profile of paclitaxel from BPPES-A and BPPES-C. Values represent the mean ± SD of five stents at each time piont.

explanted stents was then tested using HPLC and a drug release curve was generated. Again, similar drug release kinetics were observed for both sirolimus (Figure 2A) and paclitaxel (Figure 2B) coated stents, with the drug release rates steadily increasing over the 28-day time-course, reaching 90–100 percent at 28 days. In the case of both the sirolimus-eluting and the paclitaxel-eluting stents, the rates of drug release *in vivo* were lower for the asymmetrically-coated stents than for the conventionally-coated stents throughout the time-course, as seen *in vitro*.

4.3. Regression analysis

To investigate the correlation between *in vitro* and *in vivo* drug release by the sirolimus and paclitaxel coated stents, regression analysis was carried out on the kinetic data (Figure 3). For BPSES-A, the regression equation was y=0.9159x+8.756 and the correlation coefficient was R=0.9671 (Figure 3A), whereas for BPSES-C the regression equation was y=0.7981x+15.14 and the correlation coefficient was R=0.9323 (Figure 3B). Both of these values were greater than the critical correlation coefficient of 0.917, $P<0.01$, indicating that the *in vitro* release rates from sirolimus coated stents were positively correlated with the *in vivo* release rates for this drug. For BPPES-A, the regression equation was y=0.9051x+8.389 and the correlation coefficient was R=0.9713 (Figure 3C), whereas for BPPES-C the regression equation was y=0.8457x+13.86 and the correlation coefficient was R=0.9460 (Figure 3D). Both of these values were also greater than the critical correlation coefficient of 0.917, $P<0.01$, indicating that, similarly to sirolimus, the *in vitro* release rates from paclitaxel coated stents were positively correlated with the *in vivo* release rates for this drug.

4.4. Drug distribution in tissues

To determine the *in vivo* distribution of the drugs from the implanted stents, tissue samples were taken from the stented artery, as well as the liver, spleen, lung, kidney, skin and small intestine. The content of sirolimus and paclitaxel in each of these specimens was analyzed. However, the drug concentration in the peripheral organs of the liver, spleen, lung, kidney, skin and small intestine was too low to be determined (less than 0.4 ng/mg) (data not shown). Values were determined for the stented arteries and Figure 4 shows the average concentration of sirolimus (Figure 4A) and paclitaxel (Figure 4B) in the arterial wall. The drug concentration profile for both drugs was similar over the 28-day time-course, with the concentration of each drug in the arterial wall being consistently slightly higher for the asymmetrically-coated stents than for the conventionally-coated stents. Asymmetrical coating of the stent is therefore favorable for maintaining a higher and more effective level of the eluted drug in the local arterial wall.

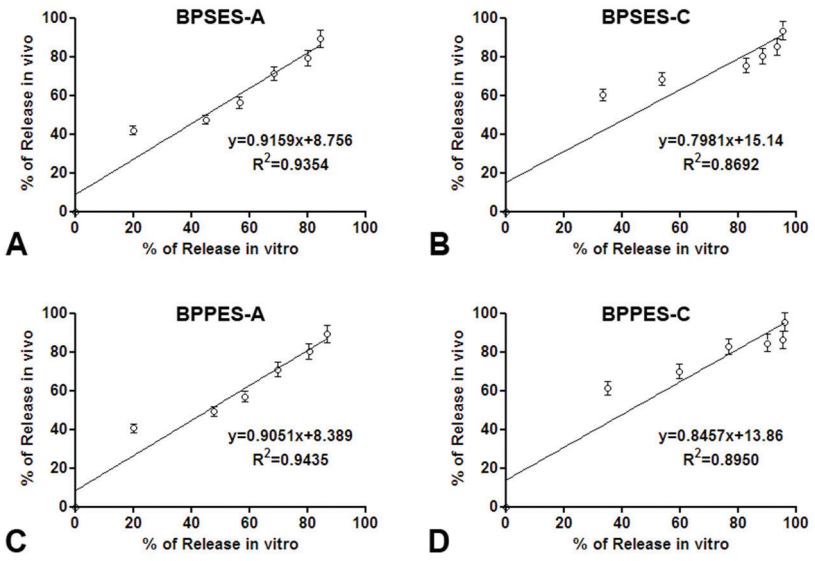

Figure 3. The correlation between *in vitro* and *in vivo* drug release. A,B. The correlation between the *in vitro* and *in vivo* release of sirolimus by BPSES-A (A) and BPSES-C (B). C,D. The correlation between the *in vitro* and *in vivo* release of paclitaxel by BPPES-A (C) and BPPES-C (D).

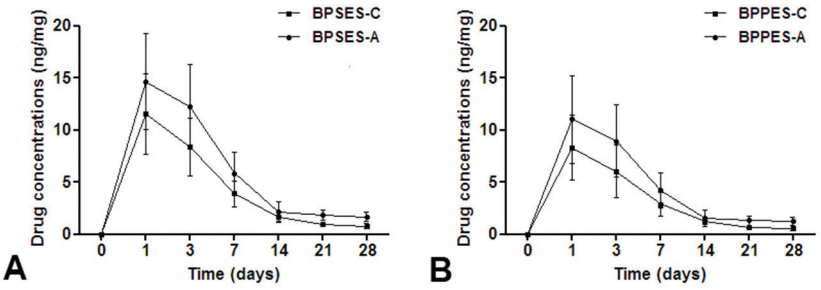

Figure 4. Drug concentration in the arterial wall after stent implantation. A. Concentration of sirolimus in the arterial wall after implantation of BPSES-A and BPSES-C. B. Concentration of paclitaxel in the arterial wall after implantation of BPPES-A and BPPES-C. Values represent the mean ± SD of five stents at each time piont.

4.5. *In vivo* drug loss into the bloodstream

To further investigate the *in vivo* distribution of the drugs from the implanted stents in the blood, local coronary (Table 1) and peripheral venous (Table 2) blood samples were collected and analyzed 60 min, and 1, 3, 7, 14, 21 and 28 days after stent implantation. The drug concentrations were below the detection limit for both the local and systemic blood samples from 3 days onwards. However, at the early time points (60 min and 24 h), a general trend was observed that the drug concentration in both local and systemic blood samples was higher when conventionally-coated stents were used compared with asymmetrically-coated stents, indicating that *in vivo* drug loss into the bloodstream is reduced by the use of asymmetrically-coated stents.

5. DISCUSSION

The introduction of DES marked a significant advance in cardiovascular medicine. However, there are elements of stent design that have recently been, or remain to be, optimized. For example, thinner struts have been shown to reduce intimal hyperplasia and thrombotic potential, improving clinical outcomes (31, 32). However, the formulation and application of the coating to optimize drug delivery and device biocompatibility remains under investigation. In addition, current DES technology is not optimized with regard to the pharmacokinetics of drug delivery. Here, we evaluated the effect of the coating methodology on stability of the drug and the kinetics of drug delivery. *In vitro* analysis of the drug release kinetics by HPLC over 28 days indicated that asymmetrical coating of DES resulted in steadier drug release kinetics compared with symmetrical coating. *In vivo* analysis involving implantation of DES into porcine coronary arteries and HPLC analysis of the drug residue in the explanted stents over a 28 day time-course, similarly revealed lower drug release rates for the asymmetrically-coated stents than for the conventionally-coated stents, confirming the *in vitro* findings. The *in vitro* and *in vivo*

Table 1. Coronary stented distal blood drug concentration

	Time						
	60 min	1 d	3 d	7 d	14 d	21 d	28 d
Drug concentration (ng/ml)							
BPSES-C	4.86±2.15	1.06±0.49	<0.4	<0.4	<0.4	<0.4	<0.4
BPSES-A	3.65±1.15*	0.86±0.36*	<0.4	<0.4	<0.4	<0.4	<0.4
BPPES-C	3.54±1.47	0.7.9±0.41	<0.4	<0.4	<0.4	<0.4	<0.4
BPPES-A	2.63±0.89#	0.66±0.28#	<0.4	<0.4	<0.4	<0.4	<0.4
Values represent the mean ± SD of five stents at each time piont. *P < 0.05 vs. BPSES-C group; #P < 0.05 vs. BPPES-C group							

Table 2. Systemic venous blood drug concentration after stent implantation

	Time						
	60 min	1 d	3 d	7 d	14 d	21 d	28 d
Drug concentration (ng/ml)							
BPSES-C	3.54±1.47	0.79±0.41	<0.4	<0.4	<0.4	<0.4	<0.4
BPSES-A	2.63±0.89*	0.66±0.28*	<0.4	<0.4	<0.4	<0.4	<0.4
BPPES-C	1.94±0.74	0.63±0.21	<0.4	<0.4	<0.4	<0.4	<0.4
BPPES-A	0.93±0.61#	0.51±0.18#	<0.4	<0.4	<0.4	<0.4	<0.4
Values represent the mean ± SD of five stents at each time piont. *P < 0.05 vs. BPSES-C group; #P < 0.05 vs. BPPES-C group							

drug release rates were found to be positively correlated by regression analysis. From tissue analysis of the peripheral organs of pigs implanted with the DES, it was clear that systemic dissemination of the drug from each of the stents was below detection levels confirming effective containment of the drug within the stented artery. The local concentration of the drug in the arterial wall was similar for both sirolimus- and paclitaxel-eluting stents following implantation, however, asymmetrical coating of the stent was found to be favorable for maintaining a higher and more effective level of the eluted drug in the local arterial wall. *In vivo* analysis of drug loss into the bloodstream using local and systemic blood samples, indicated detection only at early time points (60 min and 24 h) and a general reduction in drug loss into the bloodstream by the use of asymmetrically-coated stents compared with symmetrically-coated stents. Taken together, these findings indicated that the use of asymmetrically-coated DES minimized the initial drug burst and allowed for steady levels of drug release to be maintained following implantation.

In-stent restenosis remains a significant negative side effect of endovascular stenting, limiting the long-term success of this therapeutic procedure. The implantation of a stent exacerbates neointimal formation within that vessel that may lead to restenosis, which, particularly in smaller vessels, may negate the beneficial effects of vessel widening conferred by the stent. The estimated overall restenosis rate with bare metal stents is ~20–25 percent compared with ~12 percent for DES (33–35). The inclusion of an anti-proliferative, immunosuppressive agent, such as sirolimus or paclitaxel, in the stent design has had a significant impact on reducing coronary restenosis rates (3, 14–17). The presence of such a drug at an appropriate therapeutic dose is thought to allow for reendothelialization whilst limiting intimal hyperplasia. Furthermore, an asymmetrically coated DES elutes the drug specifically to the abluminal surface and this refinement in stent design has been linked with improved reendothelialization (23), thereby potentially decreasing serious complications such as in-stent thrombosis and late restenosis. In summary, asymmetrically-coated DES provide an attractive strategy for attenuating restenosis. We present *in vitro* and *in vivo* pharmacokinetic evidence that drug release from such stents occurs at a steady and stable rate favoring local containment of the drug rather than systemic spread, thereby increasing the potency of the therapeutic agent within the stented vessel and improving clinical outcomes.

6. ACKNOWLEDGEMENTS

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Abbreviations: BPSES-A: Biodegradable polymer sirolimus-eluting stent with asymmetrical coat; BPSES-C: Biodegradable polymer sirolimus-eluting stent with conventional coat; BPPES-A: Biodegradable polymer paclitaxel-eluting stent with asymmetrical coat; BPPES-C: Biodegradable polymer paclitaxel-eluting stent with conventional coat; DES: drug-eluting stents; PCI: percutaneous coronary interventions

Key Words: Biodegradable Polymer, Drug-eluting Stent, Drug Release Kinetics, Sirolimus, Paclitaxel

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