Effectiveness and Safety of Drug-Eluting Stents in a Cardiology Clinic in Curitiba, PR, Brazil

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Abstract

Background: The effectiveness and safety of drug-eluting stents (DES) have still been questioned.

Objective: The objective of this study was to evaluate the effectiveness and safety of these stents, as well as the incidence of target lesion revascularization (TLR), in addition to identifying possible variables influencing the need for TLR.

Methods: A total of 203 patients from Hospital Costantini who were clinically followed up for one to 3 years were selected.

Results: The sample characteristics were as follows: 470 lesions; 171 (84.24%) male patients; 54 (26.6%) had diabetes; 131 (64.35%) had hypertension; 127 (62.56%), dyslipidemia; 40 (19.70%) were smokers; and 79 (38.92%) had a family history of coronary artery disease. Also: 49 (24.14%) patients presented with stable angina; 58 (28.57%), unstable angina; and 6 (2.96%), myocardial infarction. Eighty five (41.87%) patients were asymptomatic, and 146 (71.92%), had multivessel disease. As for the characteristics of the lesions, 77.45% were B2/C (AHA/ACC). Taxus was implanted in 73.62% of the patients. Stents with diameter > 2.5 mm were used in 381 (81.96%) patients. The stent length was < 30 mm in 67.87% of the lesions, with a mean of 2.3 stents per patient. After follow-up, 19 patients (9.3%) underwent TLR. Four patients died (1.97%), two of them of MI (0.98%), one of stroke (0.49%), and one of abdominal aneurysm (0.49%). Also, one patient died of late thrombosis (0.49%), and one of reinfarction (0.49%). In the statistical analysis carried out, only the bifurcation lesions variable reached values close to the statistical significance level, with $p < 0.06$.

Conclusion: In conclusion, drug-eluting stents have good effectiveness and safety profiles; the incidence of TLR was 9.3%, and we did not identify a variable correlated with the need for TLR. (Arq Bras Cardiol. 2010; [online]. ahead print, PP.0-0)

Key words: Drug-eluting stents/utilization; effectiveness; safety/economics; diagnostic services; Curitiba (PR); Brazil.

Introduction

Cardiovascular diseases (CVD) account for the largest number of early deaths and work disabilities in the general population, and are the leading cause of death worldwide, with approximately 12 million deaths per year. According to the World Health Organization's (WHO) estimates[1], this figure will double by 2020, and 80% of the cases will occur in developing countries, with the entire social and economic burden that these diseases represent. One of the main causes of CVD is coronary artery disease (CAD).

Coronary syndromes are caused by the presence of coronary obstruction leading to mild to severe myocardial ischemia. Thus, interventions in the stenosis of these arteries are required to allow free blood flow and reestablishment of an adequate ventricular function. These may be medical, fibrinolytic, percutaneous and surgical interventions. In 1977, Grüntzig et al[2] introduced the percutaneous technique for the approach of CAD known as percutaneous transluminal coronary angioplasty (PTCA). Palmaz et al[3] and Sigwart et al[4] were the first to use the percutaneous treatment by means of a solid structure - a coronary endoprosthesis, the stent - which kept the dilated vessel lumen open. This was a major landmark in interventional cardiology, with the purpose of combating restenosis. In 1995, the idea emerged of using drugs capable of preventing the restenotic process using the stent itself as the drug-delivery vehicle[5]. Polymers were used as the drug bond, and thus the successful triad of pharmacological stents was formed: stent, polymer and drug.

Revascularization of a previously treated lesion, known as target lesion revascularization, has been associated with the assessment of percutaneous treatment effectiveness, whereas thrombosis is associated with stent safety. Therefore, although this safety has been recently questioned[6], several meta-analyses were later carried out and demonstrated the effectiveness and safety of drug-eluting stents in comparison to bare metal stents[7-9]. In a single-center registry from Ontario, Canada[7], a decrease in the frequency of repeat revascularization procedures was observed in high-risk patients using drug-eluting stents in comparison to bare metal stents; no differences were observed as regards death and infarction.

The objective of the present study was to evaluate the effectiveness and safety of drug-eluting stents in the

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clinical practice, and to verify the incidence of target lesion revascularization in a cardiology referral center, in addition to identifying variables influencing the occurrence of TLR.

Methods

Patients

A total of 203 consecutive patients from a cardiology hospital in the city of Curitiba in the period from October 2002 to January 2005 were selected. The patients underwent PTCA with implantation of two or more paclitaxel (Taxus™) or sirolimus (Cypher™) eluting stents. The clinical follow-up lasted at least one year after PTCA. Patients with the following clinical characteristics were included:

1) Diabetes mellitus (DM) as diagnosed by means of laboratory tests (fasting plasma glucose above 99 mg/dl) and use of hypoglycemic agents and/or insulin, provided adequately controlled.

2) High blood pressure (HBP) as defined by levels higher than 140/90 mmHg, and adequate use of antihypertensive drugs such as angiotensin-converting enzyme inhibitors (ACEI) for patients with HBP and DM, and other classes of medications.

3) Cigarette smoking: patients currently smoking or who have quit smoking in the past two years as of the day of inclusion in the study.

4) Dyslipidemia: abnormal levels of at least one of the lipids (total cholesterol above 200 mg/dl, LDL-cholesterol above 130 mg/dl, HDL-cholesterol below 40 mg/dl and triglycerides above 150 mg/dl) and receiving statin.

5) Family history: presence of conditions such as coronary artery disease in first-degree relatives.

6) Clinical manifestations of stable angina (SA) or unstable angina (UA) according to Braunwald's classification (Table 1), or myocardial infarction (MI). Asymptomatic patients underwent PTCA when their functional tests were strongly suggestive of ischemia. The Duke score was used as a risk criterion for the assessment, showing at least moderate to high risk, and coronary angiography consistent with severe lesions.

The angiographic characteristics were defined as: eccentric or concentric lesions, bifurcation lesions, ostial lesions, presence of calcium (characterized as mild, moderate or severe), presence of thrombus, presence of aneurysmatic dilatation of the artery, stent diameter of up to 2.5 mm, and total stent length above 30 mm.

All patients treated with drug-eluting stents received clopidogrel for at least six months and acetylsalicylic acid in combination with the other medications required for the treatment of their ischemic heart disease. The inclusion criteria were: age above 18 years (regardless of gender, risk factors and clinical manifestations), no ventricular dysfunction, single or multivessel disease, normal creatinine levels up to 1.5 mg/ml, all types of atherosclerotic lesions classified according to the AHA/ACC task force grading system, and all types of in-stent restenosis whether in bare metal or drug-eluting stents.

The exclusion criteria were: economic or medical impediment for the combined use of the antiplatelet agents clopidogrel and acetylsalicylic acid for at least six months, concomitant severe disease (with a high probability of death within one year), pregnant women and patients with ventricular dysfunction.

Table 1 - Demographics of the patients undergoing TLR or not

	No TLR (184 pat.) (81.5%)	TLR (19 pat.) (9.5%)	Total (203) pat. (%)
Age	63.32 ± 11.57 years	63.05 ± 12.95	-
Male	156 (84.78%)	15 (78.95%)	171(84.24%)
Female	28 (15.22%)	4(21.05%)	32(15.76%)
Dyslipidemia	114 (61.96%)	13 (68.42%)	127(62.56%)
Diabetes mellitus	49 (26.63%)	5(26.32%)	54(26.60%)
Hypertension	120 (65.22%)	11 (57.89%)	131(64.53%)
Smoking	34 (18.48%)	6(31.58%)	40(19.7%)
Stable angina	43(23.37%)	6(31.58%)	49(24.14%)
Unstable angina	55(29.89%)	3(15.79%)	58(28.57%)
MI	5 (2.72%)	1(5.26%)	6 (2.96%)
Family history	72 (39.13%)	7(36.84%)	79 (38.92%)
Asymptomatic	76(41.30%)	9(47.37%)	85(41.87%)
Multivessel disease	135(73.36%)	11(57.89%)	146(71.92%)

Pat. - number of patients, (%) - percentage of pat., TLR - target lesion revascularization.

Methods

This is a prospective analytic observational follow-up clinical study for the evaluation of drug-eluting stent effectiveness and verification of the incidence of target-lesion revascularization (TLR) in order to identify possible variables influencing the probability of TLR. TLR was defined as any repeat percutaneous revascularization or coronary artery bypass grafting in the original site of the lesion treated, up to 5 mm of the proximal or distal segment, occurring within the period of approximately one year. The indication for TLR could have been based on clinical findings (presence of ischemic symptoms such as angina or myocardial infarction and/or functional tests positive for ischemia in the area treated).

All patients underwent functional tests within the one-year follow-up period (exercise test or myocardial scintigraphy). Coronary angiography was performed only in the cases of typical symptoms of coronary heart disease or functional tests showing signs of ischemia. The present study was approved by the Institutional Ethics Committee in conformity with the Declaration of Helsinki.

The clinical follow-up started from the day of hospital admission. After angioplasty, the patients remained in the hospital for approximately three days. During this period, the patients were given ASA (200 mg), clopidogrel (75 mg), statin, and whatever other medications they were previously receiving. Only metformin was discontinued for

a period of 48 hours before and after the procedure, due to the risk of renal acidosis. General laboratory tests and electrocardiography (ECG) were performed for all patients in the pre and post-procedural periods. At hospital discharge, ASA (200 mg), clopidogrel (75 mg) for six months, statin and other medications required were prescribed.

Data from all patients undergoing intervention treatment in the hospital, observing the inclusion and exclusion criteria, were recorded in a worksheet which included: presence of risk factors, cardiologic clinical manifestations, and angiographic characteristics. The patients were followed up for one year after PTCA in relation to the need for TLR, by means of clinical interview showing the presence of clinical symptoms and/or abnormal functional tests indicating the need for repeat diagnostic coronary angiography and TLR.

Statistical analysis

For the analysis of the clinical characteristics, the Cox regression model was adjusted to identify the variables influencing the event-free time (revascularization). The Cox-Mantel test was used for the comparison of two groups in relation to the event-free time. For the identification of the variables influencing the probability of the event, the logistic regression model and the Wald test were adjusted. This model was also adjusted for the assessment of variables influencing the occurrence of the event when the angiographic characteristics were analyzed. In the univariate analyses, the Student's t test was used for continuous quantitative variables for independent samples, considering the homogeneity of the variances. The chi square test and Fisher's exact test were used for the assessment of the nominal variables. The confidence intervals were set at 95%, and p values < 0.05 were considered statistically significant.

Results

The 203 patients were followed up from one to three years, with a mean of 1.86 years. The event-free survival for TLR, as assessed by the survival curve (Kaplan-Meier) was 88% (Chart 1), and TLR occurred within up to two years.

Of the 203 patients analyzed in the study, 171 (84.24%) were males and 32 (15.76%) females. A total of 54 patients (26.6%) had diabetes mellitus; 131 (64.35%), HBP; 127 (62.54%), dyslipidemia; 40 (19.70%) were cigarette smokers; and 79 (38.92) had a family history of coronary artery disease. Also: 49 (24.14%) patients had stable angina; 58 (28.57%), unstable angina; and 6 (2.96%), myocardial infarction. There were 85 (41.87%) asymptomatic patients, and 146 (71.92%) had multivessel disease.

A total of 19 patients (9.3%) underwent repeat percutaneous revascularization of the lesion treated; no coronary artery bypass grafting was required. During the clinical follow-up, four patients (1.97%) died: two (0.98%) of MI, one (0.49%) of stroke, and one (0.49%) of abdominal aneurysm. In this case series, we observed one patient with late thrombosis (0.49%) in the fifth month after angioplasty, and one patient with reinfarction (0.49%). Therefore, major cardiovascular events occurred in 3 patients (1.47%) with MI, of which two were fatal and one nonfatal cases.

The demographics of these patients are shown in Table 1. The attempt to construct a mathematical model did not result in a regression equation. The univariate and multivariate analyses of the clinical characteristics did not show any variable with statistical significance for the occurrence of TLR (Table 2).

As for the characteristics of the lesions, most were classified as AHA/ACC task force B2/C lesions, in a total of 364 lesions (77.45%), of which 12.55% resulted from in-stent restenosis.

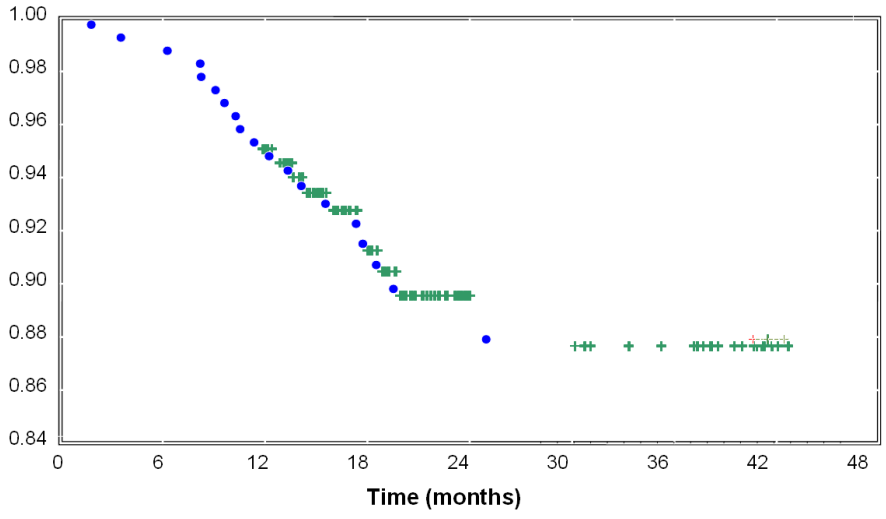

Chart 1 - Event-free survival curve for TLR (Kaplan-Meier method).

Table 2 - Univariate and multivariate statistical analysis for the clinical characteristics as possible variables influencing the probability of TLR

	p values		
	(univariate)*	(multivariate)**	OR (95% CI)
Age	-	0.996	1.00 (0.96-1.05)
Gender	0.416	0.228	0.49 (0.13-1.84)
Diabetes	0.935	0.831	0.88 (0.28-2.82)
Smoking (past 2 years)	0.209	0.169	2.24 (0.70-7.17)
Dyslipidemia	0.501	0.628	1.31 (0.44-3.92)
Family history	0.771	0.638	0.77 (0.26-2.32)
Hypertension	0.681	0.533	0.72 (0.25-2.04)
Stable angina	0.426	0.787	1.35 (0.15-12.23)
Unstable angina	0.188	0.630	0.54 (0.04-6.69)
MI	0.461	0.547	2.53 (0.12-52.66)
Asymptomatic	0.640	0.861	1.21 (0.14-10.64)

**Cox-Mantel. **Cox regression.*

Long lesions above 20 mm were observed in 41.49%, and from 10 to 20 mm in 39.57%. Of the total of the lesions treated, 81.91% had a lower than 45° angle (Tables 3 and 4). Bifurcation lesions were observed in 50 patients (64% of the cases), ostial lesions in 24.47%, and eccentric lesions in 83.62%. Lesion calcification (from moderate to severe) was observed in 6.81% of the cases. Drug-eluting stents with diameter up to 2.5 mm were implanted in 18.94% of the procedures, and with length up to 30 mm in 67.87% of the cases. Bifurcation lesions showed a trend to statistical significance, with $p < 0.06$. Results of the multivariate analysis for angiographic characteristics are shown in Table 5.

In relation to the target vessels, the anterior descending artery was the most frequently affected, with a total of 207 lesions. Also, 107 lesions were observed in the right coronary artery, 88 in the circumflex artery, 28 in the left main coronary, five in the diagonal artery, and 25 in arterial and venous grafts (Chart 2). A total of 470 lesions were treated in 203 patients, with a mean of 2.3 stents implanted per patient. Taxus was the most frequently implanted stent, in 346 lesions (73.62%).

In this case series, coronary angiography was performed in 35 patients (16.7%) and TLR was observed to be necessary in 19; however, a good angiographic outcome was observed for the stents previously implanted in 16 patients. In these 16 patients, catheterization was required because of functional tests showing signs of ischemia in another vessel, thus demonstrating *de novo* coronary lesions requiring treatment due to the progression of the atherosclerotic disease.

Discussion

Patients undergoing percutaneous angioplasty with drug-eluting stent implantation have a more favorable outcome, with less need for repeat interventions in comparison to bare metal stents[8,9]. Thus, this procedure has been verified to be well accepted by the scientific community, except for the cases of high-risk patients with more complex lesions, as was recently established by the Food and Drug Administration (FDA)[10] in a consensus for the use of drug-eluting stents. According to this consensus for the indications of DES, the lesions are classified as on-label, which include short lesions, *de novo* lesions, and arteries with greater diameter; and as off-label, which include long lesions, small-diameter arteries, venous or arterial grafts,

Table 3 - Characteristics of the lesions (AHA/ACC task force)

	No TLR (no./ %)	TLR (no./%)	Total (no./%)
A	9 (2%)	0	9 (1.91%)
B1	27 (5.9%)	1 (5.26%)	28 (5.96%)
B2	177 (39.25%)	7 (36.84%)	184 (39.15%)
C	174 (38.58%)	6 (31.58%)	180 (38.30%)

Table 4 - Morphological characteristics of the lesions

	No TLR	TLR	Total
Lesion length up to			
10 mm	85 (18.85%)	4 (21.05%)	89 (18.94%)
10-20 mm	178 (39.47%)	8 (42.11%)	186 (39.57%)
Above 20 mm	188 (41.68%)	7 (36.84%)	195 (41.49%)
Lesion angle			
< 45°	367 (81.37%)	18 (94.74%)	385 (81.91%)
45°-90°	72 (15.96%)	1 (5.26%)	73 (15.33%)
>90°	12 (2.66%)	0	12 (2.55%)
Thrombus	1 (4.70%)	0	1 (4.70%)
Aneurysmatic dissection	1 (4.70%)	0	1 (4.70%)
SR	52 (11.53%)	3 (15.79%)	55 (11.70%)
BR	9 (2%)	1 (5.26%)	10 (2.13%)
DESR	3 (67%)	1 (5.26%)	4 (0.85%)

SR - bare metal in-stent restenosis; RB - balloon restenosis; DESR - drug-eluting stent restenosis.

Table 5 - Multivariate analysis of the angiographic characteristics as possible variables influencing the probability of TLR

Variables	p value	OR (95% confidence interval)
Lesion aspect (eccentric or concentric)	0.484	1.75 (0.36-8.39)
Bifurcation	0.061	0.30 (0.08-1.06)
Ostial	0.142	2.85 (0.70-11.60)
Calcium (mod-sev)	0.741	1.31 (0.26-6.58)
Stent diameter (< 2.5 mm)	0.155	0.41 (0.12-1.41)
Stent length (> 30 mm)	0.115	2.32 (0.81-6.65)

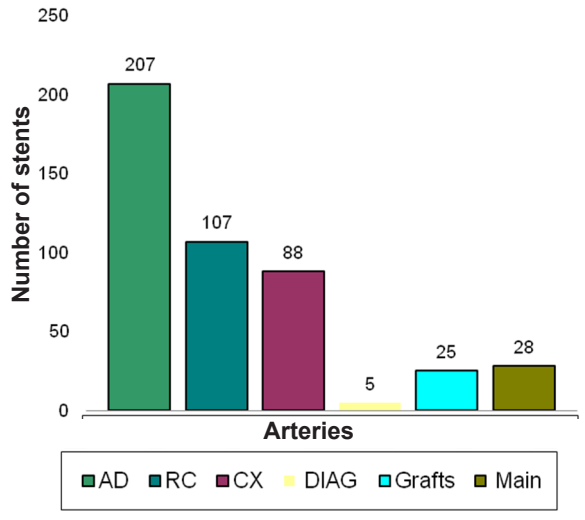

Chart 2 - Arteries receiving drug-eluting stents. AD - anterior descending artery, RC - right coronary artery, CX - circumflex artery, DIAG - diagonal artery, grafts - arterial and venous, Main - main left coronary artery.

total occlusions, bifurcation lesions, main coronary artery lesions, and more complex lesions. DES are indicated for on-label lesions. Therefore, a lot remains to be discussed in relation to the indications of drug-eluting stent implantation. Although higher risks are observed for off-label situations, specific studies are being developed to better elucidate this issue.

Thus, interventional treatment with wide use of DES has been questioned, especially as regards their long-term safety and effectiveness. Despite the controversies, several studies have proven the long-term effectiveness of these stents[7,9]. As regards safety, a higher incidence of late stent thrombosis is observed after one year of DES implantation[11]. For this reason, antiplatelet agents such as acetylsalicylic acid and clopidogrel are indicated for a period of at least one year. However, some patients still require TLR, so that it is important to search for scientific evidences that could show predictors of a poor outcome in order to provide these patients with an adequate approach and treatment.

In our case series, most of the lesions were off-label, with outcomes similar to those found in international registry studies, such as those from Canada[7] and Sweden[12]. Patients with creatinine levels above 1.5 mg/ml and ventricular dysfunction were excluded because these are more severe cases with higher mortality, and this could affect the clinical follow-up.

The present study showed a TLR rate of 9.3%, which can be considered low in comparison to that found for bare metal stents; this rate is in agreement with those of large studies on Taxus[11-14] and Cypher[15,16] implantation. The event-free survival curve for TLR was 88%, similar to data from the literature for the use of DES[11-15]. When the patient profile is analyzed, no clinical aspect alone was found to be a variable influencing the probability of TLR.

Some relevant aspects of diabetic patients should also be addressed. We should recall some early studies, such as the BARI Registry[17], which compared percutaneous balloon angioplasty with coronary artery bypass grafting in diabetic patients, and showed worse outcomes in patients undergoing angioplasty, with a 58% restenosis rate. With the advent of stent endoprostheses, a reduction by approximately 30% in the angiographic restenosis rate was observed.

The ARTS study[18], with an approximately 5-year follow-up, did not show differences in death, stroke, and MI among diabetic patients undergoing surgical revascularization with DES implantation, and showed that these stents were able to significantly reduce neointimal hyperplasia. The ISAR-DIABETES study[19] compared Taxus™ to Cypher™ stents and did not find significant differences in TLR rates, which were low (approximately 10%). In the subgroup analysis, the different studies on Taxus™ and Cypher™ demonstrated favorable results in diabetic patients[11-16]. According to Kereiakes and Young[20], in this new era of treatment, the use of Taxus™ or Cypher™ DES in diabetic patients with multivessel disease proved effective in reducing angiographic restenosis and TLR rates. Thus, there has been a change of concept in the approach to these multivessel disease patients, for whom surgical treatment was previously more frequently indicated. Today, new possibilities such as percutaneous angioplasty exist, and this, combined with drug therapy for a strict control of blood glucose, can provide better clinical results. In a sub-analysis of the RAVEL trial[21], 238 patients were randomized (44 with diabetes: 19 treated with sirolimus-eluting stent, and 25 with bare metal stents), and the impact of the use of sirolimus-eluting stent on cardiac events was observed. TLR was analyzed in a 12-month clinical follow-up; a zero rate of restenosis was observed in the sirolimus group (diabetic and nondiabetic patients) in comparison to a 42% rate of restenosis in the bare metal stent group. The event-free survival curve was 90%. When diabetic patients were analyzed separately, there was no TLR in the sirolimus group compared to a 36% TLR rate observed in the bare metal stent group. The group of diabetic patients was not the main focus of the RAVEL trial[21]. However, despite the small number of diabetic patients, these results provide a reference for further clinical studies involving this type of patients.

Kuchulakanti et al[22] evaluated 1,320 consecutive diabetic patients in their institution and prospectively compared Taxus and Cypher stents for a period of six months. These authors verified similar results between the stents as regards the efficacy and safety in relation to repeat TLR, stent thrombosis and major cardiac events, namely infarction and death, of approximately 11%, 0.3%, 18% and 7%, respectively. In these patients, the progression of the atherosclerotic plaques due to diabetes itself requires a strict control of diabetes, in addition to the treatment of the coronary lesions. Given that diabetes is a metabolic disease, it can lead to endothelial dysfunction and other processes that accelerate atherosclerosis[19,22]. The FREEDOM study (Future revascularization evaluation in patients with diabetes mellitus: optimal management of multivessel disease) - probably the one with the greatest impact on this subject and still underway, was designed specifically for multivessel diabetic patients and will evaluate strategies for

strict blood glucose control, secondary prevention and types of myocardial revascularization. The results are expected to contribute to a more accurate indication of DES in multivessel diabetic patients. Although it is accepted that diabetic patients have a worse outcome and high restenosis rates, this old concept was maintained in the BARI study[17] due to the use of balloon angioplasty. However, with the technological evolution of stents and drugs, there have been encouraging results in more recent studies. Therefore, randomized multicenter studies specific for diabetic patients will be able to evaluate the efficiency of the percutaneous treatment with DES, thus providing a new paradigm for the treatment of diabetic patients with heart diseases.

In the present study, analysis of a subgroup of diabetic patients was not carried out, since the number of patients was too small, therefore not suitable for statistical analysis. Nevertheless, its results corroborated the data from the RAVEL trial sub-analysis which showed a good outcome with DES in diabetic patients. Therefore, diabetes is not the variable that influences the probability of TLR in this study. Qasim et al[23] carried out a multivariate analysis of patients followed up for on and off-label DES implantation, and found that diabetes mellitus is associated with increased rates of TLR and cardiac events ($p < 0.002$, $p < 0.001$). However, off-label DES implantation was not associated with increased in-stent thrombosis, infarction or death, thus demonstrating that off-label DES implantation is not a risk factor for TLR and cardiac event.

As for the analysis of implantation of stents longer than 30 mm, therefore in long lesions, the Long-DES II study authors[24] conducted a randomized prospective multicenter study on the use of paclitaxel-eluting stents (PS) ≥ 25 mm and sirolimus-eluting stents (SS) ≥ 32 mm for the treatment of these lesions in native coronary arteries. The primary endpoint was angiographic restenosis at six months. For both stents, the patients' baseline clinical characteristics and lesion aspect were similar. Low rates of restenosis for both stents, with more significance for SS (approximately 3.3%, $p < 0.001$), and low rates of TLR at nine months (2.4% with SS and 7.2% with OS, ($p < 0.0012$) were observed. That study demonstrated that DES have a favorable outcome in long lesions, with better results for sirolimus-eluting stents. In the present study, stents with up to 30 mm were implanted in 67.87%, and above 30 mm, in 36.13% of the lesions treated. Most lesions were more complex; approximately 77.45% were type B2/C. Based on AHA/ACC task force definition, long lesions above 20 mm were observed in 41.49% of the cases; between 10 and 20 mm in 39.57%; and short lesions up to 10 mm in only 18.94%. In this case series of consecutive patients, implantation of stents > 30 mm was not a variable able to influence the probability of TLR, thus demonstrating results consistent with those of the literature, in which DES show a favorable outcome in long lesions in the one-year clinical follow-up.

In relation to the implantation of stents with diameter lower than 2.5 mm, therefore in small coronary vessels, the ISAR-SMART study[25] evaluated the use of DES in 360 patients with arteries with a diameter of ≤ 2.8 mm who randomly received paclitaxel (PS) or sirolimus-eluting stents (SS). The primary endpoint of in-stent late luminal loss and secondary endpoint of angiographic restenosis and need for TLR were compared. Follow-up angiography was performed in 87% of the patients. Late luminal loss was greater in PS than in SS; angiographic restenosis was found in 19% of the lesions in PS and 11.4% in SS; TLR was performed in 14.7% in PS and 6.6% in SS. Thus, better results were observed with SS in patients with small coronary arteries.

In the SES-Smart study[26], Ardissimo observed a significant reduction in angiographic restenosis in small vessels (2.2 mm) using sirolimus-eluting stents in comparison to bare metal stents. Angiographic analysis showed 9.8% of restenosis in the sirolimus group versus 53.1% in the bare metal stent group. The TLR rate was 7% in the sirolimus group and 19.3% in the control group. In a prospective multicenter study[27], the results of late luminal loss in *de novo* coronary artery lesions (artery diameter between 2.25 and 2.75 mm, length ≥15 to ≤ 30 mm) were compared. In an eight-month period, after sirolimus-eluting stent implantation (SS), data from the SIRIUS trial (sirolimus-Cypher stents and bare metal stents) were compared. A TLR rate of 0% was observed in the SS group versus 13.2% with bare metal stent group, and 4.6% in the Cypher stent group, thus confirming that SS are superior to bare metal stents. In this study, the patients were not randomized and were selected from one single health care service, so that smaller arteries (≤ 2.5 mm) were not observed as a possible variable influencing the probability of repeat revascularizations. Perhaps a study with a larger number of patients and long-term clinical and angiographic follow-up will be able to show more clearly the outcome of these cases.

Another relevant aspect regarding the characteristics of the lesions that could be predictive of TLR is related to bifurcation lesions. The sub-analysis of the ARTS II study[28] assessed bifurcation lesions of 607 patients in a one-year follow-up. A total of 324 patients had at least one bifurcation lesion (465 lesions), and the group of patients with these lesions was associated with more complex lesions and procedural characteristics. In that study, no significant differences were observed between the groups of patients with bifurcation lesions and other lesions regarding the rate of major cardiac events. Although follow-up angiography was not performed, the presence of bifurcation lesions did not affect the one-year rate of cardiac events (death, MI, TLR, revascularization).

Chen et al[29] evaluated cardiac events in bifurcation lesions treated with PS and SS in 112 patients, in a total of 226 lesions. Angiographic analysis in 46 patients showed restenosis in eight individuals (7.14%) and TLR in five (4.46%); one patient underwent myocardial revascularization. Other important findings were: restenosis in paclitaxel in 5/18 (8%); sirolimus in 2/17 (11.8%), and Firebird (sirolimus-eluting stent) in 1/11 (9.1%). The total rate of angiographic restenosis was 17.4%. These rates of restenosis were higher than those of large studies on DES, which were of approximately 10%. Possibly, new stent platforms, specific designs for bifurcations, and new procedural techniques will be developed to improve the approach to these lesions. However, other authors in the SCANDSTENT trial[30] analyzed sirolimus-eluting stent implantation in complex lesions such as bifurcations lesions. That was a randomized controlled trial comparing bare metal stents to sirolimus-eluting stents in 126 patients. SS reduced

the rates of restenosis from 28.3% to 4.9% in the main branch, and from 43.3% to 14.8% in the side branches ($p < 0.01$). In addition to lower rates of major cardiac events, of 9% versus 28% in comparison to bare metal stents, stent thrombosis was observed in 0% *versus* 9% (bare metal stents) ($p < 0.02$), thus demonstrating favorable results with sirolimus-eluting stents in the approach of bifurcation lesions.

In our study, 36.87% of the lesions required TLR in bifurcations. Perhaps a greater number of patients in this study could lead to statistically significant results, thus making this aspect of the lesions be more carefully considered at the moment of the percutaneous treatment.

Yanaga et al's study[31], whose purpose was to find possible predictors of TLR, found that factors related to more severe diseases such as hemodialysis, previous CABG, ostial lesions, and more significant stenoses were predictive of TLR. Likewise, in the present study, bifurcation lesions, which are similar to ostial lesions, had a trend to statistical significance ($p < 0.06$), and this represents a possible variable influencing the probability of TLR. Therefore, whenever a choice has to be made between percutaneous treatment and just medical drug therapy, a more careful reflection is still necessary.

The question regarding the worse outcome of bifurcation lesions may be related to the more intense inflammation in the borders and to the apposition of these stent platforms. Several authors correlate the presence of inflammation with DES. Virmani et al[32] studied patients who received QuaDS-QP2 paclitaxel-derivate eluting polymer stents for 12 months; atherectomy specimens from these patients were collected and sent to pathological anatomy for electron microscopy analysis. This analysis showed that the restenotic tissue was composed of proteoglycan-rich matrix and type-III collagen interspersed with smooth muscle cells. Fibrin was present focally adjacent to the stent struts; there were CD68-positive macrophages and T lymphocytes adjacent to the areas rich in fibrin, and large areas of chronic inflammation. These pathological findings indicate that drug-eluting stents lead to adverse arterial responses such as delayed healing, with incomplete vessel endothelialization, hypersensitivity to the polymer lining that controls the kinetics and release of the drug dose[33], thus inducing chronic inflammation, this being the main difference in relation to bare metal stents, which are devoid of polymers. Toutozas et al[34] made an important review on inflammation and restenosis following PTCA. These authors describe, in the pathological studies, that a mural thrombus is formed in the initial phase post-stent implantation, followed by invasion of smooth-muscle cells, T lymphocytes, and macrophages. This early neointima which covers the stent struts contains extracellular matrix. Later, this extracellular matrix increases (neointimal hyperplasia), thus demonstrating the expression of local macrophage activity. The authors reviewed several studies demonstrating inflammation in the restenosis process by means of increased cytokines, interleukins IL1 and IL6, serum amyloid, monocytes, macrophages, T lymphocytes, and genetic changes such as IL-1ra polymorphism as a protective factor for a lower risk of restenosis, especially in younger patients.

Ijsselmuiden et al[35] compared stenting after balloon predilatation with direct stenting (bare metal stent) and found similar in-stent restenosis rates and MACE at six months. They demonstrated that the baseline increase of C-reactive protein (CRP) was an independent predictor of adverse events and long-term restenosis after stent implantation. According to these authors, there is an inflammatory reaction associated with the restenotic process.

Some studies were conducted in the attempt to minimize the inflammatory effects, with the purpose of preventing restenosis. The IMPRESS study (Immunosupressive therapy for the prevention of restenosis after coronary artery stent implantation)[36] used predinisone for the prevention of restenosis and selected patients after PTCA with increased CRP levels; these patients were randomized to receive prednisone or placebo for 45 days. The TLR rates at six months and luminal loss were lower in the group treated with prednisone. The 12-month event-free survival estimate was favorable for the prednisone group.

Sousa et al[37] analyzed in a large institutional registry from a Brazilian health service - the DESIRE study (Drug eluting stents in the real world), which included 2,043 patients receiving Taxus™ and Cypher™ stents and found cardiac event rates higher than 8.6%: repeat revascularizations in 3.3%, deaths in 2.51%, and myocardial infarction in 2.8% of the patients. These findings are quite similar to those of the literature on drug-eluting stents.

The search for variables influencing target lesion revascularization is important for the adequate management of patients undergoing percutaneous angioplasty with drug-eluting stent implantation. Since these polymer and drug-associated endoprostheses were developed, innumerous scientific studies have been conducted to demonstrate their effectiveness and safety. In the present study, we were able to demonstrate good effectiveness and safety of drug-eluting stents in the treatment of coronary artery diseases, with revascularization event-free survival of approximately 90%, and lower rates of target lesion revascularization of approximately 9%, a result that is consistent with that of the literature. The rates of mortality, late thrombosis and reinfarction were of approximately 2%, 0.5% and 0.5%, respectively.

Ramsdale et al[38] studied 411 patients undergoing off-label DES implantation and found rates of 7% for TLR, 0.8% for thrombosis, and 2% for mortality, thus demonstrating that, in the real world, late complication rates are low. Other studies[39-41] showed rates lower than 10% of TLR in off-label lesions, and did not find increased rates of cardiac death and non-fatal infarction.

Despite the limitations of the present study, namely, the fact that it was a single center observational study in which most of the lesions analyzed were off-label, we did not evidence any clinical characteristic as a variable influencing the probability of target lesion revascularization, and demonstrated good outcomes with drug-eluting stent implantation in the treatment of obstructive coronary artery diseases in the clinical practice. When TLR rates are compared to those of randomized clinical studies and observational registries, higher levels are found due to the inclusion of more severely ill patients in the sample; that is, of the 77 patients, 45% had B2/C type lesions, and more than 50% of the patients presented with multivessel disease associated with hypertension and dyslipidemia. This

combination of factors has probably an influence on the rate of repeat revascularizations.

Further studies combining the use of specific local inflammation markers with randomized controlled patients with or without diabetes, with or without complex lesions and other relevant aspects will thus contribute to a better understanding of the vascular effects of drug-eluting stents. New technologies related to the stent material, whether metallic or absorbable, specific platforms designed for the use in bifurcations, biodegradable polymers and new drugs will enable Cardiology to give hope to the hearts of physicians and patients to keep on pulsating for life.

Conclusion

Drug-eluting stents have good effectiveness and safety in reducing the need for target lesion revascularization. The present study found a 9.3% incidence of target lesion revascularization and did not identify any variable that influenced the probability of target lesion revascularization.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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