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Original Article

Angiographic and 5-Year Clinical Follow-Up After Implantation of Drug-Eluting Stents with Biodegradable Coating in Patients at High Risk of Restenosis: The PAINT Randomized Trial

Wilton Francisco Gomes[1], Julio F. Marchini[1], Bruno Moulin[2], Marco A. Perin[3], Ludmilla A.R.R. Oliveira[4], J. Airton Arruda[5], Valter C. Lima[6], Antonio A.G. Lima[7], Paulo R.A. Caramori[8], Cesar R. Medeiros[9], Mauricio R. Barbosa[10], Fabio S. Brito Jr.[11], Expedito E. Ribeiro[1], Pedro A. Lemos[1]

ABSTRACT

Background: Biodegradable polymers were developed to reduce the hypersensitivity reaction associated to durable polymers found with the first generation drug-eluting stents, while maintaining antiproliferative efficacy and increasing safety. This study evaluated the 9-month angiographic follow-up and long-term clinical outcomes of biodegradable polymer-coated drug-eluting stents compared with identical platform metallic stents in patients with high-risk for restenosis. **Methods:** Patients with a reference diameter ≤ 2.5 mm, lesion length ≥ 15 mm, diabetes, or a combination of these characteristics were selected from the population of the PAINT trial. These patients were previously randomized and allocated for percutaneous coronary intervention with either a sirolimus-eluting biodegradable polymer-coated stent, a paclitaxel-eluting biodegradable polymer-coated stent, or an identical metallic platform stent, at a ratio of 2:2:1. **Results:** One hundred and seventy-eight patients were treated with biodegradable polymer-coated drug-eluting stents (n = 142) or bare metal stents (n = 36). At the 9-month angiographic follow-up, biodegradable polymer-coated drug-eluting stents had lower rates of late loss (0.40 ± 0.42 mm vs. 0.90 ± 0.47 mm; $p < 0.01$) and binary restenosis (7.4% vs. 25%; $p < 0.01$). In the 5-year clinical follow-up, the group with biodegradable polymer-coated drug-eluting stents had lower rates of the composite endpoint of cardiac death, myocardial infarction, and target vessel revascularization (16.2% vs. 38.0%; $p = 0.03$), especially due to the reduction of target vessel revascularization (9.9% vs. 36.1%; $p < 0.01$). Total death, cardiac death and myocardial infarction were not different among groups. Probable or definitive stent thrombosis

RESUMO

Resultados Angiográficos e do Seguimento Clínico de 5 Anos Após Implante de Stents Farmacológicos com Revestimento Biodegradável em Pacientes com Alto Risco de Reestenose. Análise de Subgrupo do Estudo Randomizado PAINT

Introdução: Polímeros biodegradáveis foram desenvolvidos para reduzir a reação de hipersensibilidade associada aos polímeros duráveis dos stents farmacológicos de primeira geração, mantendo sua eficácia antiproliferativa e aumentado sua segurança. Avaliamos os resultados angiográficos de 9 meses e os resultados clínicos de longo prazo dos stents farmacológicos com polímeros biodegradáveis em pacientes com alto risco de reestenose. **Métodos**: Pacientes com diâmetro de referência ≤ 2,5 mm, extensão da lesão ≥ 15 mm, diabetes, ou uma combinação dessas características foram selecionados da população do estudo PAINT. Esses pacientes foram previamente randomizados e alocados para intervenção coronária percutânea recebendo os stents farmacológicos com polímeros biodegradáveis com sirolimus ou com paclitaxel ou stents metálicos, na razão 2:2:1. **Resultados:** Cento e setenta e oito pacientes foram tratados com stents farmacológicos com polímeros biodegradáveis (n = 142) ou stents metálicos (n = 36). No acompanhamento angiográfico de 9 meses, os primeiros mostraram menor perda tardia (0,40 ± 0,42 mm vs. 0,90 ± 0,47 mm; $p < 0,01$) e reestenose binária (7,4% vs. 25%; $p < 0,01$). No acompanhamento clínico de 5 anos, o grupo com stents farmacológicos com polímeros biodegradáveis mostrou menores taxas do desfecho combinado de morte cardíaca,

[1] Instituto do Coração, Hospital das Clínicas, Universidade de São Paulo, São Paulo, SP, Brazil.
[2] Hospital Universitário Cassiano Antonio de Moraes, Vitória, ES, Brazil.
[3] Hospital Santa Marcelina, São Paulo, SP, Brazil.
[4] Natal Hospital Center, Natal, RN, Brazil.
[5] Hospital Meridional, Vitória, ES, Brazil.
[6] Escola Paulista de Medicina, Universidade Federal de São Paulo, São Paulo, SP, Brazil.
[7] Hospital Universitário Walter Cantídio, Fortaleza, CE, Brazil.
[8] Hospital São Lucas, Pontifícia Universidade Católica do Rio Grande do Sul, Porto Alegre, RS, Brazil.
[9] Rede D'Or de Hospitais, Rio de Janeiro, RJ, Brazil.
[10] Hospital Biocor, Belo Horizonte, MG, Brazil.
[11] Hospital São Camilo, São Paulo, SP, Brazil.

Corresponding Author: Pedro A. Lemos. Avenida Dr. Enéas de Carvalho Aguiar, 44, bloco I, 3º andar, Hemodinâmica – Cerqueira César – CEP: 05403-000 – São Paulo (SP), Brazil
E-mail: pedro.lemos@incor.usp.br

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occurred in 2.8% vs. 0% (p = 0.30). **Conclusions:** Paclitaxel or sirolimus-eluting biodegradable polymer-coated stents were effective in reducing angiographic restenosis at 9 months and the need of reintervention for clinical restenosis in 5 years, without increasing the risk of stent thrombosis.

Descriptors: Drug-eluting stents. Polymers. Coronary restenosis. Coronary thrombosis.

infarto do miocárdio e revascularização do vaso-alvo (16,2% vs. 38,0%; p = 0,03), principalmente devido à redução da revascularização do vaso-alvo (9,9% vs. 36,1%; p < 0,01). Morte total, morte cardíaca e infarto do miocárdio não foram diferentes entre os grupos. A trombose do stent, provável ou definitiva, ocorreu em 2,8% vs. 0% (p = 0,30). **Conclusões**: Os stents farmacológicos com polímeros biodegradáveis eluidores de paclitaxel ou sirolimus foram eficazes na redução de reestenose angiográfica aos 9 meses e na necessidade de reintervenção por reestenose clínica em 5 anos, sem aumentar o risco de trombose do stent.

Descritores: Stents farmacológicos. Polímeros. Restenose coronária. Trombose coronária.

Drug-eluting stents (DES) have emerged as a strategy for increasing the effectiveness of percutaneous coronary intervention, reducing restenosis and therefore the need for repeat revascularization, compared to bare metal stents (BMS).[1,2] This is particularly important in the subgroup of patients with higher risk of restenosis, such as diabetics, patients with small-caliber vessels, and patients with extensive lesions.[3-6] The greatest risk of restenosis, in general, is also associated with a greater risk of stent thrombosis. Durable polymers have been implicated in this phenomenon, at least in part, since evidence suggests that the continued presence of the polymer stimulates a hypersensitivity reaction.[7,8] Biodegradable polymers have been developed to reduce the inflammatory response, by accelerating arterial healing and allowing for a complete re-endothelialization of stent struts.

Data from long-term clinical follow-up of biodegradable-polymer drug-eluting stents (BP-DES) are still limited. Moreover, comparisons of these devices have been performed among different stents, such that the results cannot be explained only by different polymers or drugs, but also by the variable metallic platforms used.

The PercutAneous INTervention with biodegradable-polymer based paclitaxel-eluting or sirolimus-eluting versus bare stents for *de novo* coronary lesions (PAINT) study, which uses the same metallic platform for DES and BMS, allows for a specific comparison, by evaluating the presence of the polymer and the different drugs. This study aimed to analyze the angiographic results at 9 months and clinical outcomes at 5 years of BP-DES, compared to BMS with identical platform, in patients at high risk of restenosis.

METHODS

The primary outcome and the 3-year results of PAINT study were previously published.[9-11] In summary, PAINT is a randomized study which allocated patients to coronary intervention in *de novo* lesions to receive: (1) Infinium® paclitaxel-eluting stent; (2) Supralimus® sirolimus-eluting stent; or (3) SM Millennium Matrix® (all manufactured by Sahajanand Medical Technologies Pvt. Ltd. – Surat, India) at a ratio of 2:2:1, respectively. Stents were manufactured with the same metal platform of 316L stainless steel and the same delivery system. The drug carrier (thickness: 4-5 µm) for the two DES used consisted of a mixture of biodegradable polymers, including poly(L-lactide) 50/50 poly(D,L-lactide-co-glycolide), 71/25 poly(L-lactide-co-caprolactone), and polyvinylpyrrolidone. The polymeric matrix is biodegraded into water and carbon dioxide. The two DES formulations release approximately 50% of the drug content in the first 9 to 11 days, 90% in 38 days, and 100% at 48 days. Detailed information about the protocol can be obtained from another source.[9]

This study is an analysis of a subgroup of patients at high risk of restenosis, defined as patients whose treated vessels had a reference diameter ≤ 2.5 mm, or with an injury ≥ 15 mm in length; or patients with diabetes or any combination of the above. The primary endpoint of this study was defined as the combined endpoint of cardiac death, myocardial infarction, or target vessel revascularization due to ischemia. Other adverse events, including stent thrombosis, according to the Academic Research Consortium (ARC), were also analyzed.

Statistical analysis

Categorical variables were expressed as absolute numbers and percentages, and compared by chi-squared test or Fisher's exact test, as appropriate. Continuous variables were presented as means and standard deviations, and compared by Student's *t*-test. The incidence of clinical adverse events was estimated by Kaplan-Meier method and compared with log-rank test. *P values* < 0.05 were considered significant. In the statistical analysis, Stata v. 12 (College Station, United States) was used.

RESULTS

The PAINT study total population included 274 patients, of whom 178 (65%) had at least one of the features implying high risk of restenosis. These patients

were allocated to receive BP-DES (n = 142) or BMS (n = 36). The mean follow-up was 4.6 ± 0.9 years. The clinical, angiographic, and procedural characteristics (Table 1) were similar between groups.

The angiographic diameters pre- and immediately post-procedure showed no differences between groups (Table 2). In the angiographic follow-up of 9 months, BP-DES showed a greater minimum lumen diameter (1.9 ± 0.5 mm vs. 1.4 ± 0.65 mm, $p < 0.01$), less late loss (0.40 mm ± 0.42 vs. 0.90 ± 0.47 mm; $p < 0.01$), and less binary restenosis (7.4% vs. 25%, $p < 0.01$), compared to BMS.

The figure shows the cumulative events through 5 years of follow-up. BP-DES group showed lower rates of combined endpoint of cardiac death, myocardial infarction, and target vessel revascularization (16.2% vs. 38.9%; $p < 0.01$) at the expense of lower rates of target vessel revascularization (9.9% vs. 36.1%; $p < 0.01$). There was no difference in cardiac death and myocardial infarction rates between groups. There was also no difference in the incidence of probable or definite stent thrombosis (2.8% vs. 0%, $p = 0.30$; Table 3).

TABLE 1
Clinical and procedural characteristics

Variables	DES (n = 142)	BMS (n = 36)	*p value*
Age, years	60.4 ± 9.5	57.8 ± 10.2	0.85
Male gender, n (%)	87 (61.3)	23 (63.9)	0.08
Diabetes mellitus, n (%)	69 (48.6)	15 (41.7)	0.46
Smoking, n (%)	26 (18.3)	5 (13.9)	0.59
Hypercholesterolemia, n (%)	108 (76.1)	29 (80.6)	0.57
Hypertension, n (%)	124 (87.3)	33 (91.7)	0.47
Previous myocardial infarction, n (%)	38 (26.8)	12 (33.3)	0.43
Prior CABG, n (%)	11 (7.8)	1 (2.8)	0.29
Prior PCI, n (%)	22 (15.5)	7 (19.4)	0.57
Previous stroke, n (%)	1 (1.4)	0	0.47
Clinical presentation, n (%)			0.61
Silent ischemia	6 (4.2)	3 (8.3)	
Stable angina	96 (67.6)	24 (66.7)	
Unstable angina	34 (23.9)	7 (19.4)	
Recent myocardial infarction	6 (4.2)	2 (5.6)	
Affected vessels, n (%)			0.58
1	87 (61.3)	18 (50.0)	
2	34 (23.9)	14 (38.9)	
3	21 (14.8)	4 (11.1)	
Target vessel, n (%)			0.39
Right coronary	35 (24.6)	4 (11.1)	
Circumflex	32 (22.5)	10 (27.8)	
Anterior descending	75 (52.8)	22 (61.1)	
Reference diameter, mm	2.5 ± 0.54	2.6 ± 0.49	0.68
Lesion length, mm	13.6 ± 5.7	13.7 ± 4.9	0.69
> 1 stent implanted	4 (2.8)	2 (5.6)	0.42
Stent diameter, mm	3.0 ± 0.3	3.0 ± 0.4	0.85
Total length of the stent, mm	22.6 ± 5.0	23.2 ± 5.1	0.40
Direct stenting, n (%)			0.23
Successful	73 (51.4)	24 (66.7)	
Unsuccessful	10 (7.0)	1 (2.8)	
Unrealized	59 (41.6)	11 (30.6)	

DES, drug-eluting stent; BMS, bare-metal stent; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention.

DISCUSSION

The use of BP-DES compared to BMS with the same platform was effective in reducing angiographic restenosis after 9 months of follow-up and the incidence of major adverse cardiac events in the 5-year follow-up in a population at high risk for restenosis. A long-term benefit was obtained by reducing the need for target vessel revascularization, which translated into less clinical restenosis. Furthermore, BP-DES demonstrated good safety, with no difference in the occurrence of stent thrombosis according to the ARC definition when compared to BMS.

It has been shown that DES reduce the restenosis rate,[2] with some remaining issues related to safety, particularly the incidence of late and very late thrombosis.[7,8,12] BP-DES devices were developed to reduce this problem, thus facilitating stent strut re-endothelialization, making them similar to BMS after drug delivery, and with less tendency towards stent thrombosis. Another condition observed in some studies with long-term follow-up is the catch-up phenomenon, that is, a delayed reduction in the luminal area of the stent, which could be caused by an inflammatory response produced by the polymer in the stent.[13,14] Theoretically, this problem could be minimized by the use of biodegradable polymers.

There is no information on the effectiveness and safety of these devices in the very long-term, especially in the subgroup of patients at high risk of restenosis, that is, the subgroup theoretically more benefited by this strategy. While diabetes, small-caliber vessels, and extensive lesions increase the occurrence of restenosis, a complication which, arguably, is generally minimized with the use of DES;[3-5] these features are also described as predictors of stent thrombosis, which is a concern when using DES.[15] This study demonstrated the effectiveness of BP-DES in reducing angiographic restenosis at 9 months and in diminishing clinical events compared with BMS in a long-term clinical follow-up, with no significant increase in probable or definite stent thrombosis, according to ARC.

TABLE 2
Quantitative coronary angiography

Variables	BP-DES (n = 142)	BMS (n = 36)	*p value*
Pre-procedure			
Reference diameter, mm	2.60 ± 0.49	2.50 ± 0.54	0.68
Minimal luminal diameter, mm	1.10 ± 0.24	1.10 ± 0.24	0.66
Post-procedure			
Minimal luminal diameter, mm	2.30 ± 0.35	2.30 ± 0.42	0.96
Late follow-up (nine months)			
Minimal luminal diameter, mm	1.90 ± 0.50	1.40 ± 0.65	< 0.01
Stenosis diameter, %	25.5 ± 14.5	42.2 ± 23.1	< 0.01
Late loss, mm	0.40 ± 0.42	0.90 ± 0.47	< 0.01
Net gain, mm	0.90 ± 0.51	0.30 ± 0.60	< 0.01
Binary restenosis, %	7.4	25	< 0.01

BP-DES, Biodegradable-polymer drug-eluting stents; BMS, bare-metal stent.

A recent meta-analysis covering 258,544 patient-years of follow-up compared various types of DES with durable polymers with BP-DES. In that study, the authors noted that sirolimus-eluting stents with biodegradable polymers were superior to the first-generation of paclitaxel-eluting stents (relative risk [RR] = 0.66; 95% confidence interval [95% CI]: 0.57-0.78) and to Endeavor® zotarolimus-eluting stent (RR = 0.69; 95% CI: 0.56-0.84), but not superior to the new-generation DES with durable polymer (e.g., RR = 1.03; 95% CI: 0.89 = 1.21) vs. everolimus-eluting stents with chromium-cobalt platform. However, in relation to stent thrombosis, BP-DES were superior to sirolimus-eluting stents for definite stent thrombosis (RR = 0.29; 95% CI: 0.10-0.92), but the use of that device was associated with greater mortality, compared with new-generation everolimus-eluting stents with durable polymer and a chromium-cobalt platform (RR = 1.52; 95% CI: 1.02-2.22).[16] None of these studies, however, was designed specifically for patients at high risk of restenosis.

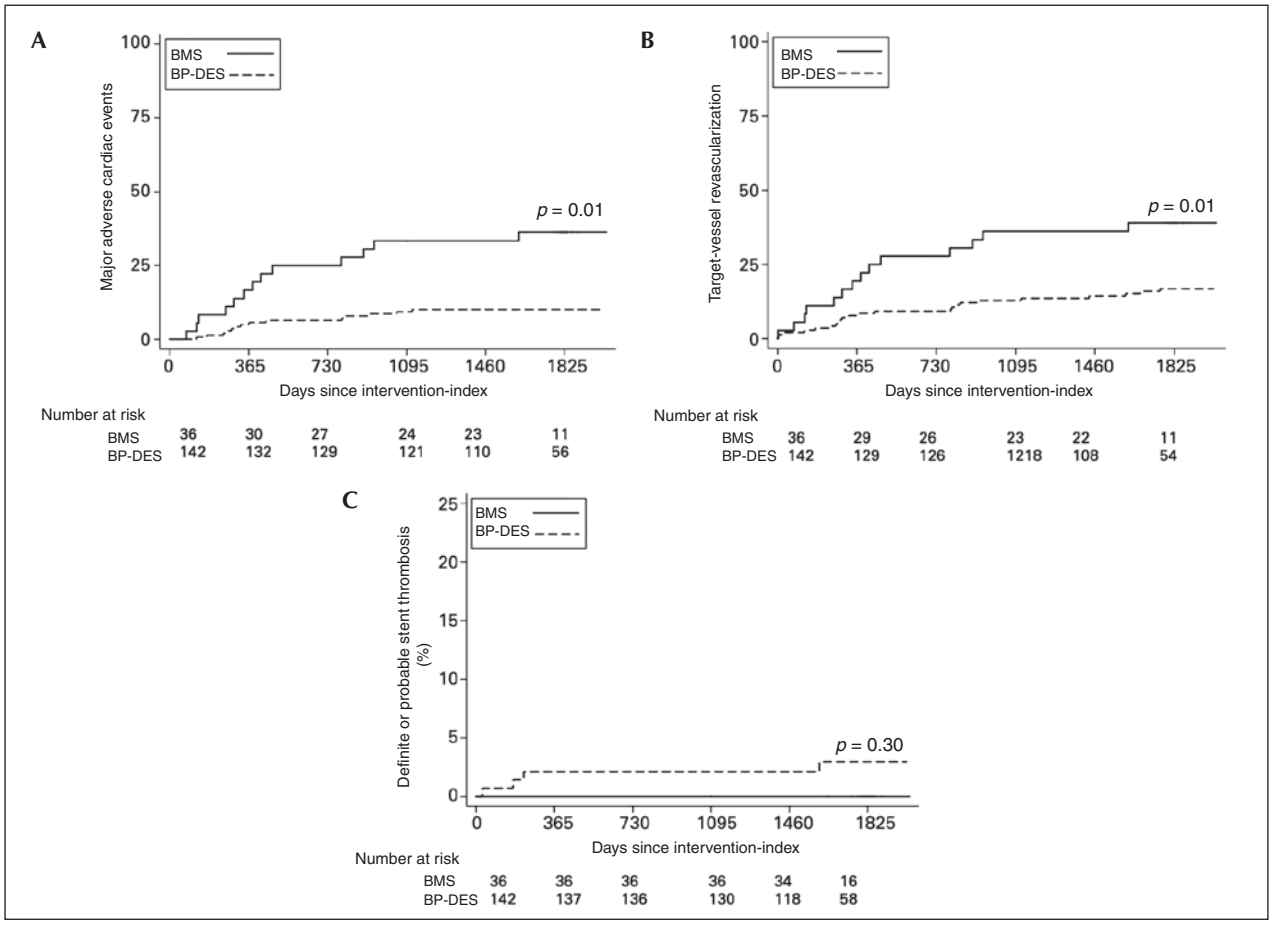

Figure – Kaplan-Meier curves for major adverse cardiac events (A), target-vessel revascularization (B) and stent thrombosis (C). BMS, bare metal stent; BP-DES, biodegradable-polymer drug-eluting stent.

TABLE 3
Clinical events at 5-year follow-up

Outcomes	BP-DES (n = 142)	BMS (n = 36)	*p value*
Death, n (%)	17 (12.0)	1 (2.8)	0.10
Cardiac	7 (4.9)	0	
Non-cardiac	10 (7.0)	1 (2.8)	
Myocardial infarction, n (%)	15 (10.6)	4 (11.1)	0.92
Q-wave	9 (6.3)	1 (2.8)	
No Q-wave	6 (4.2)	3 (8.3)	
Target-lesion revascularization, n (%)	10 (7.0)	13 (36.1)	< 0.01
Surgical	0	2 (5.6)	
Percutaneous	10 (7.0)	11 (30.6)	
Target-vessel revascularization, n (%)	14 (9.9)	13 (36.1)	< 0.01
Surgical	1 (0.7)	2 (5.6)	
Percutaneous	13 (9.2)	11 (30.6)	
MACE, n (%)	23 (16.2)	14 (38.9)	< 0.01
Stent thrombosis, n (%)			
Final	3 (2.1)	0	0.37
Probable	1 (0.7)	0	0.61
Probable	3 (2.1)	0	0.37
Definite or probable	4 (2.8)	0	0.30
Definite, probable, or possible	7 (4.9)	0	0.17

BP-DES, biodegradable-polymer drug-eluting stents; BMS, bare-metal stent; MACE, major adverse cardiac events.

CONCLUSIONS

This study supported the evidence that drug-eluting stents with biodegradable polymers are effective in reducing restenosis, without increasing the risk of stent thrombosis in long-term follow-up, compared to bare metal stents with the same platform, in a population at high risk of restenosis.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

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None.

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