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Comparative Effectiveness and Safety of New-Generation Versus Early-Generation Drug-Eluting Stents According to Complexity of Coronary Artery Disease

A Patient-Level Pooled Analysis of 6,081 Patients

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ABSTRACT

OBJECTIVES The purpose of this study was to compare the 2-year safety and effectiveness of new- versus early-generation drug-eluting stents (DES) according to the severity of coronary artery disease (CAD) as assessed by the SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score.

BACKGROUND New-generation DES are considered the standard-of-care in patients with CAD undergoing percutaneous coronary intervention. However, there are few data investigating the effects of new- over early-generation DES according to the anatomic complexity of CAD.

METHODS Patient-level data from 4 contemporary, all-comers trials were pooled. The primary device-oriented clinical endpoint was the composite of cardiac death, myocardial infarction, or ischemia-driven target-lesion revascularization (TLR). The principal effectiveness and safety endpoints were TLR and definite stent thrombosis (ST), respectively. Adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated at 2 years for overall comparisons, as well as stratified for patients with lower (SYNTAX score ≤11) and higher complexity (SYNTAX score >11).

RESULTS A total of 6,081 patients were included in the study. New-generation DES (n = 4,554) compared with early-generation DES (n = 1,527) reduced the primary endpoint (HR: 0.75 [95% CI: 0.63 to 0.89]; p = 0.001) without interaction (p = 0.219) between patients with lower (HR: 0.86 [95% CI: 0.64 to 1.16]; p = 0.322) versus higher CAD complexity (HR: 0.68 [95% CI: 0.54 to 0.85]; p = 0.001). In patients with SYNTAX score >11, new-generation DES significantly reduced TLR (HR: 0.36 [95% CI: 0.26 to 0.51]; p < 0.001) and definite ST (HR: 0.28 [95% CI: 0.15 to 0.55]; p < 0.001) to a greater extent than in the low-complexity group (TLR p_{int} = 0.059; ST p_{int} = 0.013). New-generation DES decreased the risk of cardiac mortality in patients with SYNTAX score >11 (HR: 0.45 [95% CI: 0.27 to 0.76]; p = 0.003) but not in patients with SYNTAX score ≤11 (p_{int} = 0.042).

CONCLUSIONS New-generation DES improve clinical outcomes compared with early-generation DES, with a greater safety and effectiveness in patients with SYNTAX score >11. (J Am Coll Cardiol Intv 2015;8:1657–66) © 2015 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass surgery

CAD = coronary artery disease

DES = drug-eluting stent(s)

PCI = percutaneous coronary intervention

Drug-eluting stents (DES) have improved outcomes compared with bare-metal stents among patients undergoing percutaneous coronary intervention (PCI) owing to potent reduction of neointimal hyperplasia and the need for repeat revascularization (1). Early-generation DES delayed arterial healing of the stented segment and, as a result, were associated with an increased risk of stent-related thrombotic events and late restenosis (2,3). New-generation DES were introduced featuring thinner stent struts, more biocompatible durable or biodegradable polymer coatings, different antiproliferative agents, and lower drug loads (4). These refinements translated into improved clinical outcomes, and new-generation DES are the current standard of care (5–9).

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The likelihood of treatment failure directly correlates with the complexity of underlying coronary artery disease (CAD). In the large-scale SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) trial comparing early-generation paclitaxel-eluting stents with coronary artery bypass surgery (CABG) among patients with multivessel disease, PCI was inferior in terms of the composite of cardiovascular death, myocardial infarction, and repeat revascularization in the overall cohort, and differences were particularly pronounced among patients with increased SYNTAX score (10). Similarly, PCI with the use of early-generation sirolimus- or paclitaxel-eluting stents was inferior compared with CABG among diabetic patients with multivessel disease in the randomized FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial (11). Currently, it is not well established whether the clinical benefits of new- over early-generation DES are influenced by the anatomic complexity of CAD. We, therefore, sought to investigate the safety and effectiveness of new- compared with early-generation DES in relation to anatomic CAD complexity—defined by the SYNTAX score—in a large, broadly inclusive population of PCI patients enrolled in 4 all-comers randomized clinical trials.

METHODS

STUDY POPULATION. We pooled individual patient-level data from 4 randomized clinical studies: the SIRTAX (Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Revascularization) trial (NCT00297661) (12), the LEADERS (Limus Eluted from A Durable versus ERodable Stent coating) trial (NCT00389220) (13), the RESOLUTE All Comers (Randomized Comparison of a Zotarolimus-Eluting Stent with an Everolimus-Eluting Stent for Percutaneous Coronary Intervention) trial (NCT00617084) (14), and the BIOSCIENCE (Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization) trial (NCT01443104) (15). All trials had an all-comers design and were conducted between 2004 and 2013 at European institutions, with the exclusive use of DES. Early-generation DES including sirolimus-eluting (Cypher or Cypher Select, Cordis, Miami Lakes, Florida) and paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts) were investigated in the SIRTAX and LEADERS trials (12,13). New-generation DES encompassing everolimus-eluting (Xience V or Prime or Xpedition, Abbott Vascular, Santa Clara, California), zotarolimus-eluting (Resolute, Medtronic Inc., Santa Rosa, California), biodegradable polymer biolimus-eluting (BioMatrix Flex, Biosensors Inc., Newport Beach, California), and biodegradable polymer sirolimus-eluting stents (Orsiro, Biotronik AG, Bülach, Switzerland) were evaluated in the LEADERS, RESOLUTE All Comers, and BIOSCIENCE trials (13–15). Details on study designs and trial results were reported elsewhere (12–16). Briefly, patients with either stable CAD or acute coronary syndrome were eligible if they had at least 1 lesion with a diameter stenosis ≥50% in a vessel with reference diameter of 2.25 to 4.0 mm (SIRTAX, RESOLUTE All Comers, and BIOSCIENCE trials) or 2.25 to 3.5 mm (LEADERS trial). Inclusion

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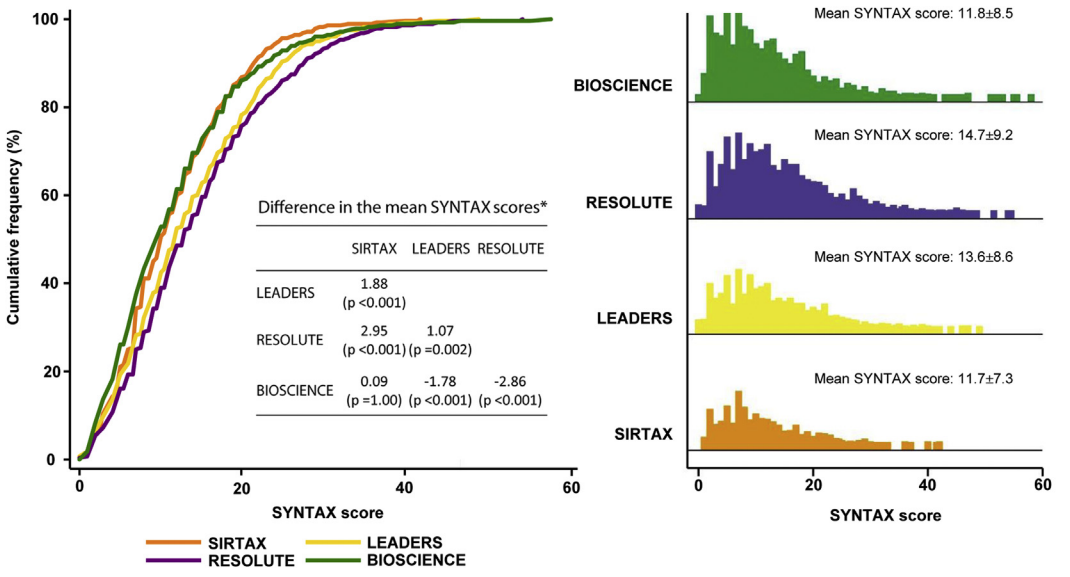
FIGURE 1 SYNTAX Score Distribution Across Included Randomized Trials



*Mean differences were calculated with the 1-way analysis of variance using the Bonferroni multiple comparison test. BIOSCIENCE = Ultrathin Strut Biodegradable Polymer Sirolimus-Eluting Stent Versus Durable Polymer Everolimus-Eluting Stent for Percutaneous Coronary Revascularization; LEADERS = Limus Eluted from A Durable versus ERodable Stent coating; RESOLUTE All Comers = Randomized Comparison of a Zotarolimus-Eluting Stent with an Everolimus-Eluting Stent for Percutaneous Coronary Intervention; SIRTAX = Sirolimus-Eluting and Paclitaxel-Eluting Stent for Coronary Revascularization; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

criteria were broad to reflect routine clinical practice. None of the trials imposed any restriction with respect to number of treated lesions, treated vessels, lesion length, or number of stents implanted. The main inclusion and exclusion criteria for each trial are reported in the Online Table 1. For the purpose of the present study, we excluded patients with prior coronary artery bypass grafting (CABG) or patients in whom the SYNTAX score was unavailable.

All trials complied with the Declaration of Helsinki, and the study protocols were approved by the ethics committees at each study center. All patients provided written, informed consent for participation in the individual studies.

SYNTAX SCORE. All baseline coronary lesions with a diameter stenosis ≥50% in a vessel with reference diameter ≥1.5 mm were included for the assessment of the SYNTAX score. The score algorithm was described in full elsewhere and is freely available on the web site (17). In the LEADERS and RESOLUTE trials, all of the angiographic variables needed to derive the SYNTAX score were prospectively collected by a team of 2 core laboratory analysts. In contrast, the SYNTAX score was retrospectively assessed in the SIRTAX and BIOSCIENCE trials by 2 experienced interventional cardiologists. At the time of SYNTAX score calculation, all investigators were blinded to patient data, and in case of disagreement, the opinion of a third analyst was acquired and the final decision was made by consensus.

ENDPOINT DEFINITIONS. The primary, device-oriented clinical endpoint of this study was the composite of cardiac death, nonfatal myocardial infarction, or ischemia-driven target lesion revascularization (TLR). The principal effectiveness and safety endpoints were TLR and definite stent thrombosis (ST), respectively. Secondary endpoints included each individual component of the composite endpoint, target vessel revascularization (TVR), and the composite of definite or probable ST. Stent thrombosis was defined according to Academic Research Consortium criteria in all trials (18). Endpoint definitions were comparable across the 4 trials, and a blinded clinical events committee independently adjudicated all adverse events for each trial.

STATISTICAL ANALYSIS. Continuous variables are presented as mean ± SD (or as median with interquartile range) and were compared with independent samples Student *t* test. Categorical variables are

TABLE 1 Baseline Clinical Characteristics

	New-Generation DES (n = 4,554)	Early-Generation DES (n = 1,527)	p Value
Age, yrs	64.5 ± 11.2	62.7 ± 11.1	<0.001
Female	1,117 (24.5)	380 (24.9)	0.78
Body mass index, kg/m^2	27.7 ± 4.4	27.4 ± 4.2	0.06
Diabetes	1,012 (22.2)	298 (19.5)	0.03
Insulin-requiring	330 (7.2)	101 (6.6)	0.42
Hypertension	3,160 (69.4)	998 (65.4)	0.003
Hypercholesterolemia	2,915 (64.0)	934 (61.2)	0.05
Renal failure*	625 (14.3)	172 (13.3)	0.39
GFR, ml/min	85.2 ± 29.2	85.2 ± 25.4	0.92
Current smoker	1,317 (28.9)	512 (34.3)	<0.001
Family history of CAD	1,347 (31.8)	606 (39.7)	<0.001
Previous MI	1,043 (23.1)	432 (28.3)	<0.001
Previous PCI	1,297 (28.5)	387 (25.3)	0.02
Left ventricular ejection fraction, %	56.1 ± 11.8	56.4 ± 11.7	0.48
Clinical presentation			0.01
Stable CAD	1,752 (40.6)	648 (42.4)	0.22
NSTE-ACS	1,678 (38.9)	528 (34.6)	0.003
ST-segment elevation MI	887 (20.5)	351 (23.0)	0.05
SYNTAX score	13.3 ± 8.9	12.5 ± 8.0	0.003
≤22	3,867 (84.9)	1,350 (88.4)	
23-32	530 (11.6)	147 (9.6)	
>32	157 (3.4)	30 (2.0)	

Values are mean ± SD or n (%). *Defined as GFR <60 ml/min.

CAD = coronary artery disease; DES = drug-eluting stent(s); GFR = glomerular filtration rate; MI = myocardial infarction; NSTE-ACS = non-ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

TABLE 2 Angiographic and Procedural Characteristics

	New-Generation DES (n = 4,554)	Early-Generation DES (n = 1,527)	p Value
GPI use*	675 (14.8)	435 (28.5)	<0.001
No. of treated lesions per patient†	1.48 ± 0.75	1.41 ± 0.66	0.043
Multivessel treatment per patient*	1,076 (23.6)	277 (18.1)	<0.001
Lesions, n	6,764	2,152	
Target vessel location per lesion			<0.001
Right coronary artery	2,169 (32.2)	724 (33.6)	
Left main artery	75 (1.1)	12 (0.6)	
Left anterior descending artery	2,885 (42.8)	975 (45.3)	
Left circumflex artery	1,610 (23.9)	441 (20.5)	
Bypass graft	4 (0.1)	0 (0.0)	
De novo lesion per lesion	6,289 (93.8)	2,061 (95.9)	0.001
Occlusion per lesion	640 (9.6)	148 (6.9)	<0.001
Stents per lesion	1.32 ± 0.67	1.20 ± 0.56	<0.001
Total stent length per lesion, mm	25.29 ± 15.66	21.20 ± 12.58	<0.001
Mean stent diameter per lesion, mm	2.99 ± 0.46	2.90 ± 0.44	<0.001

Values are n (%) or mean ± SD. The p values comparing new- versus early-generation DES are from p values from models accounting for lesions clustered within patients using robust standard errors. *p values from logistic regression. †p value from Poisson regression.

DES = drug-eluting stent(s); GPI = glycoprotein IIb/IIIa inhibitors.

expressed as counts and percentages and were compared with chi-square or Fisher exact tests as appropriate. Baseline lesion variables were analyzed using general or generalized linear mixed models, accounting for lesions nested within patients.

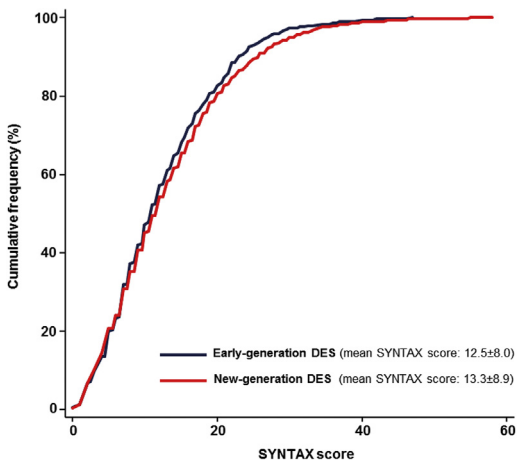
Clinical outcomes at 2 years were expressed as counts with incidence rates computed according to the Kaplan-Meier method. Cox regression analysis was used to calculate hazard ratios (HRs) with 95% confidence intervals (CIs). Adjusted hazard ratios (HR_{adj}) were derived from multiple imputation estimated Cox regressions (20 datasets created using chained equations and estimates combined using the Rubin's rule), adjusting for baseline variables associated with the primary composite endpoint (age, diabetes, renal failure, or previous myocardial infarction). Two definitions of anatomical CAD complexity were applied. Patients were categorized into low or high CAD complexity according to the median SYNTAX score (11) observed in the study population. To evaluate the possibility that the differences in outcomes between new- and early-generation DES were due to categorization, we also analyzed SYNTAX scores as a continuous variable. We tested the interaction between the type of DES (new- vs. early-generation DES) and the SYNTAX score (after logarithm transformation) in the Cox-regression analyses and graphically represented the results with spline curves by using a flexible model (xblc command). All analyses were carried out with Stata Statistical Software, release 13 (StataCorp LP, College Station, Texas).

RESULTS

An overview of the selection process and patient flow is provided in the Online Figure 1. The initial pooled population consisted of 7,130 patients. After the exclusion of patients with prior CABG (n =724) or unavailability of the SYNTAX score (n = 325), 6,081 PCI patients were included in the present analysis. The cumulative frequency and the distribution of the SYNTAX score for each trial is shown in **Figure 1**. New- and early-generation DES were used in 4,554 (74.8%) and 1,527 (25.2%) patients, respectively. The mean SYNTAX score in the overall population was 13.1 ± 8.7 (median 11, interquartile range 7 to 18). Two-year follow-up was available in 5,912 patients (97.2%).

Patients allocated to new-generation DES were older; more frequently had a history of diabetes, hypertension, or previous PCI; and were less likely to have smoking habits, a family history of CAD, or previous myocardial infarction (**Table 1**). Angiographic and procedural characteristics indicated a

FIGURE 2 SYNTAX Score Frequency in Patients Treated With New- and Early-Generation DES



DES = drug-eluting stent(s); SYNTAX = Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery.

higher complexity among patients receiving new-generation DES (Table 2), also reflected by a higher SYNTAX score (13.3 ± 8.9 vs. 12.5 ± 8.0; p = 0.003). The cumulative frequency of SYNTAX score among patients treated with new- and early-generation DES is displayed in the Figure 2. Baseline clinical, angiographic, and procedural characteristics in patients with low (SYNTAX score ≤11; n = 3,053) versus high CAD complexity (SYNTAX score >11; n = 3,028) are shown in Tables 3 and 4. In the group with low CAD complexity, the mean SYNTAX score was 6.3 ± 2.9 in patients treated with new-generation DES and 6.5 ± 2.9 in patients treated with early-generation DES (p = 0.153). In the group with high CAD complexity, the mean SYNTAX score was 20.2 ± 7.4 in patients treated with new-generation DES and 19.2 ± 6.5 in patients treated with early-generation DES (p = 0.001). The mean SYNTAX score in patients with diabetes mellitus and in patients undergoing single-vessel or multivessel PCI at the time of the index procedure is reported in Online Table 2.

CLINICAL OUTCOMES IN THE OVERALL POPULATION. Clinical outcomes at 2 years for the overall comparison of new- versus early-generation DES are reported in Table 5. The primary composite endpoint occurred less frequently among patients receiving new-generation compared to those treated with early-generation DES (10.4% vs. 13.2%; HR_{adj}: 0.75 [95% CI: 0.63 to 0.89]; p < 0.001) (Figure 3A). New-generation DES were associated with a lower risk of

TABLE 3 Baseline Clinical Characteristics According to SYNTAX Score

	SYNTAX Score ≤11			SYNTAX Score >11			
	New-Generation DES (n = 2,253)	Early-Generation DES (n = 800)	p Value	New-Generation DES (n = 2,301)	Early-Generation DES (n = 727)	p Value	p Value for Interaction
Age, yrs	63.6 ± 11.2	61.6 ± 10.8	<0.001	65.5 ± 11.1	64.0 ± 11.2	0.002	0.498
Female	583 (25.9)	197 (24.6)	0.509	534 (23.2)	183 (25.2)	0.293	0.206
Body mass index, kg/m^2	27.6 ± 4.4	27.6 ± 4.3	0.616	27.7 ± 4.4	27.3 ± 4.1	0.025	0.210
Diabetes	447 (19.8)	146 (18.3)	0.349	565 (24.6)	152 (20.9)	0.045	0.478
Insulin-requiring	130 (5.8)	42 (5.3)	0.655	200 (8.7)	59 (8.1)	0.704	0.917
Hypertension	1569 (69.7)	521 (65.1)	0.019	1591 (69.2)	477 (65.6)	0.075	0.720
Hypercholesterolemia	1462 (64.9)	493 (61.6)	0.103	1453 (63.1)	441 (60.7)	0.235	0.765
Renal failure	265 (12.2)	82 (12.1)	1.000	360 (16.3)	90 (14.6)	0.320	0.509
GFR, ml/min	86.4 ± 32.5	86.8 ± 24.6	0.764	84.1 ± 25.5	83.3 ± 26.1	0.514	0.515
Current smoker	675 (30.0)	284 (36.3)	0.001	642 (27.9)	228 (32.2)	0.033	0.498
Family history of CAD	667 (31.5)	329 (41.1)	<0.001	680 (32.1)	277 (38.1)	0.004	0.216
Previous MI	475 (21.2)	228 (28.5)	<0.001	568 (25.0)	204 (28.1)	0.108	0.079
Previous PCI	647 (28.7)	209 (26.1)	0.169	650 (28.2)	178 (24.5)	0.050	0.636
Left ventricular ejection fraction, %	57.6 ± 11.1	58.6 ± 10.4	0.037	54.6 ± 12.2	53.8 ± 12.5	0.205	0.020
Clinical presentation			0.077			0.004	<0.001
Stable CAD	928 (43.3)	382 (47.8)	0.033	824 (37.9)	266 (36.6)	0.536	
NSTE-ACS	839 (39.2)	281 (35.1)	0.050	839 (38.6)	247 (34.0)	0.027	
ST-segment elevation MI	376 (17.5)	137 (17.1)	0.827	511 (23.5)	214 (29.4)	0.002	
SYNTAX score	6.3 ± 2.9	6.5 ± 2.9	0.153	20.2 ± 7.4	19.2 ± 6.5	0.001	

Values are mean ± SD or n (%).
Abbreviations as in Table 1.

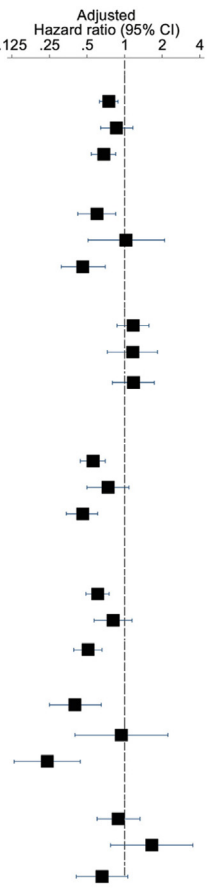
TABLE 4 Angiographic and Procedural Characteristics According to SYNTAX Score

	SYNTAX Score ≤11			SYNTAX Score >11			
	New-Generation DES (n = 2,253)	Early-Generation DES (n = 800)	p Value	New-Generation DES (n = 2,301)	Early-Generation DES (n = 727)	p Value	p Value for Interaction
GPI use	234 (10.4)	184 (23.0)	<0.001	441 (19.2)	251 (34.5)	<0.001	0.30
Treated lesions per patient	1.26 ± 0.52	1.27 ± 0.52	0.76	1.70 ± 0.87	1.56 ± 0.75	0.011	0.0495
Multivessel treatment per patient	280 (12.4)	102 (12.8)	0.82	796 (34.6)	175 (24.1)	<0.001	<0.001
Lesions, n	2,846	1,018		3,918	1,134		
Target vessel location per lesion			0.12			<0.001	<0.001
Right coronary artery	1,057 (37.3)	402 (39.5)		1,112 (28.4)	322 (28.4)		
Left main artery	9 (0.3)	2 (0.2)		66 (1.7)	10 (0.9)		
Left anterior descending artery	1,046 (36.9)	394 (38.7)		1,839 (47.0)	581 (51.2)		
Left circumflex artery	720 (25.4)	220 (21.6)		890 (22.8)	221 (19.5)		
Graft	0 (0.0)	0 (0.0)		4 (0.1)	0 (0.0)		
De novo per lesion	2622 (92.9)	974 (95.8)	0.004	3,667 (94.4)	1,087 (96.0)	0.066	0.48
Occlusion per lesion	148 (5.3)	27 (2.7)	0.001	492 (12.7)	121 (10.8)	0.095	0.034
Number of stents per lesion	1.25 ± 0.58	1.14 ± 0.44	<0.001	1.37 ± 0.72	1.26 ± 0.64	<0.001	0.90
Total stent length per lesion, mm	22.95 ± 13.50	19.42 ± 10.71	<0.001	27.00 ± 16.87	22.82 ± 13.87	<0.001	0.33
Mean stent diameter per lesion, mm	3.02 ± 0.48	2.93 ± 0.52	<0.001	2.97 ± 0.45	2.87 ± 0.35	<0.001	<0.001

Values are n (%) or mean ± SD.
Abbreviations as in Table 1.

TABLE 5 Clinical Outcomes at 2 Years

	New-Generation DES (%) (n = 4,554)	Early-Generation DES (%) (n = 1,527)	Crude Analysis			Adjusted Analysis		
			HR (95% CI)	p Value	p Value for Interaction	HR (95% CI)	p Value	p Value for Interaction
Primary endpoint					0.185			0.219
Overall	462 (10.4)	200 (13.2)	0.78 (0.66–0.92)	0.003		0.75 (0.63–0.89)	0.001	
Syntax score ≤11	175 (8.0)	71 (8.9)	0.89 (0.67–1.17)	0.388		0.86 (0.64–1.16)	0.322	
Syntax score >11	287 (12.7)	129 (17.8)	0.70 (0.57–0.86)	0.001		0.68 (0.54–0.85)	0.001	
Cardiac death					0.016			0.042
Overall	106 (2.4)	50 (3.3)	0.72 (0.51–1.01)	0.056		0.60 (0.42–0.85)	0.004	
Syntax score ≤11	39 (1.8)	10 (1.3)	1.41 (0.71–2.83)	0.330		1.03 (0.51–2.09)	0.930	
Syntax score >11	67 (3.0)	40 (5.5)	0.53 (0.36–0.79)	0.002		0.46 (0.31–0.70)	<0.001	
Any MI					0.965			0.876
Overall	228 (5.1)	69 (4.6)	1.12 (0.86–1.47)	0.403		1.17 (0.87–1.57)	0.311	
Syntax score ≤11	87 (4.0)	28 (3.5)	1.12 (0.73–1.71)	0.609		1.16 (0.73–1.84)	0.540	
Syntax score >11	141 (6.2)	41 (5.7)	1.10 (0.78–1.56)	0.590		1.18 (0.80–1.73)	0.410	
Clinically-indicated TLR					0.083			0.059
Overall	217 (5.0)	129 (8.6)	0.56 (0.45–0.70)	<0.001		0.56 (0.44–0.70)	<0.001	
Syntax score ≤11	88 (4.1)	45 (5.7)	0.71 (0.49–1.01)	0.060		0.74 (0.50–1.08)	0.117	
Syntax score >11	129 (5.9)	84 (11.9)	0.47 (0.36–0.62)	<0.001		0.46 (0.34–0.61)	<0.001	
Clinically-indicated TVR					0.057			0.039
Overall	277 (6.4)	152 (10.1)	0.61 (0.50–0.74)	<0.001		0.61 (0.49–0.75)	<0.001	
Syntax score ≤11	110 (5.1)	52 (6.6)	0.76 (0.55–1.06)	0.110		0.81 (0.57–1.15)	0.233	
Syntax score >11	167 (7.6)	100 (14.1)	0.51 (0.40–0.65)	<0.001		0.51 (0.39–0.66)	0.000	
Definite ST					0.026			0.013
Overall	42 (0.9)	38 (2.5)	0.37 (0.24–0.58)	<0.001		0.40 (0.25–0.65)	<0.001	
Syntax score ≤11	20 (0.9)	10 (1.3)	0.73 (0.34–1.55)	0.409		0.94 (0.40–2.23)	0.888	
Syntax score >11	22 (1.0)	28 (3.9)	0.25 (0.14–0.43)	<0.001		0.24 (0.13–0.44)	<0.001	
Definite or probable ST					0.041			0.051
Overall	108 (2.4)	44 (2.9)	0.83 (0.59–1.18)	0.307		0.89 (0.60–1.33)	0.575	
Syntax score ≤11	43 (1.9)	11 (1.4)	1.42 (0.73–2.75)	0.301		1.65 (0.77–3.52)	0.200	
Syntax score >11	65 (2.9)	33 (4.6)	0.63 (0.41–0.95)	0.028		0.66 (0.41–1.06)	0.083	



CI = confidence interval; DES = drug-eluting stent(s); HR = hazard ratio; MI = myocardial infarction; ST = stent thrombosis; TLR = target lesion revascularization; TVR = target vessel revascularization.

TLR (5.0% vs. 8.6%; HR_{adj}: 0.56 [95% CI: 0.44 to 0.70]; $p < 0.001$) (Figure 4A) and definite ST (0.9% vs. 2.5%; HR_{adj}: 0.40 [95% CI: 0.25 to 0.65]; $p < 0.001$) (Figure 5A).

CLINICAL OUTCOMES ACCORDING TO SYNTAX SCORE. Table 5 summarizes 2-year clinical outcomes of new- compared with early-generation DES in patients with SYNTAX score ≤11 versus >11. There was no significant interaction ($p = 0.219$) in the treatment effect of new- versus early-generation DES for the primary composite endpoint between patients with SYNTAX score ≤11 (HR_{adj}: 0.86 [95% CI: 0.64 to 1.16]; $p = 0.322$) and >11 (HR_{adj}: 0.68 [95% CI: 0.54 to 0.85]; $p = 0.001$). The reduction in the risk of ischemia-driven TLR was more evident in patients with SYNTAX score >11 (HR_{adj}: 0.46 [95% CI: 0.34 to 0.61]; $p < 0.001$) than in patients with SYNTAX score ≤11 (HR_{adj}: 0.74 [95% CI: 0.50 to 1.08]; $p = 0.117$), although the interaction test was formally not significant ($p = 0.059$). Compared with early-generation DES, new-generation DES did not lower the risk of definite ST among patients with SYNTAX score ≤11 (HR_{adj}: 0.94 [95% CI: 0.40 to 2.23]; $p = 0.888$), but reduced the risk among patients with SYNTAX score >11 (HR_{adj}: 0.24 [95% CI: 0.13 to 0.44]; $p < 0.001$), with a significant interaction ($p = 0.013$). New-generation DES were also associated with a lower risk of cardiac death among patients with SYNTAX score >11 (HR_{adj}: 0.46 [95% CI: 0.31 to 0.70]; $p < 0.001$) compared with those with a SYNTAX score ≤11 (HR_{adj} : 1.03 [95% CI: 0.51 to 2.09]; $p = 0.93$), with a significant interaction ($p = 0.042$).

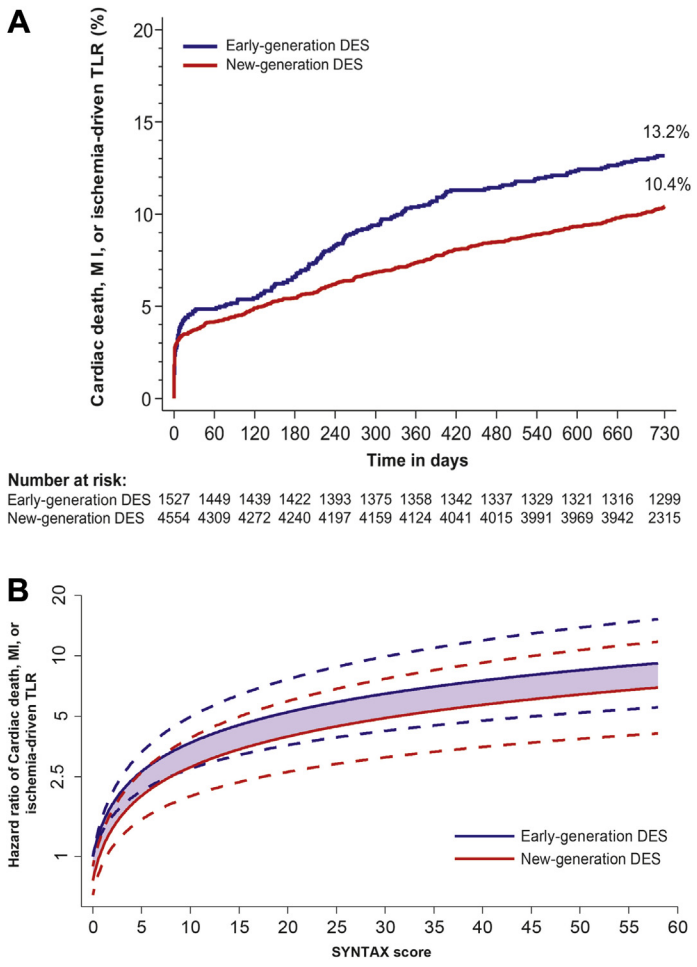
The results of Cox regression analyses, in which the interaction by the type of DES (new- vs. early-generation devices) and the SYNTAX score were tested, are reported in the Online Table 3. The graphical representations of these findings are shown in Figures 3B, 4B, and 5B. Of interest, there was no significant interaction between the effects of new- versus early-generation DES and the SYNTAX score for the primary composite endpoint ($p = 0.16$), TLR ($p = 0.25$), and definite ST ($p = 0.11$), suggesting that the improved effectiveness and safety profile of new- compared with early-generation DES were not affected by the SYNTAX score. Furthermore, there was no significant interaction between the type of new-generation DES and the primary endpoints of the study (Online Table 4), suggesting a consistent effect within new-generation devices.

DISCUSSION

This study evaluated the safety and effectiveness of new- compared with early-generation DES according to CAD complexity as defined by the SYNTAX score among 6,081 participants enrolled in 4 all-comer PCI trials. The principal findings of this patient-level pooled analysis are 2-fold:

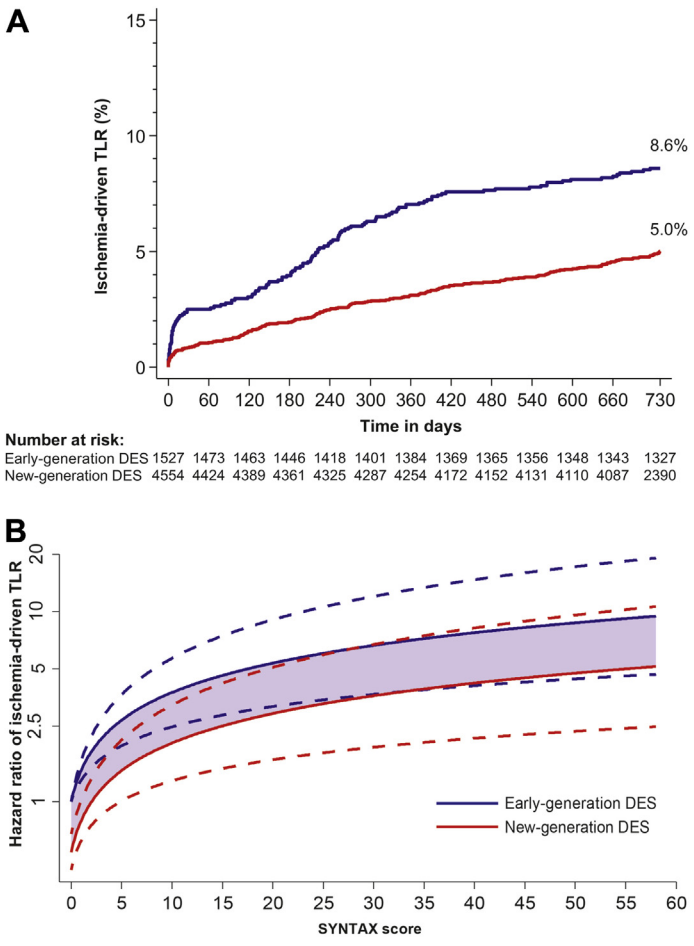
1. New-generation DES provide greater safety and effectiveness compared with early-generation DES in the overall population by reducing the risk of the primary device-oriented endpoint, ischemia-driven TLR, and definite ST; and

FIGURE 3 Analysis of the Primary, Device-Oriented Clinical Endpoint With New- Versus Early-Generation DES



(A) Kaplan-Meier time-to-event curves showing the 1-year occurrence of the composite of cardiac death, myocardial infarction (MI), or ischemia-driven target lesion revascularization (TLR) between the 2 study groups. **(B)** Cox-regression analysis of the hazard ratios among new- and early-generation DES according to the severity of disease (SYNTAX score, plotted on **x-axis**). The **blue shaded area** is the benefit associated with new- versus early-generation DES that persisted across the entire spectrum of SYNTAX score (p for interaction = 0.95). Early-generation DES patients with a SYNTAX score of 0 were considered to be at a hazard ratio of 1. Abbreviations as in Figure 2.

FIGURE 4 Analysis of the Principal Effectiveness Endpoint: Ischemia-Driven Target Lesion Revascularization



(A) Kaplan-Meier time-to-event curves for new- and early-generation DES. **(B)** Cox regression analysis of the hazard ratios for TLR among new- and early-generation DES according to SYNTAX score. Abbreviations as in Figures 2 and 3.

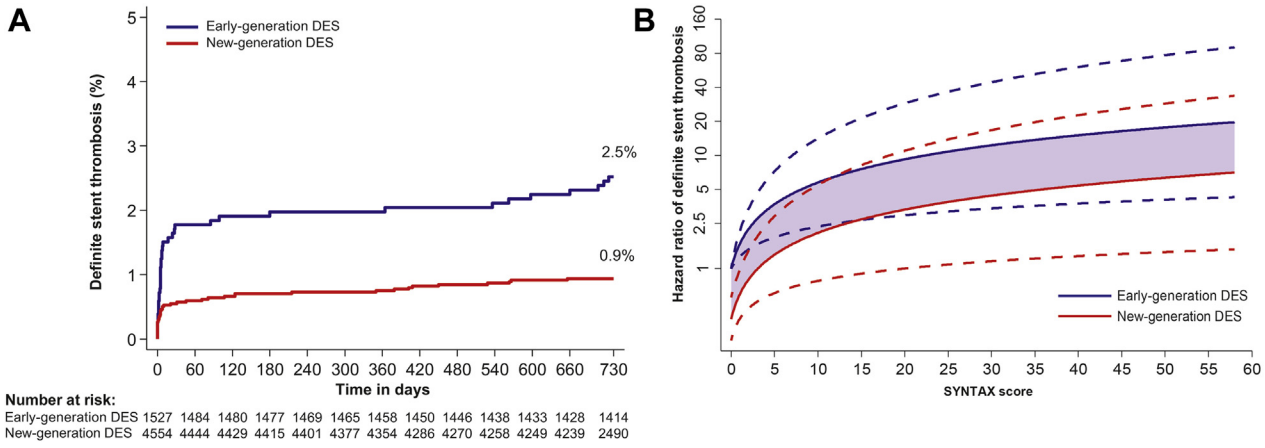
2. The anatomic complexity of CAD did not alter the benefits of new-generation DES, which tended to be greater in patients with SYNTAX score >11.

Currently DES are indicated as therapy of choice in nearly all patient and lesion subsets (5). However, the benefit of new-generation DES has not been systematically assessed according to the complexity of the underlying CAD. This is important, as the treatment effect of new-generation DES may be camouflaged by the overriding effect of the underlying CAD. Moreover, early-generation DES failed to be noninferior to CABG in the SYNTAX and FREEDOM trials, in whom patients with multivessel CAD were investigated (10,11). We, therefore, performed the present analysis that, with approximately 6,000 patients, represents one of the largest sources assessing the effect of the SYNTAX score on outcomes between patients treated with new-generation compared to those treated with early-generation DES across a wide spectrum of CAD.

We observed significant improvements in the safety and effectiveness of new- compared with early-generation DES in the overall population—a finding that corroborates results from previous studies (1,4). Despite a higher baseline risk profile, new-generation DES were associated with a 25% relative risk reduction of the primary composite endpoint, as well as decreased risks of TLR (54%) and definite ST (60%). In addition, we analyzed the differential outcome between new- and early-generation DES in relation to the underlying CAD severity as assessed by the SYNTAX score. Our study further extends the findings of the LEADERS trial, which reported a trend toward reduction of definite ST with biolimus-eluting stents in more anatomically complex CAD (19). With increased event rates through 2 years, we found that new-generation DES were associated with a 76% relative reduction in the risk of definite ST in patients with SYNTAX score >11 compared with patients with SYNTAX score ≤11 (p for interaction = 0.013). Moreover, new-generation DES were associated with a somewhat greater effectiveness in the subgroup of patients with SYNTAX score >11, as suggested by the interaction tests for TLR (p = 0.059) and TVR (p = 0.039). Therefore, the significant interaction in the treatment effect between new- and early-generation DES observed for cardiac mortality (p = 0.015) may be interpreted as the result of improved safety and effectiveness with new-generation DES in patients with more advanced CAD severity (20).

The SYNTAX score was initially developed to quantify the anatomic complexity of coronary lesions in the randomized SYNTAX trial that compared PCI with the use of paclitaxel-eluting stents versus CABG in patients with left main or 3-vessel disease (10,17). After validation in the ARTS-II (Arterial Revascularization Therapies Study part II) (21), several studies subsequently confirmed its predictive value among patients undergoing PCI (22); its use is recommended by American and European guidelines in the decision making process to determine the optimal revascularization strategy (23,24). The final 5-year results of the SYNTAX trial showed significantly higher rates of the primary composite endpoint of death, stroke, myocardial infarction, or repeat revascularization in patients undergoing PCI compared with CABG, with increasing divergence between the 2 treatment modalities with higher SYNTAX score terciles (25). There is broad agreement

FIGURE 5 Analysis of the Principal Safety Endpoint: Definite Stent Thrombosis



(A) Kaplan-Meier time-to-event curves for new- and early-generation DES. **(B)** Cox regression analysis of the hazard ratios for stent thrombosis among new- and early-generation DES according to SYNTAX score. Abbreviations as in Figure 2.

in preferring CABG over PCI in patients with severely advanced CAD, and current American and European guidelines on revascularization give preference to CABG in patients with 3-vessel disease and SYNTAX score ≥23 (23,24). As these data as well as those obtained in the FREEDOM trial were obtained with early-generation DES, it is tempting to speculate whether the use of new-generation DES may alleviate the existing gap between CABG and early-generation DES in patients with severe multivessel disease. Although prematurely terminated after the enrolment of 880 patients, a recent trial reported a significantly lower risk of death, myocardial infarction, or TLR among patients with multivessel CAD randomly allocated to CABG compared with PCI with the use of the new-generation everolimus-eluting stent (26). The benefit in favor of CABG was driven by a lower risk of repeat revascularization, due to a higher risk of non-TLR among PCI-treated patients (26).

STUDY LIMITATIONS. First, although this study supported the superiority of new- compared with early-generation DES across the range of CAD complexity, our results cannot be extrapolated to strategies trials comparing PCI with CABG. Indeed, patients with SYNTAX score in the intermediate or high terciles (≥23) were under-represented in the study, and conclusions drawn in this population should be considered hypothesis generating and preliminary. Second, the graphical representation of the interaction between the type of DES and the SYNTAX score should be interpreted in view of the limitation of any post-estimation model. Third, we were unable to compare outcomes associated with new-generation DES against a CABG arm. Therefore, the results of our study should be considered hypothesis-generating in view of ongoing randomized trials of PCI with new-generation DES vs. CABG (NCT01205776, NCT02100722).

CONCLUSIONS

New-generation DES improve clinical outcomes compared with early-generation DES at 2-year follow-up. The therapeutic benefit of new- compared with early-generation DES in terms of safety and effectiveness was not diminished in patients with increased anatomic CAD complexity but tended to be more evident in patients with SYNTAX score >11.

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PERSPECTIVES

WHAT IS KNOWN? New-generation DES are associated with improved safety and efficacy compared with early-generation DES.

WHAT IS NEW? Complexity of underlying CAD as defined by the angiographic SYNTAX score does not affect the benefits of new- over early-generation DES. The effectiveness and safety of new- over early-generation DES may be more pronounced among patients with moderate to high anatomic complexity.

WHAT IS NEXT? The use of new-generation DES is expected to improve clinical outcomes irrespective of the SYNTAX score. New-generation DES have the potential to reduce the existing gap between percutaneous and surgical myocardial revascularization in patients with advanced CAD.

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KEY WORDS coronary artery disease complexity, drug-eluting stent(s), percutaneous coronary intervention, SYNTAX score

APPENDIX For a supplemental figure and tables, please see the online version of this article.