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A propensity score matched analysis to determine if second-generation drug-eluting stents outperform first-generation drug-eluting stents in a complex patient population

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ABSTRACT

Background: Drug-eluting stents (DES) are routinely used in complex patients, but the impact of 1st- versus 2nd-generation DES on clinical outcomes has not been well described. This study aimed to assess the efficacy and safety of 2nd-generation (everolimus-eluting) DES compared to 1st-generation (sirolimus- and paclitaxel-eluting) DES in a selected, higher-risk population with complex clinical and angiographic features.

Methods: The study included 5693 consecutive patients with the presence of ≥1 predefined complex clinical and angiographic characteristic treated with either generation DES. Using propensity score matching, the clinical outcomes of 1076 patients treated with 2nd-generation DES were compared with the outcomes of a matched population treated with 1st-generation DES over 1-year follow-up.

Results: After matching, baseline clinical and angiographic characteristics were similar between groups. At 1-year follow-up, the rate of major adverse cardiac events was 9.4% with 2nd-generation DES and 11.3% with 1st-generation DES ($p = 0.16$). There were no significant differences in the rates of death (3.2 vs. 4.0%, $p = 0.30$), myocardial infarction (1.6 vs. 1.3%, $p = 0.57$), target vessel revascularization (5.9 vs. 7.3%, $p = 0.17$) or target lesion revascularization (4.4 vs. 5.0%, $p = 0.50$). Definite stent thrombosis was less frequent with 2nd-generation DES (0.1 vs. 0.8%, $p = 0.011$), as was definite or probable stent thrombosis (0.7 vs. 1.6%, $p = 0.040$).

Conclusion: In this propensity score matched patient population with complex features undergoing percutaneous coronary intervention, the use of 2nd-generation DES was associated with lower rates of stent thrombosis, and similar 1-year major adverse cardiac events compared to 1st-generation DES.

1. Introduction

Since their introduction, sirolimus-eluting stents (SES) (Cypher, Cordis, Johnson and Johnson, Miami Lakes, FL) and paclitaxel-eluting stents (PES) (Taxus, Boston Scientific Corp., Natick, MA), compared to bare metal stents, have reduced restenosis rates and the need for repeat revascularization with durable long-term results [1–4]. Even in more complicated patient and lesion subsets predicting lower procedural success and more unfavorable clinical outcomes, 1st-generation drug-eluting stents (DES) have been shown to be more effective than bare metal stents [5,6]. However, there were safety concerns regarding the occurrence of late stent thrombosis with the 1st-generation DES, especially in off-label use [7–9]. Newer 2nd-generation everolimus-eluting DES (Xience V, Abbott Vascular, Santa Clara, CA; or Promus, Boston Scientific Corp., Natick, MA), have been developed with improved stent designs, biocompatible polymers, and improved drug-elution kinetics [10]. The everolimus-eluting stent (EES) has been compared to 1st-generation DES in several randomized trials [11–13]. We aimed to assess the impact on clinical outcomes of 2nd-generation DES compared to 1st-generation DES in a selected, higher-risk population based on complex clinical and angiographic characteristics.

2. Methods

The study population was identified from a prospective percutaneous coronary intervention (PCI) registry of consecutive patients who underwent DES implantation from 2003 to 2011 at our institution. Patients were included in the study if they received a 2nd-generation DES (Xience V or Promus) or 1st-generation DES (Cypher or Taxus), and had ≥1 of the following predefined complex features: presentation with acute myocardial infarction, left ventricular ejection fraction ≤30%, chronic renal insufficiency (defined as previously diagnosed or treated with medication, diet or dialysis by a physician, or on admission if baseline creatinine >2.0 mg/dL is found), unprotected left main coronary artery target lesion, ostial lesion, lesion in a bypass graft, in-stent restenosis lesion, any lesion with thrombus, totally occluded lesion (defined as Thrombolysis In Myocardial Infarction grade 0 flow), American College of Cardiology/American Heart Association classification type C lesion, ≥1 target lesion, and stent implantation length ≥28 mm.

The 2nd-generation DES group was restricted to patients receiving a Xience V or Promus stent from July 2008 onwards (n = 1374). The control group (n = 4319) was comprised of patients receiving 1st-generation DES (Cypher or Taxus) before the availability of Xience V and Promus. A complete data set to allow for propensity score matching and 1-year follow-up was required for patients to be included in either study group. Propensity score matching was conducted to match the baseline clinical characteristics of the two groups. The in-hospital, 30-day and 1-year clinical outcomes of 1076 patients who received 2nd-generation DES were compared to the 1076 propensity score matched patients who received 1st-generation DES.

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All patients provided written, informed consent. The study complied with the Declaration of Helsinki for investigation in humans and was approved by the institutional ethics committee. PCI was performed according to standard guidelines, with the majority of cases via the femoral approach. The interventional strategy, device use, and pharmacotherapy were at the discretion of the operator. Patients treated with 1st-generation DES received either Cypher (diameters 2.5–3.5 mm, lengths 8–33 mm) or Taxus stents (diameters 2.5–3.5 mm, lengths 8–32 mm). Patients treated with 2nd-generation DES received Xience V or Promus stents (diameters 2.5–4.25 mm, lengths 8–28 mm). All patients were loaded with aspirin 325 mg and clopidogrel 300–600 mg prior to the procedure. Dual antiplatelet therapy with aspirin and clopidogrel was recommended to all patients for 12 months' post intervention. Procedural anticoagulation consisted of either unfractionated heparin adjusted to targeted activated clotting time, or bivalirudin 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure. Angiographic success was defined as a residual stenosis ≤30% with Thrombolysis In Myocardial Infarction grade 3 flow.

Death was defined as all-cause mortality. Cardiac death included all deaths where a non-cardiac cause could not be demonstrated. Myocardial infarction was defined as a total creatinine kinase of ≥2× the upper limit of normal and/or creatine kinase-MB ≥20 ng/ml, together with symptoms and/or ischemic electrocardiographic changes. Q-wave myocardial infarction was defined as evidence of new pathologic Q waves in ≥2 contiguous leads on electrocardiogram. Target lesion revascularization was defined as revascularization, either percutaneous or surgical, of a stenosis in the stent or within 5-mm proximal or distal to the stent edge. Target vessel revascularization was defined as either percutaneous or surgical revascularization of the stented epicardial vessel. The composite end point of major adverse cardiac events (MACE) included death, myocardial infarction and target vessel revascularization. Stent thrombosis that occurred in the target vessel was defined using the Academic Research Consortium definitions as definite (angiographic or pathological confirmation, and ≥1 of the following: ischemic symptoms, ischemic ECG changes, elevated cardiac biomarkers) or probable (any unexplained death within 30 days of stent implantation, or any myocardial infarction that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause) [14].

Demographic, clinical and procedural data, along with in-hospital outcomes, were prospectively collected and entered into a database. Data were obtained from hospital chart reviews by independent research personnel blinded to the study objectives. All data management and analyses were performed by a dedicated data coordinating center (Data Center, MedStar Health Research Institute, Washington, DC). Clinical follow-up was performed by telephone contact or office visit at 30 days, 6 months and 1 year by trained quality assurance nurses who worked exclusively with the database to determine post-intervention clinical events. An independent committee of physicians blinded to the study objectives and treatment groups adjudicated all clinical events. One-year follow-up was available on all patients in this study.

Propensity score was determined from a non-parsimonious logistic regression model for treatment with 2nd-generation versus 1st-generation DES. The following variables were included in the model to calculate the propensity score: age; sex; African–American race; diabetes mellitus; insulin-requiring diabetes mellitus; systemic hypertension; hyperlipidemia; smoking; family history of coronary artery disease; previous myocardial infarction; previous coronary artery bypass graft, previous percutaneous coronary intervention; peripheral vascular disease; history of congestive heart failure; chronic renal insufficiency; clinical presentation of stable angina pectoris, unstable angina pectoris, acute myocardial infarction, and cardiogenic shock; number of lesions treated; target vessel location; ostial location of lesion; type C lesion; in-stent restenosis lesion; glycoprotein IIb/IIIa receptor inhibitor use. In order to perform propensity score matching, the selected patients required complete data sets for these predefined clinical and angiographic variables, as well as complete follow-up data.

Patients receiving 2nd-generation DES were matched 1:1 to patients receiving 1st-generation DES using the closest available pair matching method. Subgroups were well-matched comparing 2nd-generation and 1st-generation DES defined by propensity score quartiles. Hosmer and Lemeshow Goodness-of-Fit test was used to assess the model fit to the data. The Chi-square test statistic was 6.05 ($p = 0.64$), indicating a good fit to the data. The c-statistic for the model was 0.8 indicating good discrimination. All analysis was stratified by the matching pairs.

Statistical analysis was performed using SAS version 9.1 (SAS Institute Inc., Cary, NC). Continuous variables are expressed as mean ± SD. A generalized linear model was used to compare the groups adjusting for the matched pair. Categorical variables are expressed as frequencies and percentages and compared with Cochran–Mantel–Haenszel test adjusting for the matched pair. A Cox proportional hazard model that accounted for the 1:1 matching was used to calculate hazard ratios comparing the two groups. All p values and 95% confidence intervals are two-sided. A p value of <0.05 was considered to indicate statistical significance.

3. Results

A total of 1076 patients treated with 2nd-generation DES were matched to 1076 patients treated with 1st-generation DES [of which 722 (67.1%) received SES, 310 (28.8%) received PES and 44 (4.0%) received both]. Both groups were well balanced in baseline clinical characteristics (Table 1). Table 2 shows the lesion and procedural characteristics. Both groups were similar in number of lesions treated per patient and the complexity of lesions treated. Patients receiving 2nd-generation DES were treated with shorter stents and more stents

Table 1
Baseline characteristics.

	1st-generation DES (n = 1076)	2nd-generation DES (n = 1076)	p value
Age (years)	64.3 ± 11.7	64.2 ± 11.0	0.83
Men	731 (67.9%)	712 (66.2%)	0.38
Body mass index (kg/m^2)	29.8 ± 6.1	30.0 ± 5.9	0.44
Caucasian	719 (66.8%)	706 (65.6%)	0.55
AfricanAmerican	292 (27.1%)	306 (28.4%)	0.50
Diabetes mellitus	396 (36.8%)	391 (36.3%)	0.82
Insulin-requiring diabetes mellitus	148 (13.8%)	139 (12.9%)	0.57
Systemic hypertension	923 (85.8%)	935 (86.9%)	0.45
Dyslipidemia	949 (88.2%)	945 (87.8%)	0.79
Current smoker	204 (19.0%)	219 (20.4%)	0.42
Familial history	558 (51.9%)	529 (49.2%)	0.21
Chronic renal insufficiency	127 (11.8%)	151 (14.0%)	0.12
Peripheral vascular disease	140 (13.0%)	143 (13.3%)	0.85
Prior myocardial infarction	223 (20.7%)	243 (22.6%)	0.30
Prior coronary bypass surgery	201 (18.7%)	200 (18.6%)	0.96
Prior percutaneous coronary intervention	337 (31.3%)	346 (32.2%)	0.68
Procedure indication			
Stable angina pectoris	372 (34.6%)	347 (32.2%)	0.25
Unstable angina pectoris	538 (50.0%)	542 (50.4%)	0.86
Acute myocardial infarction	174 (16.2%)	190 (17.7%)	0.36
Cardiogenic shock	3 (0.3%)	9 (0.8%)	0.08
Left ventricular ejection fraction ≤ 30%	54 (7.2%)	49 (5.6%)	0.20
Mean left ventricular ejection fraction (%)	50 ± 13	51 ± 12	0.21

DES, drug-eluting stent.

Table 2
Angiographic and procedural characteristics.

	1st-generation DES (n = 1076; lesions, n = 1512)	2nd-generation DES (n = 1076; lesions, n = 1499)	p value
Target coronary vessel			
Left main	36 (2.4%)	32 (2.1%)	0.65
Left anterior descending	610 (40.3%)	599 (40.0%)	0.83
Left circumflex	367 (24.3%)	361 (24.1%)	0.90
Right	409 (27.1%)	441 (29.4%)	0.15
Saphenous vein graft	84 (5.6%)	65 (4.3%)	0.12
Lesion characteristics			
Ostial location	44 (2.9%)	41 (2.7%)	0.76
Proximal location	453 (30.1%)	441 (29.5%)	0.70
ACC/AHA type C	671 (44.5%)	684 (45.6%)	0.54
In-stent restenosis	41 (2.1%)	40 (2.7%)	0.94
Total occlusion	72 (4.8%)	30 (2.0%)	<0.001
Thrombus-containing lesion	33(3.2%)	36 (2.4%)	0.22
Lesion in small vessel (diameter ≤ 2.5 mm)	161 (15.1%)	165 (15.4%)	0.86
Procedural characteristics			
Number of narrowed coronary vessels	1.4 ± 0.6	1.4 ± 0.7	0.58
Number of stents per patient	1.5 ± 0.7	1.6 ± 0.8	0.003
Stent length (mm)	21.0 ± 6.7	18.2 ± 6.0	<0.001
Stent diameter (mm)	3.0 ± 0.5	3.2 ± 0.4	0.33
Sirolimus-eluting stent	1047 (69.2%)	–	–
Paclitaxel-eluting stent	465 (30.8%)	–	–
Everolimus-eluting stent	–	1499 (100%)	–
IVUS performed	1013 (67.2%)	911 (60.8%)	<0.001
Intra-aortic balloon pump	18 (1.7%)	19 (1.8%)	0.88
Glycoprotein IIb/IIIa inhibitor	35 (3.3%)	33 (3.1%)	0.81
Angiographic success	1496 (99.1%)	1486 (99.2%)	0.86

DES, drug-eluting stent; ACC/AHA, American College of Cardiology/American Heart Association; IVUS, intravascular ultrasound.