

Efficacy and Safety of Drug-Eluting Stents in the Real World: 8-Year Follow-Up

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Abstract

Background: Drug-eluting stents have been used in daily practice since 2002, with the clear advantages of reducing the risk of target vessel revascularization and an impressive reduction in restenosis rate by 50%–70%. However, the occurrence of a late thrombosis can compromise long-term results, particularly if the risks of this event were sustained. In this context, a registry of clinical cases gains special value.

Objective: To evaluate the efficacy and safety of drug-eluting stents in the real world.

Methods: We report on the clinical findings and 8-year follow-up parameters of all patients that underwent percutaneous coronary intervention with a drug-eluting stent from January 2002 to April 2007. Drug-eluting stents were used in accordance with the clinical and interventional cardiologist decision and availability of the stent.

Results: A total of 611 patients were included, and clinical follow-up of up to 8 years was obtained for 96.2% of the patients. Total mortality was 8.7% and nonfatal infarctions occurred in 4.3% of the cases. Target vessel revascularization occurred in 12.4% of the cases, and target lesion revascularization occurred in 8% of the cases. The rate of stent thrombosis was 2.1%. There were no new episodes of stent thrombosis after the fifth year of follow-up. Comparative subanalysis showed no outcome differences between the different types of stents used, including Cypher®, Taxus®, and Endeavor®.

Conclusion: These findings indicate that drug-eluting stents remain safe and effective at very long-term follow-up. Patients in the “real world” may benefit from drug-eluting stenting with excellent, long-term results. (*Arq Bras Cardiol.* 2014; 103(3):174-182)

Keywords: Drug-Eluting Stents/trends; Treatment Outcome; Effectiveness; Long-Term Effect.

Introduction

Drug-eluting stents (DES) have been used in clinical practice since 2002. Multicenter clinical trials have clearly demonstrated the advantages of these stents in reducing major cardiovascular outcomes, particularly target vessel revascularization (TVR), compared with bare metal stents¹. Randomized clinical trials have not included DES, despite their increased use; thus, their efficacy and safety in the real world has been questioned. Considerations regarding DES safety have increased since 2006, when preliminary data indicated higher rates of in-stent thrombosis with DES compared with bare metal stents²⁻⁵. Despite the widespread use of DES in subsequent years, there is still a lack of long-term studies of patients who have received these devices.

A patient registry was created within this scenario. All the patients from two Brazilian institutions who received DES between 2002 and 2007, often with *off-label* indications, were clinically followed up for 8 years. Patient outcomes were analyzed based on the current definitions, and the efficacy and safety of this technology were assessed.

Methods

Population

This study included all patients who underwent percutaneous coronary intervention using at least 1 DES (Costar®, Cypher®, Endeavor®, Inffinnium®, Janus®, Supralimus®, and Taxus®) from January 2002 to April 2007 at the São Lucas and Mãe de Deus hospitals in Porto Alegre (RS). Every patient that presented with acute coronary syndrome and stable angina, with or without ST-segment elevation, was included. The type of DES used during the procedure was left to the discretion of the interventional cardiologist. Given the predominant use of the Cypher®, Endeavor®, and Taxus® stents, a sub-analysis comparing the performance of these stents was conducted.

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Definitions and clinical follow-up

Data regarding the patients' clinical presentations at the time of the procedure were collected through a detailed review of medical records. The patient groups were defined as follows: stable angina, unstable angina, nonST elevation myocardial infarction, ST segment elevation, and recent myocardial infarction (MI) (<3 months before the procedure). Data regarding the procedure and in-hospital outcomes were prospectively collected. Chronic renal failure was defined as a glomerular filtration rate (GFR) of <60 ml/min/1.73 m² ⁶.

Clinical outcomes were defined as follows: mortality due to any cause; nonfatal MI; CK-MB increase greater than or equal to three times the upper normal limit, and/or electrocardiographic changes compatible with infarction (i.e., ST-segment elevation or new inactive zone); or in patients who underwent coronary artery bypass graft surgery, CK-MB increase greater than or equal to five times the upper normal limit; target lesion revascularization (TLR) (i.e., percutaneous or surgical revascularization to treat lesions in the segment of the stent or 5 mm proximal or distal to the prior implant); and TVR (i.e., any revascularization of the vessel treated with DES in the index procedure).

Stent thrombosis was classified according to the definition given by the Academic Research Consortium (ARC) as follows: defined (i.e., acute coronary syndrome with visualization of a thrombus in the segment where the DES was deployed), probable (i.e., unexplained death within 30 days or target vessel infarction), and possible (i.e., any unexplained death after 30 days). Based on the time of occurrence, stent thrombosis was defined as follows: acute (i.e., within the first 24 h), subacute (i.e., within 30 days), late (i.e., after 30 days), and very late (i.e., after 1 year)⁷.

Total mortality, nonfatal MI, and TVR that occurred during the follow-up period were defined as major adverse cardiac events (MACEs).

Angiographic success was defined as stenosis < 20% and thrombolysis in myocardial infarction (TIMI) flow grade 3 by the end of the procedure. Clinical success was defined as angiographic success and the absence of clinical complications such as death, MI, urgent revascularization, and stroke during the index hospitalization.

The first intervention was considered the index procedure for patients with more than one intervention during the study period.

Clinical follow-up was conducted through medical appointments, phone interviews with the patient, reviews of outpatient and in-hospital medical records, and contact with the attending physician. All the clinical events were adjudicated by analysis of the documentation's sources by a cardiologist who was blinded to the other clinical data. The first clinical follow-up was performed 12 months after the index procedure and a biannual clinical follow-up was performed thereafter.

Quantitative coronary angiographic analysis

An experienced interventional cardiologist analyzed the baseline and post-procedure coronary angiograms. *Offline* quantitative coronary angiography of the index intervention was performed using a guiding catheter for calibration of

the image magnification (*CardioNow Websend DICOM Study Sharing Software*, HeartLab, Inc., Westerly, Rhode Island). The minimal luminal diameter and the reference vessel diameter were measured, both before and after the intervention, from a single shot showing the smaller luminal diameter. Coronary lesions were classified according to the American Heart Association and the American College of Cardiology (AHA / ACC) guidelines⁸.

Statistical Analysis

Statistical analysis was performed using the SPSS 19.0 software, assuming a significance level of 5%. Quantitative variables were expressed as a mean \pm standard deviation. Categorical variables were presented as absolute and relative frequencies and were compared by the chi-square test or Fisher's exact test, as appropriate. Adjusted residuals greater than 1.96 ($\alpha = 0.05$) were considered statistically significant, thereby indicating a positive association between the categories. Kaplan-Meier curves were developed for analysis of the clinical outcomes. Cox regression analysis was used to investigate the association between explanatory variables and outcomes. The multivariate analysis initially included all of the variables, for which the p value was < 0.20 in the univariate analysis. Those with the highest p values were removed one by one and only the variables with p values < 0.05 were maintained in the final model.

Results

In total, 611 patients were included in the registry. Clinical follow-up was available for 96.2% of the patients, with an average follow-up of 84 (± 12) months and a maximum of 96 months. The demographic characteristics and clinical presentations of the patients are presented in Table 1.

The mean average age was 63.7 years, and the male gender was predominant (63%). One-third of the subjects exhibited renal failure or diabetes, more than two-thirds had hypertension and dyslipidemia, and slightly more than one-half were smokers. Stable angina was the most common clinical presentation.

Regarding the angiographic characteristics, most of the lesions were located in the left anterior descending artery (in 348 patients or 56.4%). The majority of the lesions (96.4%) were either type B2 or type C lesions (Table 2).

The mean reference diameter of the target vessel before the procedure was 2.87 mm (± 0.46), with a minimal luminal diameter of 0.92 mm (± 0.51) and a mean lesion length of 15.75 mm (± 8.37). A total of 748 DES and 83 bare metal stents were used in the index procedure. Angiographic success was observed in 98.2% of the cases. Additional angiographic characteristics are presented in Table 3.

The event-free Kaplan Meier curves are shown in Figure 1. Total mortality was 8.7% at an average follow-up of 84 months (± 12). Only 4.3% of the patients experienced a new nonfatal MI. Eight percent of the patients required new revascularization of the target lesion; 5.4% of the procedures were percutaneous and 2.6% were performed via bypass surgery. The incidence of defined or probable DES thrombosis was 2.1%. Target vessel revascularization and TLR were 12.4% and 8.0%, respectively

Table 1 – Demographic and clinical characteristics at baseline

Age	63.7 (±11)
Male gender	338 (62.4%)
GFR < 60 ml/min/1.73 m ²	165 (32.7%)
Diabetes	204 (34.3%)
Insulin dependent	73 (12.4%)
Noninsulin dependent	166 (28.2%)
Hypertension	468 (76.2%)
Dyslipidemia	453 (76.8%)
Previous coronary angioplasty	174 (28.7%)
Prior CABG	67 (11.1%)
Current smoking	96 (15.7%)
Initial clinical presentation	
Stable angina	363 (60.4%)
Unstable angina	151 (25.1%)
NSTEMI	41 (6.8%)
STEMI	24 (4.0%)
Recent myocardial infarction	22 (3.7%)

GFR: glomerular filtration rate; CABG: coronary artery bypass grafting; NSTEMI: NonST segment elevation myocardial infarction; STEMI: ST segment elevation myocardial infarction.

Table 2 – Qualitative characteristics of the target vessels and lesions

Patients	611
Target vessel	
Left main coronary artery	13 (1.8%)
Anterior descending artery	394 (56.4%)
Circumflex artery	128 (18.0%)
Right Coronary artery	177 (23.0%)
Treated lesions	712
Lesions per patient	1.17
Type of lesion*	
Tipo A	3 (0.4%)
Type B1	22 (3.6%)
Type B2	355 (49.8%)
Type C	332 (46.6%)

*Classification according to the American Heart Association and the American College of Cardiology (AHA / ACC) guidelines.

(Table 4). The occurrence of stent thrombosis during the follow-up period is described in Table 5. Every TVR and TLR was treated by the same operator who performed the index procedure. Of the 13 episodes of thrombosis, 10 were admitted and treated in the same hospital where the index procedures were performed; however the operators were not the same. All of them had a favorable outcome. The three remaining

Table 3 – Quantitative coronary angiography and procedure data

Pre-TIMI flow grade 3	n (%)
0	38 (6.20)
1	14 (2.40)
2	30 (4.90)
3	529 (86.50)
	Média (DP)
Reference diameter (mm)	2.87 (0.46)
Minimal luminal diameter before the procedure (mm)	0.92 (0.51)
Lesion length (mm)	15.75 (8.37)
Maximum pressure of the DES implant (ATM)	14.88 (2.75)
Final minimal luminal diameter in the stent (mm)	2.82 (0.48)
Final minimal luminal diameter in the segment (mm)	2.41 (0.61)
Average number of stents / patient	1.3
Type of drug-eluting stent	n (%)
Costar®	25 (3.34)
Cypher®	255 (34.2)
Endeavor®	118 (15.7)
Infinium®	9 (1.20)
Janus®	6 (0.80)
Supralimus®	44 (5.80)
Taxus®	291 (38.09)
Angiographic success	600 (98.20)
Post-TIMI flow grade 3	n (%)
0	1 (0.16)
1	2 (0.32)
2	5 (0.81)
3	603 (98.7)
Use of IIb/IIIa inhibitor	24 (3.90%)
Pre-dilation of the lesion	397 (65.0%)

The data represent the absolute numbers and percentages or the means and standard deviations.

patients were treated in other hospitals by different operators; two of them died in the first 24 h after the rescue procedure.

The medical therapy used at the time of the final clinical follow-up is listed in Table 6. At the first year evaluation, 95% of patients were using aspirin and 87% were using clopidogrel. At the end of follow-up, most of the patients were using aspirin (ASA) and statins, and less than one-quarter of the patients were using clopidogrel.

Multivariate analysis revealed that mortality was correlated with being greater than 60 years old and having a previous MI. TLR was correlated with being greater than 60 years old and the presence of calcium in the lesion. Myocardial infarction events were positively associated with the presence of calcium in the lesion. The only associated predictor for thrombosis was an ECC of < 60 ml/min/1.73 m². Previous MI was positively correlated with MACE.

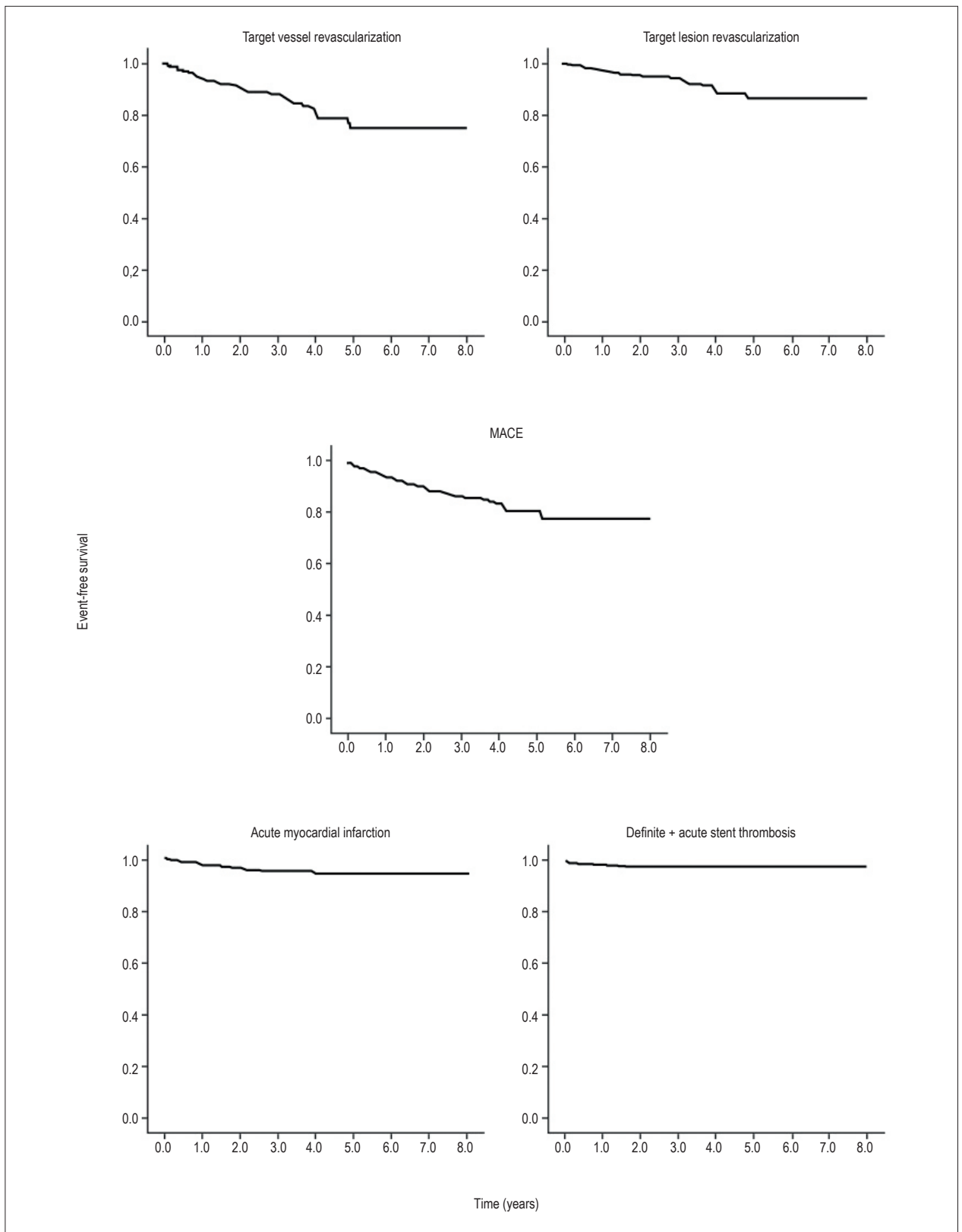


Figure 1 – Kaplan Meyer curves for the outcomes.

Table 4 – Clinical outcomes at final follow-up

	n (%)
Global mortality	53 (8.7)
Nonfatal AMI	26 (4.3)
TVR	76 (12.4)
TLR	49 (8.0)
CABG	16 (2.6)
PTCA	33 (5.4)
Thrombosis	13 (2.1)

AMI: acute myocardial infarction; TVR: target vessel revascularization; TLR: target lesion revascularization; CABG: coronary artery bypass grafting; PTCA: percutaneous transluminal coronary angioplasty.

Table 5 – Occurrence of thrombosis during follow-up

Follow-up year	n
First	1
Second	2
Third	2
Fourth	3
Fifth	5
Sixth	0
Seventh	0
Eighth	0

Table 7 – Predictors of outcomes by multivariate analysis

	HR (IC 95%)	p
Mortality		
Age > 60 years	3.33 (1.01 - 10.97)	0.048
Previous myocardial infarction	5.9 (1.91 - 18.19)	0.002
GFR < 60 ml/min/1.73 m ²	6.96 (2.7 - 17.95)	0
TLR		
Age > 60 years	0.48 (0.25 - 0.90)	0.022
GFR < 60 ml/min/1.73 m ²	2.73 (1.18 - 6.33)	0.019
Presence of calcium in the lesion	2.88 (1.23 - 6.72)	0.015
Infarction		
GFR < 60 ml/min/1.73 m ²	2.91 (0.96 - 8.83)	0.06
Presence of calcium in the lesion	4.43 (1.69 - 11.63)	0.003
Stent thrombosis		
GFR < 60 ml/min/1.73 m ²	3.33 (0.88 - 12.63)	0.077
MACE		
Previous myocardial infarction	113.74 (48.14 - 268.75)	< 0.0001
GFR < 60 ml/min/1.73 m ²	2.75 (1.23 - 6.16)	0.014

GFR: glomerular filtration rate; TLR: target lesion revascularization; MACE: major adverse cardiac events.

An ECC of < 60 ml/min/1.73 m² showed a significant positive correlation with all outcomes (Table 7).

Comparative sub-analysis between the three most frequently used DES revealed that the Taxus® device trended towards a positive association with the need for TVR in 16.8% of the cases (p = 0.053) compared with the Cypher® and Endeavor® stents, with 9.5% and 10.2%, respectively. This difference was not confirmed when only TLR was evaluated (Table 8). The occurrence of MACE, stent thrombosis (defined + probable), and infarction was not significantly different between the three stents.

Discussion

The results of the registry demonstrate that the use of DES is effective long-term. We further showed that the results of

Table 6 – Medication in use at the final follow-up

ASA	424 (69.6%)
Clopidogrel	147 (24.4%)
ASA + clopidogrel	138 (22.5%)
Statin	420 (71.6%)
Beta-blocker	292 (4.6%)
ACE inhibitor	200 (33.2%)
AT2 receptor antagonists	94 (15.6%)
Nitrate	102 (16.9%)

ASA: acetylsalicylic acid ; ACE: angiotensin-converting enzyme inhibitors

Table 8 – Differences between the stents regarding outcomes

	Cypher®	Endeavor®	Taxus®	p value
n	255	118	291	
Mortality	11 (4.3)	2 (1.7)	10 (3.4)	0.47
TVR	19 (9.5)	9 (10.2)	39 (16.8)	0.05
TLR	14 (7.0)	7 (8.0)	22 (9.5)	0.63
Infarction	24 (12.0)	12 (13.6)	41 (17.7)	0.24
Stent thrombosis	3 (1.5)	1 (1.1)	7 (3.0)	0.42
MACE	21 (8.20)	9 (7.6)	27 (9.2)	0.88

TVR: target vessel revascularization; TLR: target lesion revascularization; MACE: major adverse cardiac event.

randomized trials can be replicated in clinical practice, despite the inclusion of patients with a wide variety of clinical and angiographic characteristics that are high risk and complex⁹⁻¹⁷.

In the present study, the low incidence of adverse events, such as new revascularization and stent thrombosis, is similar to recent data that have demonstrated reduced occurrence of these events with DES long-term. The mortality rate observed during the 8 years of follow-up is similar to that demonstrated in most randomized trials with up to 6 years of follow-up⁹⁻¹³.

The long-term follow-up of patients is a key differentiator of this registry. The first report of the efficacy and safety of DES in unselected consecutive patients with complex disease came from the RESEARCH Registry. It demonstrated that the use of the Cypher® stent is associated with significantly lower rates of MACE and TVR compared with bare metal stents during a 6 month follow-up¹².

The reduced incidence of new revascularizations at the 8 year follow-up reported in the present investigation also corroborates the data observed in several other clinical studies. They observed a reduced requirement for new revascularization of the target lesion, especially after 1 year⁹⁻²⁰. Therefore, the hypothesis that DES would merely delay the phenomenon of restenosis has been rejected.

The incidence of stent thrombosis associated with DES was low in our study. The low number of patients using clopidogrel by the end of the follow-up period was expected because dual antiplatelet therapy has been recommended for only 12 months after DES.

The duration of dual antiplatelet therapy is a point of debate when discussing the risk of stent thrombosis²¹⁻²⁴. A higher incidence of thrombosis with DES has been demonstrated when dual antiplatelet therapy is interrupted within the first 6 months after angioplasty²⁴. Nevertheless, the impact of long-term use of dual antiplatelet therapy is debatable. The incidence of stent thrombosis was low in our study, despite the low number of patients using antiplatelet drugs at the end of the follow-up period. The highest rate of stent thrombosis was observed within the first year after the index angioplasty.

Studies comparing the incidence of stent thrombosis between DES and bare metal stents have generated conflicting data. Clinical trials have not included stent thrombosis as a primary outcome due to the low incidence of stent thrombosis

(0.5 to 1% per year). In a meta-analysis^{25,26}, the incidence of stent thrombosis was found to be similar for both DES and bare metal stents during the first year. After 1 year, the risk of thrombosis with DES was reported to be higher²⁶. In another study, no difference in stent thrombosis between DES and a bare metal stent was observed during a 15-month follow-up²⁷. In a meta-analysis of trials limited to primary angioplasty for acute MI, the stent thrombosis rate observed with DES and bare metal stents was similar at 1 year of follow-up²⁷.

The frequency of various clinical outcomes of bare metal stents and DES differs between clinical trial data and observational studies. Although clinical trials have demonstrated similar mortality and MI rates for DES and bare metal stents, observational real-world studies indicate a reduction in mortality in the DES group²¹⁻²⁵. Recent studies indicate a significant reduction in the occurrence of stent thrombosis in second-generation DES versus bare metal stents^{9,28}.

The effect of different generations of DES on clinical outcomes must also be considered. Few comparisons have been made between the Cypher®, Taxus®, and Endeavor® stents. One study indicated that the Endeavor® stent was not inferior to the Cypher® stent and was superior to the Taxus® stent when mortality from all causes, MI, and TVR were assessed at 12 months^{29,30}. In our registry, the incidence of thrombosis, MI, and TLR was similar among those three stents. We observed a significant difference in the incidence of TVR between the groups, with a higher incidence in the Taxus® group.

Head-to-head comparisons between the Cypher® and Taxus® stents indicate a lower occurrence of stent thrombosis and TLR with the Cypher® stent³¹. Another head-to-head study comparing the Endeavor® and Taxus® stents with a follow-up period of > 1 year indicated a lower incidence of stent thrombosis with the Endeavor® stent³². Although these studies suggested a higher incidence of thrombosis with the Taxus® stent compared with other first-generation stents, the results were variable and inconclusive when stent thrombosis was assessed as the primary outcome²¹. Recent studies comparing the second-generation stent Xience V® versus Taxus® have demonstrated a lower incidence of stent thrombosis with Xience V®^{9,22,23}, despite equal patient adherence to dual antiplatelet therapy during the first year of follow-up. A recent meta-analysis of clinical trials revealed a lower incidence of

thrombosis with the Xience V®, compared with the Taxus® stent³⁰. Thus, differences in stent thrombosis rates between the types of DES might exist, however, the magnitude of these differences is difficult to measure³⁴⁻³⁶.

Data from studies of this nature cannot be compared with those from clinical trials due to the nonrandomized, all-comers design. However, real world registries allow for the assessment of outcomes in clinical scenarios that are not tested in randomized studies.

The present study revealed adequate safety and efficacy of DES during a long-term clinical follow-up period in the real world. It included a significant proportion of patients at high cardiovascular risk, thereby validating the use of these stents for routine treatment of patients with coronary artery disease.

Author contributions

Conception and design of the research: Gomes VO, Lasevitch R, Caramori P, Pellegrini DO; Acquisition of data: Gomes VO, Lasevitch R, Ledur P, Caramori P, Pellegrini DO;

Analysis and interpretation of the data: Smidt L, Azeredo MA, Bodanese R, Sinnott L, Caramori P, Pellegrini DO; Statistical analysis: Ledur P, Caramori P, Pellegrini DO; Writing of the manuscript: Moriguchi E, Caramori P, Pellegrini DO; Critical revision of the manuscript for intellectual content: Moriguchi E, Caramori P.

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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