Rationale and Design for the PAINT Randomized Trial

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Abstract

Background: We describe the rationale and design for the "PercutAneous INTervention with biodegradable-polymer based paclitaxel-eluting or sirolimus-eluting versus bare stents for de novo coronary lesions - PAINT trial".

Objectives: To evaluate two novel formulations of paclitaxel-eluting stent and the sirolimus-eluting stent against a stent with the same metallic structure but without polymer coating or drug elution.

Methods: The PAINT is a multicenter 3-arm randomized trial, conducted in Brazilian tertiary institutions, which included 275 patients allocated for the Infinnium^{R} paclitaxel-eluting stent, the Supralimus^{R} sirolimus-eluting stent or the Milennium Matrix^{R} bare metal stent in a 2:2:1 ratio. Patients had de novo coronary lesions in native vessels with a diameter between 2.5 and 3.5 mm, amenable for treatment with a single stent of 29 mm or less in length. The primary objetive was to compare the in-stent late loss at 9 months of both paclitaxel- and sirolimus-eluting versus the late loss of control bare metal stents. Important secondary objectives included the comparison in outcomes between sirolimus and paclitaxel stents, as well as the analysis of the incidence of major adverse cardiac events.

Results and Conclusions: The PAINT trial had a unique design that allowed for the evaluation of the safety and efficacy profiles of two novel drug-eluting stent formulations, with a biodegradable-polymer carrier and releasing paclitaxel or sirolimus, which were compared against a bare metal stent (primary objective). As the drug-eluting stents differed by the drug, but were identical otherwise, the trial also allowed the comparison of the anti-restenosis effects of sirolimus versus paclitaxel (secondary objective). (Arq Bras Cardiol 2009; 93(6):547-553)

Key Words: Coronary restenosis; drug-eluting stents; paclitaxel; sirolimus; multicenter study.

Introduction

Coronary restenosis is recognized as a major late limitation of percutaneous revascularization techniques. It occurs as a consequence of an exacerbated healing process of the vessel wall triggered by the mechanical dilatation of the atherosclerotic lesion. Over the last years, drug-eluting stents (DES) have been proven effective in reducing restenosis and the need for subsequent revascularization[1-4]. Recently, however, the safety profile of drug-eluting stents have been questioned, especially with regards to the risk of stent thrombosis and thrombosis-related clinical events[5]. Much attention has been driven by the non-absorbable polymeric coating used in many DES formulations, raised as a possible contributor for the occurrence of unwanted effects at the site of the implantation. In this context, other initiatives have been focused on the development of stent formulations with "old" drugs but different coatings, such as biodegradable polymers, or no coating at all.

The present report describes the study protocol of the *P*ercut*A*neous *INT*ervention with biodegradable-polymer based paclitaxel-eluting or sirolimus-eluting *versus* bare stents for *de novo* coronary lesions - PAINT trial. This randomized clinical study aimed at evaluating two new drug-eluting stents, with the drugs paclitaxel (Infinnium^{R}) or sirolimus (Supralimus^{R}) eluted with biodegradable polymeric blends, compared with a control bare metal stent (Milennium Matrix^{R}) that has the same metallic structure used for the drug-eluting stents.

Description of the study novel drug-eluting stents

The stents Infinnium^{R} and Supralimus^{R}, eluting paclitaxel and sirolimus respectively will be utilized in this study. All devices utilize the same laser-cut 316L stainless metallic platform and delivery system, equal to the Milennium Matrix^{R} bare stent used in the study control arm. Therefore, the polymer/drug coating is the only difference among the stents.

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Manuscript received July 31, 2008; revised manuscript received August 07, 2008; accepted August 07, 2008.

Owing to the fact that the polymer/drug coating is not visible at the naked eye, the stents Infinnium®, Supralimus®, and Matrix® used in this study are not distinguishable regarding their external appearance and their mechanical characteristics (all study stents produced by Sahajanand Medical Technologies Pvt. Ltd., India).

Table 1 - Total drug content and stent sizes used in the study.

Diameters (mm)			Length	Total drug content (µg)		
				Matrix®	Infinnium®	Supralimus®
2.5	3.0	3.5	19 mm	-	122	125
2.5	3.0	3.5	23 mm	-	147	151
2.5	3.0	3.5	29 mm	-	185	191

Table 2 - Study Endpoints.

Primary Objective
• To compare the in-stent late loss at 9 months of paclitaxel- and sirolimus-eluting stents with the late loss of bare metal control stents.
Secondary Objectives
Safety:
• To compare the incidence of major adverse cardiac events (MACE) at 30 days, 9 months, 1 year, 3 years and 5 years among the study groups
• TTo compare the incidence of serious adverse events (SAE) until 5 years among the study groups
• To compare the incidence of stent thrombosis until 5 years among the study groups
Efficacy:
• To compare the rate of angiographic success among the study groups
• To compare the rate of procedural success among the study groups
• To compare the rate of clinically driven target lesion revascularization at 9 months and up to 5 years among the study groups
• To compare the rate of clinically driven target vessel revascularization at 9 months and up to 5 years among the study groups
• To compare the cost-effectiveness profile up to 5 years among the study groups
• To compare the 9-month in-stent late loss of paclitaxel-eluting stents to the in-stent late loss of sirolimus-eluting stents
• To compare the 9-month in-segment late loss among the study groups
• To compare the 9-month in-stent and in-segment binary restenosis rate among the study groups
• To compare the IVUS percentage neointimal obstruction among the study groups*

*IVUS=intravascular ultrasound *for patients included in the IVUS substudy*

The stents Infinnium® and Supralimus® utilize a blend of biodegradable polymers that release the drug in a sustained fashion for weeks after implantation, without retention of the drug/polymer after the completion of the degradation phase. The surface of the stents Infinnium® and Supralimus® is covered with the active drug (paclitaxel or sirolimus respectively) complexed to a blend of biodegradable polymers including Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide, 75/25 Poly L-Lactide-co-Caprolactone and Polyvinyl Pyrrolidone. Both stents have a final coating thickness of 4-5 µm, which is degraded by hydrolysis and enzymatic action to monomeric acids and eliminated from the body through the Krebs cycle (or TCA cycle), primarily as water and carbon dioxide.

The drug release in both formulations occurs in a slow and sustained way for 48 days. Approximately 50% of the drug is released in the first 9-11 days, 90% in 38 days e 100% in 48 days, after which there is no residual drug bound to the stent. Complete polymer degradation occurs after 7 months. Stent sizes used in the study and their respective total drug content are shown in Table 1.

Objectives and endpoint definitions

The main objective of this study was to evaluate the safety and efficacy of the paclitaxel-eluting Infinnium® stent and the sirolimus-eluting Supralimus® stent, in comparison with the bare metal Matrix® stent for the treatment of coronary lesions in native vessels. Primary and secondary endpoints are listed in Table 2.

For the final analysis, any adverse events were only considered as such after adjudication of the clinical details by the Independent Adverse Events Committee, according to the definitions below:

Death

Deaths were divided into cardiac and non-cardiac deaths. Non-cardiac deaths were only considered as such if a non-cardiac cause could be unequivocally documented.

Myocardial infarction

All myocardial infarctions occurring after the index procedure were classified as Q-wave or non-Q-wave infarctions[6]. A detailed description of the diagnostic criteria for myocardial infarction is shown in Table 3.

Coronary re-intervention

Coronary re-interventions (surgical or percutaneous) were defined as any coronary intervention occurring after the index procedure. The end of the index procedure was characterized by the removal of the guiding catheter. For this moment and thereafter, any new coronary intervention was considered as a new procedure and classified as:

a) Target lesion revascularization: when motivated by a stenosis located in the treated segment (within the stent + 5-mm proximal and 5-mm distal edges)

b) Target vessel revascularization: when motivated by a stenosis located in the epicardial vessel treated in the index procedure (includes the entire reject subjected to

intracoronary manipulation [e.g. guiding-catheter, guidewire, balloons, stent]).

c) Non-related vessel revascularization: when motivated by a stenosis located in a vessel different from the target vessel.

A new revascularization procedure is considered as clinically justified when:

1) Motivated by a diameter stenosis ≥ 70%, even in the absence of symptoms or documented myocardial ischemia *OR*

2) Motivated by a diameter stenosis ≥ 50% in the presence of:

- Angina pectoris presumably related to the target vessel
- Documented rest or stress-induced ischemia presumably related to the target vessel
- Abnormal invasive testing (e.g. intracoronary Doppler flow velocity reserve, intracoronary fractional flow reserve)

Major adverse cardiac event

Major adverse cardiac event are defined as the combined endpoints: 1) cardiac death, 2) Q-wave or non-Q-wave myocardial infarction, 3) clinically driven target lesion revascularization.

Stent thrombosis

Stent thrombosis were diagnosed and classified according with the definitions proposed by the Academic Research Consortium[7], as detailed in Table 4.

Study design

The PAINT is a multicenter Brazilian trial randomized in three arms for treatment with: I) Infinnium^{R} paclitaxel-eluting stent, II) Supralimus^{R} sirolimus-eluting stent, or III) control Matrix^{R} bare metal stent. A sample size of 275 patients was set to be randomized in a 2:2:1 fashion (Paclitaxel group= 110 patients; Sirolimus group = 110 patients, Control group = 55 patients).

At the index procedure, only one lesion was treated with the study stent. The target lesion had to be treated with a single stent of up to 29 mm in length. Patients with tandem lesions (*i*.e. lesions with two stenotic sites in the same artery) were included if the entire diseased segment was amenable to treatment with a single stent. In case additional stents were needed for the treatment of procedural complications, operators were instructed to use stents of the same type, according to the randomization. Operators were strongly recommended that additional stents should be implanted with an overlap of at least 2 mm, in order to avoid uncovered gaps between the stents. Balloon pre- or post-dilatation were not obligatory, but, in case they were performed, operators were advised to avoid any vessel injury outside the stented segment.

Protocol-mandated angiographic evaluation was scheduled at 9 months. An intravascular ultrasound examination was performed in a subgroup of 55 patients at the time of the

Table 3 - Diagnostic criteria for myocardial infarction (adapted from "Case Definitions for Acute Coronary Heart Disease in Epidemiology and Clinical Research Studies - A Statement From the AHA Council on Epidemiology and Prevention; AHA Statistics Committee; World Heart Federation Council on Epidemiology and Prevention; the European Society of Cardiology Working Group on Epidemiology and Prevention; Centers for Disease Control and Prevention; and the National Heart, Lung, and Blood Institute")[6].

Diagnostic criteria
• Presence of diagnostic ECG ***AND/OR*** diagnostic cardiac marker
Definitions:
I) *Diagnostic ECG must present any of the following* (interpreted according to the Minnesota Code)[28,29]:
A) No Q-code in previous study ECG or first ECG in event set of ECG(s) followed by a record with a diagnostic Q-code (Minnesota Code 1-1-1 through 1- -5 plus 1.2-7) ***OR*** any code 1-3-X or 1-2-6 in baseline ECG followed by a record with any code 1-1-X.
B) An equivocal Q-code (Minnesota Code 1-2-8 or any 1-3 code) and no major ST-segment depression in previous study ECG or first ECG in event set of ECG(s) followed by a record with a diagnostic Q-code ***PLUS*** a major ST-segment depression (Minnesota code 4-1-X or 4-2) and 100% increase in ST depression.
C) An equivocal Q-code (Minnesota Code 1-2-8 or any 1-3 code) and no major ST-segment depression in previous study ECG or first ECG in event set of ECG(s) followed by a record with a diagnostic Q-code ***PLUS*** a major T-wave inversion (Minnesota Code 5-1 or 5-2) and 100% increase in T-wave inversion.
D) An equivocal Q-code and no ST-segment elevation in previous study ECG or first ECG in event set of ECG(s) followed by a record with a diagnostic Q-code ***PLUS*** ST-segment elevation (Minnesota code 9-2) and 100% increase in ST elevation.
• **Note:** A significant Q-code change requires ≥50% increase in event Q/R ratio or ≥1-mm initial R-wave amplitude decrease in event ECG compared with corresponding lead(s) of baseline ECG.
II) *Diagnostic Cardiac Marker:*
A) At least 1 positive biomarker in an adequate set (see below) of biomarkers showing a rising or falling pattern in the setting of clinical cardiac ischemia and the absence of noncardiac causes of biomarker elevation.
• Blood cardiac biomarkers of myocardial necrosis: CK, CK-MB, CK-MBm, or troponin (cTn). The order of diagnostic value is cTn > CK-MBm > CK-MB > CK.
• Adequate set of biomarkers: At least 2 measurements of the same marker obtained at least 6 hours apart

Table 4 - Diagnosis and classification of stent thrombosis (according with the definitions proposed by the Academic Research Consortium)[7].

Degree of Certainty
1) Definite stent thrombosis
a. Angiographic confirmation
i. Vessel occlusion (TIMI flow grade 0) originating in the stent or in the 5-mm segments proximal or distal to the stent in the presence of angiographic thrombus OR
ii. Patent vessel (TIMI flow grade 1, 2, or 3) with angiographic thrombus in the stent or in 5-mm segments proximal or distal to the stent with least one of the following characteristics within 48 hours: I) new onset of ischemic symptoms at rest (typical chest pain with duration >20 min), II) new ischemic ECG changes suggestive of acute ischemia, III) or typical rise and fall in cardiac biomarkers
b. Confirmation of stent thrombosis I) by evidence of recent thrombus within the stent at autopsy or II) via examination of specimen retrieved after mechanical thrombectomy
2) Probable stent thrombosis
a. Any unexplained death within the first 30 days
b. Regardless of the time after the index procedure, any myocardial infarction in the territory of the implanted stent for which no angiographic confirmation of stent thrombosis is available and in the absence of any other obvious cause
3) Possible ST
a. Any unexplained death > 30 days
Timing
1) Acute: 0–24 hours
2) Subacute: >24 hours – 30 days
3) Late: 30 days – 1 year
4) Very late: >1 year after stent implantation

angiographic follow-up. Patients will be clinically followed-up for 60 months after the index procedure.

Study population

The study population comprises patients eligible for coronary stent implantation in native vessels for the treatment of *de novo* atherosclerotic lesions. Inclusion and exclusion criteria are detailed in Table 5.

Randomization

The randomization (2:2:1 ratio) was performed in blocks, stratified by center, and inclusion was competitive among all centers, with no minimum or maximum limits for the number of patients enrolled in each hospital. The randomization was accomplished online, via a web-based process that allowed the inclusion of patients 24 hours per day, 7 days per week.

The operators were not blinded to the allocated treatment arm. In order to minimize any bias related to the lack of treatment blindness by the operator, the interventional strategy had to be pre-established before the randomization. To proceed with the electronic randomization process, the planned target segment, stent diameter, and stent length had to be informed before final patient inclusion. And deviations from the pre-procedure plan had to be carefully detailed in the care record form.

Post-procedure care, clinical follow-up and medications

Aspirin plus clopidogrel or aspirin plus ticlopidine were administered according to the scheme below:

Aspirin, 160-500 mg introduced at least 12 hours before the index procedure, for patients who were not on aspirin. Thereafter, aspirin (80-325 mg qd) was maintained lifelong.

Clopidogrel, 75 mg/day introduced at least 3 days before the procedure. For patients on clopidogrel < 3 days, a loading dose of 300 mg was administered at least 4 hours before the procedure.

Ticlopidine, 250 mg / twice a day (daily dose 500 mg) introduced at least 3 days before the procedure. According to the original study protocol, clopidogrel (75 mg qd) or ticlopidine (250mg bid) were maintained for 6 months after the procedure. The protocol was amended to mandate for a 12-month administration.

Cardiac enzymes (CK, CKMB [troponin optional]) were collected after the procedure for all patients. A first sample was obtained after 6-8 hours and a second sample 6-8 hours after the first one. In case of enzyme increase, blood collection was continued every 6-8 hours until the markers were normalized.

After discharge, out-patient visits were scheduled at 1 month, 4 months, 9 months, 12 months, and every 6 months thereafter. Non-invasive ischemia testing was not obligatory during the follow-up, but performed at the discretion of the physician. However, it was strongly recommended for any subsequent re-intervention to be based on clinical findings (including invasive and non-invasive ischemia testing) that would justify the new procedure.

Angiographic and intravascular ultrasound follow-up

Patients were scheduled for a control coronary angiography at 9-month follow-up, or before, if clinically indicated.

The 9-month follow-up angiography was still obligatory for patients who had an unscheduled angiography in the first 6 months, in case the diagnostic catheterization was not followed by a new revascularization in the target segment (stented portion plus 5-mm proximal or distal).

If an unscheduled angiography was followed by an invasive procedure to treat the target segment, this was to be considered as the follow-up angiography, even if the revascularization had occurred before 6 months from the index procedure. Also, any unscheduled angiography obtained between 6 and 9 months after the index procedure was considered as the follow-up angiography.

All angiographic procedures (scheduled and non-scheduled) were acquired and recorded to ensure optimal quality for off-line quantitative analysis using the Coronary Angiography Analysis System (CAAS)-II® (Pie Medical Data, Maastricht, The Netherlands). Quantitative coronary angiography findings were processed by an independent angiographic core laboratory, blinded to the treatment arms and clinical outcomes.

The 55 patients included in the intravascular ultrasound (IVUS) substudy underwent this evaluation at the time of the 9-month angiography.

Quality assurance

Baseline, procedural, and follow-up data were prospectively collected and stored in a dedicated electronic web-based database. Multi-level access was permitted following international security standards to ensure confidentiality. All data were monitored by an independent board of clinical monitors, who cross-checked all information against source documents. Final database lock was only authorized after all queries and pending issues were solved. All adverse events (serious and non-serious) were adjudicated by an independent Adverse Event Committee that had the final decision over endpoint classification of any event.

Cost-effectiveness

Economic analyses were performed to evaluate the impact of the treatment with the Infinnium® and Supralimus® drug-eluting stents, in comparison with the bare stent Matrix®. For each patient, the direct resource consumption was prospectively recorded for the index procedure, as well as for the subsequent relevant diagnostic and therapeutic events (including new hospitalizations). The primary analysis of the economic evaluation is focused on the effect of the treatment on direct costs. Indirect costs will be estimated by the number of lost work days. The association between costs and effects up to 5 years will be evaluated through the calculation of the incremental cost-effectiveness rate (average cost per patient treated with drug-eluting stent minus the average cost per patient treated with bare stent divided by the percentage difference in the incidence of adverse events).

Collected information on resource utilization included (but was not limited to):

- Procedure time
- Length of index hospitalization
- Emergency visits not needing hospitalization
- Adverse events (diagnostic and therapeutic actions)
- New hospitalizations (length of stay, type of treatment)
- Re-interventions
- Unscheduled out-patient visits
- Unscheduled diagnostic tests

Sample size calculation and data analysis

In a single factor ANOVA study, sample sizes of 96, 96, and 48 were obtained from the 3 groups whose means were to be compared. The total sample of 240 subjects achieves

Table 5 - Inclusion and exclusion criteria.

Inclusion Criteria
• Age ≥ 18 years;
• Symptomatic ischemic heart disease and/or objective evidence of myocardial ischemia;
• *De novo* coronary lesion;
• Target lesion located in a native artery;
• Vessel with diameter between 2.5-3.5 mm (visual analysis);
• Target lesion amenable to treatment with a single stent of up to 29 mm in length;
• Target lesion with a diameter stenosis > 50% (visual analysis);
• Acceptable candidate for surgical revascularization;
• Signed informed consent term.
Exclusion Criteria
General Exclusion Criteria
• Q-wave myocardial infarction < 48 hours;
• Recent myocardial infarction with cardiac markers still above the upper limits;
• Left ventricle ejection fraction ≤30%
• Serum creatinine > 2.0 mg/dl (>177 µmol/l);
• Platelet count < 100,000 cells/mm3 or > 700,000 cells/mm3;
• White cell count < 3.000 cells/mm3;
• Suspected or known liver disease (including subclinical hepatitis);
• Heart transplant recipient;
• Know allergy to aspirin, clopidogrel, ticlopidine, paclitaxel, sirolimus, heparin, or stainless steel;
• Life expectancy < 12 months;
• Any medical condition that, in the opinion of the investigator, may interfere with the ideal participation in study;
• Current inclusion in another study to investigate drug or other device, or planned inclusion in another study to investigate drug or other device during the follow-up.
• Percutaneous coronary intervention < 6 months in any portion of the target vessel;
• Previous percutaneous coronary intervention, at any time, in a coronary segment < 5 mm (proximal or distal) from the target lesion;
• Percutaneous coronary intervention in any segment of the target vessel planned during the next 12 months following the index procedure.
Angiographic Exclusion Criteria
• Restenotic target lesion;
• Need for treatment of more than one lesion in the target vessel;
• Long target lesion, not amenable to treatment with a single stent of up to 29 mm in length, according to the operator's discretion;
• Significant (> 50%) unprotected left main lesion;
• Angiographic thrombus;
• Target lesion located in bypass graft;
• Occluded target vessel (antegrade flow TIMI 0 or 1);
• Target lesion in ostial location;
• Target lesion in a bifurcation site with a side branch > 2.5 mm or that may require stent implantation;
• Calcified target lesion with anticipated unsuccessful balloon pre-dilatation;
• Severely tortuous target vessel.

82% power to detect a difference of at least 0.25 using the Tukey-Kramer (Pairwise) multiple comparison test at a 0.05 significance level. The common standard deviation within a group is assumed to be 0.35. Considering an expected attrition rate of 15% of patients lost for the primary endpoint analysis, a final sample size of 275 patients was calculated, divided into 3 groups: Infinnium paclitaxel-eluting stent (n=110), Supralimus sirolimus eluting-stent (n=110), and Matrix bare metal stent (n=55)[8].

Such assumptions allow the testing of the primary objective of the study, which hypothesize that both drug-eluting stents are superior to the conventional stent, since it is expected that the difference in late loss between the pharmacological stents and the bare stents will be > 0.25 mm[9-12]. Also, as a secondary objective, the assumptions above allow us to explore the possibility that the active stents are different between each other regarding their capacity of inhibiting neointimal proliferation, in case the difference in angiographic late loss between them is ≥ 0.25 mm.

The intravascular ultrasound study will include a total of 55 patients. This sample size is sufficient to detect a difference of at least 17.3% in the mean neointimal obstruction (75% reduction of the expected value for controls[13]), with the possibility for multiple comparisons between all groups, assuming a common standard deviation of 10%, with a significance level (alpha) of 0.05 and power (beta) of 80%, considering an attrition rate of 20%[8].

All comparative analysis of the primary and secondary objectives among the study groups will be performed according to the intention-to-treat principle.

The Major Adverse Cardiac Events (MACE) will be classified per patient according to their "severity", according to the following descending hierarchical scale: 1) death, 2) myocardial infarction, 3) surgical coronary re-intervention, 4) percutaneous coronary re-intervention. Only events adjudicated by the independent Adverse Event Committee were considered for endpoint analysis.

Categorical variables were compared using the Fisher's exact test. Continuous variables were compared using the independent-sample *T* test. Logistic regression analyses were applied to binary variables to analyze associations. Linear regression analyses were performed for continuous variables to evaluate associations. The Kaplan-Meier method, Cox regression and the log-rank test were utilized to analyze the incidence of clinical events and the impact of potential predictors on outcomes during the follow-up period.

Discussion

The objectives and methods detailed above are unique, in that the "PAINT" randomized trial allows the evaluation of the safety and efficacy profiles of two novel drug-eluting stent formulations, with paclitaxel or sirolimus, eluted in a biodegradable polymeric coating, both compared against a control bare metal stent. All three study stents had an identical metallic structure and the two drug-eluting stents had similar polymeric coating.

Paclitaxel and sirolimus have been extensively proven to be efficacious in preventing restenosis when used in drug-eluting stent formulations[1-4]. However, it is clear that drug-eluting stents are complex biodevices that do not follow a "class effect"[14]. Stents with similar drugs have been shown to present marked differences in angiographic and clinical outcomes[14], which may be theoretically modulated by several other stent features such as drug release kinetics, type of coating, or platform structure. Therefore, ideally, any novel drug-eluting stent formulation should be tested in the context of clinical trials, including stents releasing "previously tested" drugs. The PAINT trial is in line with this principle – the study's primary objective is to evaluate both new stents (with paclitaxel- or sirolimus-eluting) against a control bare stent.

Many previous randomized studies have compared paclitaxel- and sirolimus-eluting stents[15-25]. However, in addition to the drug, the stents used in those studies differed in all other characteristics (coating and platform), which consequently prevented a more conclusive evaluation of the effects of the drugs themselves. It is evident that any difference between the drugs paclitaxel and sirolimus can only be directly probed when the stents are similar in all other components. In this context, an important characteristic of the PAINT trial is that its design permits a head-to-head comparison between the paclitaxel and sirolimus agents, as all other stent components are similar in both stents.

A recent pilot study has tested the performance of two stents with paclitaxel or sirolimus with identical polymer and platform[26]. Both stents proved to be clinically safe at 9 months, but the late-lumen loss was markedly higher for the paclitaxel stents (0.96 ± 0.75 mm *vs.* 0.33 ± 0.46 mm for the sirolimus stent; $p < 0.01$), as well as the rate of binary restenosis (39% vs. 12% respectively; $P < 0.01$). It is important to note that the paclitaxel stent used in that study (which is different from the one used in the PAINT) presented a high late lumen loss, indicating a worse than expected efficacy for a drug-eluting stent. Unfortunately, the actual efficacy of the paclitaxel-eluting stent could not be comprehensively assessed due to the lack of a control group with bare stents. Differently, the PAINT trial was specifically designed as a 3-arm randomized study, with careful statistical planning that included power analyses to permit adequate multiple comparison testing among the three study groups.

The PAINT trial has some limitations. Although conducted in a multicenter environment, which allows a more widespread assessment than single-center studies, the PAINT reflects only the characteristics of the patients and treatment routines of large tertiary Brazilian institutions with a high expertise level. Patients' outcomes, as well as resource utilization, are most probably influenced by the institutions' characteristics and may not be directly extrapolated to the reality of other hospital or populations. Moreover, the cost-effectiveness analysis may be biased by the performance of the protocol-mandated angiography at 9 months, which has been shown to disturb the rate of clinical events and may influence the final cost estimation[27].

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