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CLINICAL RESEARCH

Incidence and Predictors of Very Late (≥4 Years) Major Cardiac Adverse Events in the DESIRE (Drug-Eluting Stents in the Real World)-Late Registry

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Objectives Our aim was to access the incidence of late major adverse cardiac events (MACE) and stent thrombosis (ST) in nonselected, complex patients followed for a period ≥4 years.

Background Despite the efficacy of drug-eluting stents (DES) in reducing repeated target lesion revascularization, concerns regarding the occurrence of late and very late ST have partially obscured the benefits of this novel technology.

Methods All consecutive patients treated solely with DES between May 2002 and January 2005 were enrolled into this prospective, nonrandomized, single-center registry. The primary end point was long-term occurrence of MACE up to 7 years. Independent predictors of MACE, cardiac death, target lesion revascularization, and ST were obtained by a multivariate Cox proportional hazards regression model.

Results A total of 1,010 patients were enrolled. Most of them were men (77%) with a mean age of 63.7 years. Stent/patient rate was 1.4. Patients were kept in dual antiplatelet therapy for 3 and 6 months after Cypher (Cordis, Johnson & Johnson, Miami Lakes, Florida) and Taxus (Boston Scientific Corp., Natick, Massachusetts) stent implantation, respectively. Follow-up was obtained in 98.2% of the cohort (median 5.01 years). Survival free of MACE and cumulative incidence of definite/probable ST were 84.6% and 1.7%, respectively. Independent predictors of ST were percutaneous coronary intervention in the setting of acute myocardial infarction, DES overlapping, treatment of multivessel disease, presence of moderate-to-severe calcification at lesion site, and in-stent residual stenosis.

Conclusions The deployment of DES in complex, real-world patients resulted in a low rate of very long-term MACE and ST. However, ST still occurs very long after the index procedure. (J Am Coll Cardiol Intv 2010;3:12–8) © 2010 by the American College of Cardiology Foundation

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Despite the unequivocal efficacy of first-generation drug-eluting stent (DES) (Cypher, Cordis, Johnson & Johnson, Miami Lakes, Florida, and Taxus, Boston Scientific Corp., Natick, Massachusetts) in reducing the need for repeat lesion revascularization, the relatively recent introduction of this novel technology in the clinical scenario (<10 years) precludes definite assessment of very long-term maintenance of their efficacy and safety profile.

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Initial data suggest a steady annual increment in the rates of cardiac death as well as the occurrence of late and very late stent thrombosis and restenosis (after the first year of the index procedure) (1–4). However, very long-term follow-up data (>4 years) in large, nonselected populations are still limited. We sought to assess the latest clinical follow-up of a consecutive "real-world" series of patients treated with first-generation DES as well as to establish the main predictors of adverse cardiac events among these patients.

Methods

Study design and population. Between May 2002 and January 2005, all patients treated in a single, private center (Hospital do Coração, São Paulo, Brazil) with ≥1 DES were included in the nonrandomized, DESIRE (Drug-Eluting Stents In REal world)-Late registry. Clinical inclusion criteria were "all comers" for routine or emergency percutaneous coronary intervention (PCI) >18 years of age. Angiographic inclusion criteria were the presence of at least 1 documented stenosis ≥50% (by visual estimation) in a native coronary vessel or graft (arterial or venous) suitable for PCI with DES implantation. There were no protocol pre-specified limitations concerning the number of target lesions and/or target vessels that could to be treated with DES. Figure 1 shows the rate of use of bare-metal stents (BMS) and DES in our institution during the enrollment period. Since this study is based on clinical end points, patients receiving both DES and BMS were excluded from this analysis.

The study was approved by the institutional ethics committee. Written informed consent was obtained from all patients before the procedure. The institution and the participants did not receive any kind of financial support to develop this research.

Stenting procedure. All interventions were performed according to the current standard guidelines, and the final procedure strategy was entirely left to operators' discretion. Two different DES were available at that time: 1) sirolimus-eluting stents (Cypher, Cordis, Johnson & Johnson) in diameters ranging from 2.25 to 3.5 mm and lengths from 8 to 33 mm; and 2) paclitaxel-eluting stents (Taxus, Boston Scientific Corp.) in diameters ranging from 2.25 to 4.0 mm and lengths from 8 to 32 mm. The type of stent to be deployed as well as the strategy to pre- and/or post-dilatate was left to the operator's discretion. Multiple stenting procedure with the DES was allowed. Dual antiplatelet therapy including a loading dose of aspirin (200 to 325 mg) and thienopyridines (ticlopidine 250 mg twice a day or clopidogrel 300 mg) was started at least 24 h before elective procedures; otherwise a loading dose of 600 mg of clopidogrel was given immediately before the intervention. Post-procedural aspirin was continued indefinitely, and thienopyridine was maintained for only 3 months after Cypher and 6 months after Taxus deployment. During the procedure, intravenous heparin (70 to 100 IU/kg) was administered after sheath insertion to maintain an activated clotting time >250 s. Use of additional medications during the procedure, including glycoprotein IIb/IIIa inhibitors, was left to the operator's discretion. A 12-lead electrocardiogram was obtained before the procedure, immediately afterward, and 24 h later. Blood sample laboratory analysis included creatine kinase cardiac enzymes (CK and CK-MB) before the procedure (<24 h) and 12 to 18 h after treatment.

Abbreviations and Acronyms

BMS = bare-metal stent(s)
CI = confidence interval
CK = creatine kinase
DES = drug-eluting stent(s)
DS = diameter stenosis
HR = hazard ratio
MACE = major adverse cardiac events
MLD = minimum lumen diameter
PCI = percutaneous coronary intervention
QCA = quantitative coronary angiography
RD = reference diameter
TVR = target vessel revascularization

Angiographic analysis. After intracoronary nitrate administration (100 to 200 μg), serial coronary angiography was obtained at baseline and post-procedure. Offline quantitative coronary angiography (QCA) analysis was performed using the semiautomatic edge contour-detection computer analysis system CMS-GFT version 5.1 (Medis, Leiden, the Netherlands). The minimum lumen diameter (MLD) and the mean reference diameter (RD), obtained from averaging 5 mm "nondiseased" segments proximal and distal to the target lesion location(s), were used to calculate the diameter stenosis (DS): $DS = (1 - MLD/RD) \times 100$. Acute gain was the change in MLD from baseline to final post-stent implantation angiogram.

All cineangiograms images were analyzed at the Hospital do Coração Angiographic Core Laboratory (São Paulo, Brazil) by experienced senior operators blinded to procedural data.

End points, definitions, and clinical follow-up. The study's primary objective was the occurrence of major adverse cardiac events (MACE) and stent thrombosis at the very long-term (≥4 years) clinical evolution.

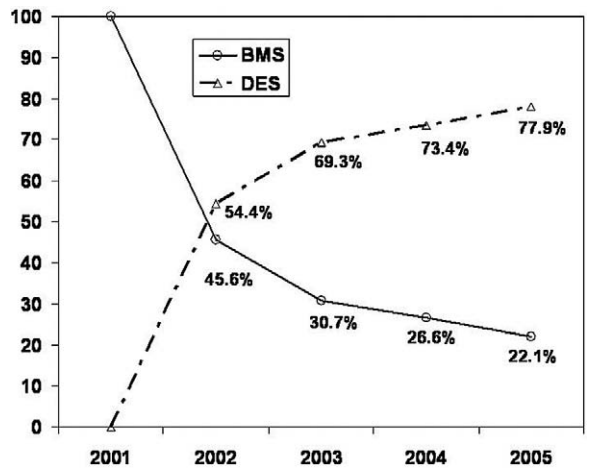

Figure 1. BMS and DES Usage in Our Center

Rates of bare-metal stent (BMS) and drug-eluting stent (DES) deployment in our institution during the enrollment phase of the DESIRE (Drug-Eluting Stents In the REal world)-Late study (May 2002 to January 2005).

MACE was defined as cardiac death, nonfatal myocardial infarction, and target vessel revascularization (TVR). TVR was only based on the presence of symptoms and/or signs of ischemia. All deaths were considered to be cardiac unless a noncardiac origin could be clearly established by clinical and/or pathological study. The diagnosis of myocardial infarction was based on either the development of new pathological Q waves in ≥2 contiguous electrocardiogram leads, and/or elevation of CK-MB isoenzyme >3 times the upper normal limit post-procedure during index hospitalization, or cardiac enzyme elevation >2 times the upper normal limit thereafter.

Stent thrombosis was classified as definite, probable, and possible according to definitions proposed by the Academic Research Consortium (5), and was stratified as acute (<24 h), subacute (24 h to 30 days), and late (1 to 12 months) and very late (>12 months).

Angiographic success was defined as attainment of <20% residual stenosis by QCA in the treated segment post-DES treatment. Procedural success was defined as angiographic success plus absence of MACE during hospitalization. During the enrollment period, detailed demographic, clinical, angiographic, and procedural information, including complications, were gathered for each patient. Clinical follow-ups, by office appointment or phone call, were scheduled at 1, 6, and 12 months after stent implantation, and then annually up to 7 years of the baseline procedure on the basis of information entered on case report forms at the time of the office visit/telephone contact. At the time of the follow-up, data were collected pertaining to current clinical status, concomitant drug-therapy (with special emphasis to the antiplatelet regimen), and interim occurrence of the pre-defined adverse events. All phone follow-up data were collected by the same person especially trained for this task and blinded to the procedure results. Individual patient data was coded to prevent the identification of study participants. Routine angiographic follow-up was not part of the study protocol. Therefore, all reinterventions were clinically (ischemia)-driven. Adverse events were adjudicated by an independent committee of 3 cardiologists not involved in the procedures.

Statistical analysis. Data are presented as mean ± 1 SD or frequencies. Categorical variables were compared with the chi-square test. When the assumptions were broken, Fisher exact test was used. For continuous variables comparison, *t* test was used. Event-free survivals for MACE, TVR, and stent thrombosis were demonstrated by Kaplan-Meier curves.

A multivariate Cox proportional hazards regression was used. Fully adjusted MACE, TVR, and stent thrombosis models were fit to include demographic characteristics, clinical presentation variables, periprocedural medications, and procedural characteristics as well as lesion complexity. Covariates were selected by forward stepwise methods and those considered biologically relevant despite their statistical significance. A value of $p < 0.05$ was considered significant. Statistical analysis was performed using SPSS version 11.0 (SPSS Inc., Chicago, Illinois).

Results

A total of 1,010 patients (1,294 lesions) were enrolled. Most of them were men (77%), and the mean age was 63.7 ± 11.6 years. Diabetes mellitus was observed in 27.1% of this population, and 54.2% of the patients had been previously submitted to a revascularization procedure either by PCI (25.5%) or coronary artery bypass grafting (28.7%). Acute coronary syndrome was the initial presentation in 37.6% of the cases (12.2% of ST-segment elevation myocardial infarction). Table 1 contains detailed baseline characteristics of this cohort.

Table 2 details the main baseline lesion characteristics. Most patients had double (30.4%) or triple (22.9%) vessel disease. Left anterior descending artery was the most frequently treated native coronary (40.4%). Of note, 6.3% of the target lesions were located in venous or arterial grafts. Also relevant, in 28.5% of the lesions, moderate-to-severe calcification could be identified by angiography.

Procedural and QCA information are displayed in Table 3. Overall, there were 1,414 DES implanted (1.4 stents per patient). Pre-dilation was performed in less than one-half of the population (41%), and 38.1% of the treated patients required more than 1 DES. Cypher was the DES used in 81% of the cases. Glycoprotein IIb/IIIa inhibitors were used in only 2.7% of cases. Mean lesion length and reference vessel diameter were 16.4 ± 8.2 mm and 2.76 ± 0.47 mm,

Table 1. Baseline Clinical Demographics (n = 1,010)

Age, yrs	63.7 ± 11.6
Female sex	232 (23.0%)
Diabetes mellitus	274 (27.1%)
Hypertension	746 (73.9%)
Hyperlipidemia	590 (58.4%)
Current smoker	313 (31.0%)
Previous MI	184 (18.2%)
Previous PCI	259 (25.5%)
Previous CABG	290 (28.7%)
Family history of CAD	498 (49.3%)
Obesity*	233 (23.9%)
Symptoms (clinical presentation)	
Silent ischemia	281 (27.9%)
Stable angina	349 (34.5%)
Unstable angina/non–ST-segment elevation MI	257 (25.4%)
ST-segment elevation MI	123 (12.2%)

*Body mass index >30 kg/m^2.
CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

respectively. Mean acute gain was estimated at 1.81 ± 0.9 mm with final in-stent minimal lumen diameter of 2.85 ± 1.0 mm and residual stenosis of 4.7 ± 3.6%. Mean nominal stent length was 19.2 ± 5.8 mm, and the stent/lesion length ratio was ~1.2. No case of intraprocedure stent thrombosis was verified in this series. Angiographic and procedure success were achieved in 99% and 98.3% of the cases.

Long-term clinical follow-up. Complete clinical follow-up was obtained in 98.2% of the cases. Mean follow-up time was 4.73 ± 0.98 years (median of 5.01 years, interquartile range 4.04 to 5.11 months).

At the end of the follow-up period, 84.6% of the patients were free of any MACE. Cardiac death was observed in 5.4% of the cohort, and only 6.6% of the individuals had TVR. Figure 2 shows the Kaplan-Meier event-free survival curves for MACE, cardiac death, and TVR up to 7 years.

Table 4 details the DES thrombosis cases according to the Academic Research Consortium definition. A total of 27 stent thromboses (2.6%) were observed in this series, including definite, probable, and possible cases. Among them, 17 cases (1.7%) were classified as definite/probable. Nine of these cases (0.9%) occurred after the first year of the index procedure (Fig. 3).

Multivariate analysis. Independent predictors of MACE were acute myocardial infarction as the initial clinical presentation (hazard ratio [HR]: 1.57; 95% confidence interval [CI]: 1.04 to 2.38, p = 0.033), treatment of lesion in grafts (HR: 1.94; 95% CI: 1.41 to 2.67, p < 0.001), residual stenosis (HR: 1.3; 95% CI: 1.1 to 1.5, p = 0.034). A strong tendency toward treatment of multivessel disease was also observed (HR: 1.3; 95% CI: 0.97 to 1.85, p = 0.07).

Independent predictors of cardiac death were age ≥75 years (HR: 2.27; 95% CI: 1.3 to 3.97, p = 0.004), treatment of lesions in grafts (HR: 2.54; 95% CI: 1.49 to 4.33, p = 0.001), and history of peripheral disease (HR: 2.54; 95% CI: 1.49 to 4.33, p = 0.001).

Independent predictors of TVR were treatment of lesions in grafts (HR: 1.59; 95% CI: 1.06 to 2.93, p = 0.001) and treatment of multivessel disease (HR: 2.72; 95% CI: 1.29 to 5.77, p = 0.009).

Finally, independent predictors of *overall* stent thrombosis were PCI in the setting of acute myocardial infarction (HR: 3.22; 95% CI: 1.40 to 7.41, p = 0.006), DES overlapping (HR: 3.02; 95% CI: 1.27 to 7.19, p = 0.012), treatment of multivessel disease (HR: 2.41; 95% CI: 1.04 to 5.81, p = 0.018), presence of moderate-to-severe calcification at lesion site (HR: 2.21; 95% CI: 1.20 to 4.07, p = 0.01), and in-stent residual stenosis (HR: 1.02; 95% CI: 1.02 to 1.07, p < 0.001).

Table 2. Pre-Procedural Lesion Characteristics (n = 1,010)

Number of disease vessels*	
1	46.7%
2	30.4%
3	22.9%
Treated vessel	
Native coronary	93.7%
LAD	40.4%
LCX	23.5%
RCA	28.7%
LM	1.1%
Grafts	6.3%
Venous	94.4%
Arterial	5.6%
Lesion class A/B1/B2/C†	4.7%/28.8%/38.6%/27.9%
TIMI flow grade	
0	1.4%
1	0.5%
2	1.0%
3	97.1%
Thrombus	3.0%
Moderate-to-severe calcification	25.0%
Ostial lesion	5.1%
Bifurcation‡	3.0%
In-stent restenosis§	4.3%
Left ventricular function‖	
Normal-to-mild dysfunction	58.4%
Moderate-to-severe dysfunction	41.6%

n = 1,294 lesions. *≥50% diameter stenosis in a major epicardial vessel; †according to the American College of Cardiology/American Heart Association lesion classification; ‡≥50% diameter stenosis in the main vessel and in a side branch ≥2.25 mm (by visual estimation); §81% post-bare-metal stent; ‖normal-to-mild dysfunction = ejection fraction ≥40%, moderate-to-severe dysfunction = ejection fraction <40%.
LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; RCA = right coronary artery; TIMI = Thrombolysis In Myocardial Infarction.

Table 3. Procedural Data (n = 1,010)

Heparin use	100%
Glycoprotein IIb/IIIa use	2.7%
Balloon dilation	
Pre-stenting	41.0%
Post-stenting	43.7%
Stent implant	
>1 stent implanted (per patient)	38.1%
Number of stents per lesion	1.3
Number of stents per patient	1.4
Total stented length, mm	19.2 ± 5.8
Type of drug-eluting stent deployed	
Cypher	81.0%
Taxus	19.0%
Nominal stent diameter, mm	2.87 ± 0.38
Pre-procedural QCA	
Lesion length, mm	16.4 ± 8.2
RVD, mm	2.76 ± 0.47
MLD, mm	1.04 ± 1.74
DS, %	67.0 ± 12.4
Post-procedural QCA	
MLD, mm	2.85 ± 1.0
DS, %	4.7 ± 3.6
Acute gain, mm	1.81 ± 0.9
Stent/lesion length ratio	1.2
Maximum pressure, atm	15.1 ± 3.9
Balloon-artery ratio	1.12
Intraprocedural stent thrombosis	0%
Acute stent thrombosis	0%
Angiographic success	99.0%
Procedure success	98.3%

n = 1,294 lesions.
DS = diameter stenosis; MLD = minimum lumen diameter; QCA = quantitative coronary angiography; RVD = reference vessel diameter.

Discussion

The outcomes of the DESIRE-Late Registry indicate the very long-term maintenance of the results of first-generation DES, with a relatively low incidence of MACE extending to 7 years after DES implantation. Despite continuous hazard of very late stent thrombosis, the occurrence of this adverse event might not be as frequent as speculated.

In the scenario of clinical controlled trials, Stone et al. (6), in a meta-analysis with more than 5,000 patients from the pivotal studies with first-generation DES had previously demonstrated the long-term (up to 4 years) sustained superiority of Cypher and Taxus over BMS in reducing the need for repeated revascularization (7.8% and 10.1% vs. 23.1% and 20.0% for their bare-metal equivalents, $p < 0.05$) without significant differences with regard to death (6.7% and 6.1% with Cypher and Taxus vs. 5.3% and 6.6% with their control studies, p = NS), myocardial infarction (6.4% and 7.0% with Cypher and Taxus vs. 6.2% and 6.3% in the control cohort, p = NS), and stent thrombosis (1.2% and

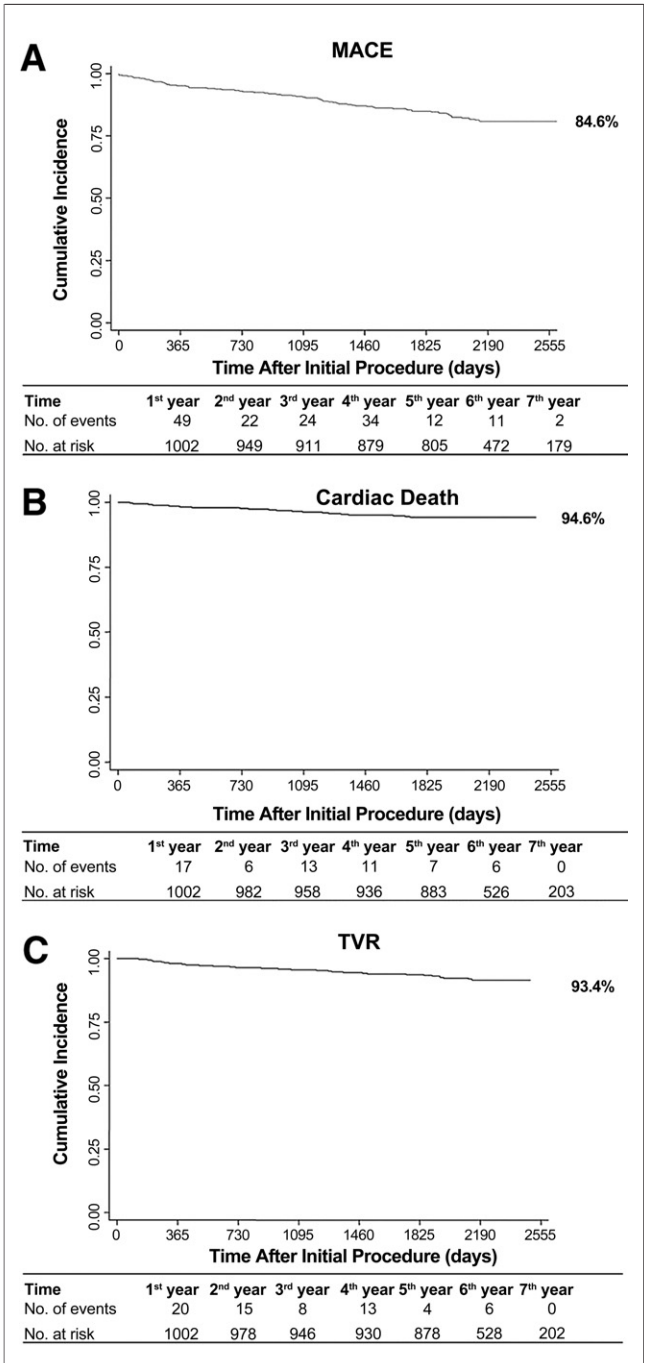

Figure 2. Survival-Free Curves

Kaplan-Meier survival-free curves of major adverse clinical events (MACE) (cardiac death, nonfatal acute myocardial infarction, and need for repeat revascularization) **(A)**, cardiac death **(B)**, and target vessel revascularization (TVR) **(C)** curves: drug-eluting stents demonstrated a very efficient and safe long-term performance in this unselected cohort of patients. At the **bottom of each panel** is the number of patients evaluated in each follow-up as well as the events noticed in each time point.

Table 4. Classification of All DES Thrombosis Cases in the DESIRE-Late Registry According to the ARC Definition (27 of 1,010 Patients)

	Definite	Probable	Possible	Total
Acute	0	0	0	0
Subacute	4	0	0	4 (0.4%)
Late	4	0	6	10 (0.9%)
Very late	9	0	4	13 (1.3%)
Total	17 (1.7%)	0	10 (0.9%)	27 (2.6%)

ARC = Academic Research Consortium; DES = drug-eluting stent(s); DESIRE-Late = Drug-Eluting Stents In the REal world-Late registry.

1.3% with Cypher and Taxus vs. 0.6% and 0.9% with their bare-metal equivalents, p = NS).

The previous longest available nonselected series of patients treated with DES also confirmed the prolonged benefits of these novel devices over BMS with respect to reduction of repeated revascularization procedures. Daemen et al. (7) published in 2006 the 3-year results of the RESEARCH (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) registry comparing Cypher to a historical cohort of patients treated with BMS and followed for an equivalent period. In their report with ~500 patients treated with DES, this novel device presented a final cumulative incidence of MACE, death, and TVR of 18.9%, 8.7%, and 9.4%. Next, Daemen et al. (8) presented the 3-year results of the combined experience with DES in Bern and Rotterdam. In their analysis of 8,146 patients treated with first-generation DES, the cumulative incidence of death/myocardial infarction and definite stent thrombosis were 13.7% and 2.9%, respectively. More recently, Wenaweser et al. (9) presented the 4-year follow-up of that same cohort, showing a cumulative incidence of death, myocardial infarction, and stent thrombosis of 10.6%, 4.6%, and 3.3%, with a steady increment in stent thrombosis of 0.53% per year. Also in 2009, Pfisterer et al. (10) published the 3-year results of the BASKET (BAsel Stent KostenEffektivitäts Trial), with 826 unselected patients randomized in a 2:1 fashion to DES versus BMS. Their study showed a continuous superiority of DES over BMS in reducing target lesion revascularization, mostly noticeable in small stents (10.7% vs. 19.8%, p = 0.03) with equivalent rates of death/myocardial infarction between the cohorts. Of notice, they observed an increase in the combination death/myocardial infarction after the first 6 months of the baseline procedure among patients receiving DES, mainly due to increased late death/myocardial infarction in patients with large stents (9.7% vs. 3.1%, p = 0.006).

Compared with these studies, our current analysis shows a better efficacy and safety profile of DES, with lower rates of MACE, TVR, and definite/probable stent thrombosis despite our having the longest follow-up time. Some possible explanations can be pointed out to enlighten our results: 1) optimization of stent deployment, using online QCA to guide all the procedures, and, whenever necessary, careful post-dilation with shorter noncompliant balloon always avoiding injuring outside the limits of the stent; and 2) conscious selection of patients and lesions that would better benefit from coronary artery bypass grafting versus PCI. For example, in our institution most unprotected left main lesions involving the origin of the left anterior descending coronary artery/left circumflex artery, selected bifurcations involving big branches (>2.5 mm in diameter) and other territories, diabetic patients with triple-vessel diffuse disease in small diameter coronary vessels, and so on are still preferably referred to cardiac surgery.

Finally, it is worthwhile to describe our population with stent thrombosis. Our incidence of this adverse event is about 0.13% per year after the first year of the DES deployment. In this cohort, death was the result of stent thrombosis in 9 cases (33% of all stent thrombosis). Also important to notice, nonadherence to dual antiplatelet therapy was not an independent predictor of thrombosis in the present study. Only 4 cases (15%) of stent thrombosis (all subacute) were clearly related to premature discontinuation of the antiplatelet medication. In our opinion, the fact that a vast majority of patients were prescribed dual antiplatelet therapy for ≤6 months, in addition to the strong emphasis dispensed to the importance of compliance to the prescribed medication at the time of the hospital discharge as well as at every follow-up visit/telephone contact, may have played a fundamental role in the aspirin/thienopiridine adherence.

Study limitations. This is not a randomized study. The nonexistence of a control group treated with BMS precludes any comparison between these 2 technologies. The current results reflect the experience of a single institution with first-generation DES. The unbalanced use of Cypher and Taxus prevents comparisons between these 2 DES. Finally,

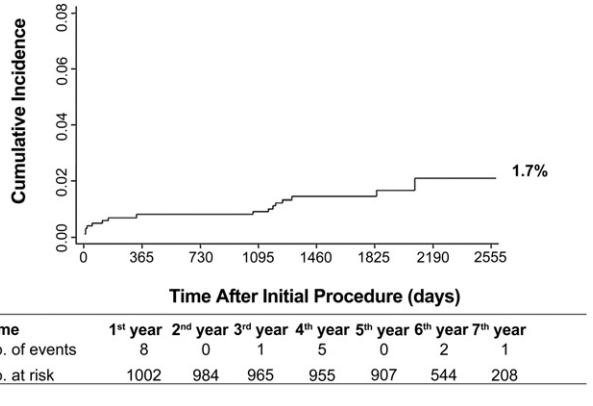

Figure 3. Stent Thrombosis Incidence

Cumulative incidence of definite/probable stent thrombosis (ARC definition) in the DESIRE (Drug-Eluting Stents In the REal world)-Late registry. Notice that 0.9% of the cases happened after the first year of the index procedure.

the relatively low number of stent thrombosis over-fitted the multivariate model built for that event, which may reduce the strength of the findings regarding independent predictors of that event.

Conclusions

The deployment of DES in complex, real-world patients resulted in excellent long-term results sustained at very long term follow-up, with low rates of MACE and stent thrombosis. Nevertheless, stent thrombosis still occurs very long after the index procedure, but at a low annual rate.

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Key Words: drug-eluting stents ■ stent thrombosis ■ very long-term outcomes.