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Differential cutoff points and clinical impact of stent parameters of various drug-eluting stents for predicting major adverse clinical events: An individual patient data pooled analysis of seven stent-specific registries and 17,068 patients

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ABSTRACT

Background: Stent parameters (length and diameter) are well-known risk factors for adverse outcomes after percutaneous coronary intervention (PCI) with stenting. This study aimed to investigate the differential cutoff criteria and clinical impact of the length and diameter of various drug-eluting stents (DES) for predicting major cardiovascular events.

Methods: Using patient-level data from seven stent-specific, prospective DES registries, we evaluated 17,068 patients who underwent PCI with either various contemporary DES or first-generation DES between July 2007 and July 2015: 3053 treated with cobalt-chromium everolimus-eluting stents (CoCr-EES), 2976 with platinum-chromium EES (PtCr-EES), 2888 with Resolute zotarolimus-eluting stents (Re-ZES), 782 with Biomatrix biolimus-eluting stents (Bi-BES), 1868 with Nobori BES (No-BES), 1934 with Xience Prime cobalt-chromium EES (Pr-CoCr-EES), and 3567 with first-generation sirolimus-eluting stents (SES). Two clinical outcomes were assessed: target-vessel failure (TVF; a composite of cardiac death, target-vessel myocardial infarction, and target-vessel revascularization [TVR]) and TVR.

Results: Stent length and stent diameter were important factors for predicting TVF or TVR in the entire cohort and in each DES cohort. For TVF risk prediction, the Youden index-based cutoff of stent length was highest with Bi-BES (45.0 mm) and lowest with No-BES (29.0 mm), and the cutoff of stent diameter was smallest with Pr-CoCr-EES (2.78 mm) and largest with No-BES (3.20 mm). For TVR risk prediction, the cutoff of stent length was the highest with PtCr-EES (48.0 mm) and the lowest with No-BES (29.0 mm), and the cutoff of stent diameter was smallest with CoCr-EES (2.72 mm) and largest with first-generation SES (3.30 mm). The 3-year TVF and TVR rates were substantially different according to the presence or absence of long lesions and small vessels determined using these cutoff points.

Conclusions: For contemporary PCI practice involving diverse types of DES, we identified differential cutoff points of stent length and diameter for predicting adverse clinical outcomes. The clinical impact of these stent parameters on outcomes and its magnitude varied according to different DES.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01186133.

Abbreviations: Bi-BES, biomatrix biodegradable-polymer biolimus-eluting stents; CoCr-EES, cobalt-chromium everolimus-eluting stents; DES, drug-eluting stents; IRIS-DES, Interventional Cardiology Research Incorporation Society – Drug-Eluting Stents; MI, myocardial infarction; No-BES, Nobori biodegradable-polymer biolimus-eluting stents; PCI, percutaneous coronary intervention; Pr-CoCr-EES, Xience Prime cobalt-chromium everolimus-eluting stents; PtCr-EES, platinum chromium everolimus-eluting stents; Re-ZES, Resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents; TVF, target-vessel failure; TVR, target-vessel revascularization.

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1. Introduction

First-generation drug-eluting stents (DES) releasing sirolimus or paclitaxel have been shown to substantially reduce the risk of restenosis and repeat revascularization, compared with bare-metal stents (BMS) [1]. Especially, the maximal benefit of the use of DES for reducing repeat revascularization was found in patients at a higher risk for restenosis (i.e., those with long lesions and small vessels) [2,3]. Thus, the total stent length (as a proxy for lesion length) and the minimum stent diameter (as a proxy for vessel diameter) were reported to be important stent parameters for predicting adverse clinical outcomes after percutaneous coronary intervention (PCI) with DES [2,4–8].

During the last decade, the technology and engineering of DES have continuously advanced, and second-generation DES have adopted different antiproliferative drugs, novel stent materials, thinner strut platforms, and more biocompatible or biodegradable polymers [9]. These newer-generation DES have been associated with better efficacy and safety outcomes than first-generation DES and bare-metal stents [10–16]. Although various types of DES are available in the current PCI practice, until recently, the clinical impact of the stent length and diameter of contemporary DES and their thresholds for predicting adverse outcomes was not determined. This knowledge may provide valuable clinical information on the relative effectiveness of several DES, and help clinicians decide the optimal choice of DES according to the lesion length and vessel size. Also, an enhanced risk stratification according to stent parameters would be of great clinical value if it could more accurately identify patients who are at an increased risk of developing major cardiovascular events.

Using individual patient-level data from several stent-specific, prospective, DES registries, we sought to investigate the clinical impact of stent parameters (length and diameter) of different contemporary DES and their cutoff values for identifying patients at a higher risk of adverse clinical outcomes.

2. Methods

2.1. Study design and population

As part of an ongoing academic project, data were pooled from the Interventional Cardiology Research Incorporation Society – Drug-Eluting Stents (IRIS-DES) registry (NCT01186133) between July 15, 2007, and July 29, 2015. The IRIS-DES registry has been described previously [17]. Briefly, the IRIS-DES involves a prospective, multicenter recruitment of unrestricted patients undergoing PCI with DES in Korea, and consists of several different arms of second- and first-generation DES in contemporary PCI situations. The pooled dataset consisted of individual patient data from seven different cohorts of DES registry. The key features of each DES registry are summarized in Appendix Table 1, including cobalt-chromium everolimus-eluting stents (CoCr-EES) (Xience V, Abbott Vascular) (K-XIENCE registry), platinum-chromium EES (PtCr-EES) (Promus Element, Boston Scientific) (IRIS-ELEMENT registry), Resolute zotarolimus-eluting stent (Re-ZES) (Resolute Integrity, Medtronic) (IRIS-INTEGRITY registry), Biomatrix biodegradable-polymer biolimus-eluting stents (Bi-BES) (BioMatrix, Biosensors) (IRIS-BIOMATRIX registry), Nobori biodegradable-polymer biolimus-eluting stents (No-BES) (Nobori, Terumo Clinical Supply) (IRIS-NOBORI registry), Xience Prime cobalt-chromium EES (Pr-CoCr-EES) (Xience Prime, Abbott Vascular) (IRIS-PRIME registry), and sirolimus-eluting stents (SES) (Cypher Select, Cordis Corp.) (DESSIAN registry).

These registries were supported by the CardioVascular Research Foundation, Seoul, Korea, and there was no industry involvement in the design, conduct, or analysis of the study. The study protocol was approved by the ethics committee at each participating center, and all patients provided written informed consent for participation in this prospective registry.

2.2. PCI procedures, follow-up, and database

In the IRIS-DES registry, PCI procedures were performed according to standard techniques at the discretion of the treating physician. Periprocedural anticoagulation was performed according to standard regimens. Glycoprotein IIb/IIIa inhibitors were administered at the discretion of the operator. All patients undergoing PCI received a loading dose of aspirin and a $P2Y_{12}$ receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) before or during PCI. After the procedure, aspirin was continued indefinitely, and $P2Y_{12}$ receptor inhibitors were prescribed for at least 12 months regardless of the DES type. Drugs for secondary prevention were prescribed according to current guidelines.

Clinical follow-up was conducted during hospitalization and at 30 days, 6 months, 12 months, and every 6 months thereafter. At each visit, information pertaining to patients' clinical status, all interventions, and outcome events were recorded. Baseline characteristics and outcome data were collected using a dedicated electronic case report form by specialized personnel at each participating center and were stored in a common database. The Internet-based system provides each center with immediate and continuous feedback on the processes and quality-of-care measures. Monitoring and verification of registry data are periodically performed in the participating hospitals by members of the academic coordinating center (Clinical Research Center, CardioVascular Research Foundation, Asan Medical Center, Seoul, Korea) [17].

2.3. Study end points and definitions

Two clinical outcomes were assessed in the current analysis: target-vessel failure (TVF) and target-vessel revascularization (TVR). TVF was defined as a composite of death from cardiac causes, target-vessel myocardial infarction (MI), or TVR.

Death was considered to have a cardiac cause unless an unequivocal noncardiac cause could be established. The protocol definition of MI was prespecified and was based on the universal definition of MI [17,18]. Procedure-related MI was defined as the presence of new Q waves or an elevation of creatine kinase-myocardial band isoenzyme to three times the normal upper limit, and spontaneous MI was defined as any increase of cardiac enzymes above the upper range limit with or without the development of Q waves on the electrocardiogram. In addition, alternative criteria of MI, defined post hoc, were examined on the basis of the Society for Cardiovascular Angiography and Interventions (SCAI) definition [19]. Using this definition, we specified post hoc an alternative definition of TVF: a composite of death of cardiac causes, SCAI-defined clinically relevant target-vessel MI, or TVR. TVR was defined as any type of percutaneous or surgical revascularization procedure involving the target vessel of the stented segment. All end points as defined and adjudicated in each individual registry were utilized. All end points were confirmed using the source documentation collected at each hospital and were centrally adjudicated by an independent clinical events committee whose members were blinded to the types of DES.

2.4. Statistical analysis

The baseline characteristics of the study population, including patient demographics, risk factors or comorbidities, clinical presentation, cardiac status, and anatomic/procedural features, were examined using proportions for categorical variables and means ± standard deviations in each cohort of the different DES. Most of the demographic, angiographic, and outcomes data that were common to most of the registries were analyzed.

In the current study, the total stent length was used as a proxy for lesion length and the smallest diameter of the inserted stents was used as a proxy for vessel diameter, as suggested in a previous key literature [2]. First, univariable and multivariable Cox proportional hazard models, through a backward, stepwise variable selection process, were used to identify important predictors of adverse clinical outcomes (TVF and TVR) and to assess the relationship of stent parameters (length and diameter) with clinical events. All variables with a P value < 0.15 in univariable analysis and stent parameters (length and diameter) were entered in a multivariable Cox regression model. Second, receiver operator characteristic analysis with the Youden index was performed to determine the model discrimination and the best cutoff value for predicting clinical events of TVF and TVR. The "optimal" cutoff value was defined by the highest Youden index value (sensitivity + specificity − 1) [20]. Third, a complementary analysis compared the time to clinical events according to a calculated cutoff point using the Kaplan-Meier method. Survival curves were compared using the log-rank test. In addition, Cox proportional hazard models were used to compare clinical events between the four subgroups of patients on the basis of the determined stent length (long [≥cutoff value] vs. short [<cutoff value]) and stent diameter (large [≥cutoff value] vs. small [<cutoff value]).

All analyses were performed with SAS software version 9.4 (SAS Institute) and the R programming language. All P values were two-sided, and values < 0.05 were considered statistically significant.

3. Results

3.1. Characteristics of the study patients

Between July 2007 and July 2015, a total of 17,068 patients from seven stent-specific, prospective IRIS-DES registries were included for the current analysis (3053 with CoCr-EES, 2976 with PtCr-EES, 2888 with Re-ZES, 782 with Bi-BES, 1868 with No-BES, 1934 with Pr-CoCr-EES, and 3567 with SES). The baseline demographics and clinical characteristics of each DES cohort are shown in Table 1. The mean age of the overall patients was 64 years, and approximately 70% of the patients were men. Overall, one-third of the patients had diabetes and more than half of the patients presented with acute coronary syndrome. According to the different cohorts of DES, there were between-group differences with regard to several clinical covariates. Table 2 shows the lesion and procedural characteristics of each DES cohort. There were also substantial differences across different DES groups with respect to anatomic, lesion, and procedural characteristics.

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Table 1
Baseline demographic and clinical characteristics of patients.

Characteristics	CoCr-EES (n = 3053)	PtCr-EES (n = 2976)	Re-ZES (n = 2888)	Bi-BES (n = 782)	No-BES (n = 1868)	Pr-CoCr-EES (n = 1934)	SES (n = 3567)
Age (year)	63.5 ± 10.8	63.8 ± 11.0	64.0 ± 10.9	64.0 ± 10.5	63.9 ± 10.8	63.9 ± 10.7	63.6 ± 10.8
Men	2061 (67.5)	2099 (70.5)	2085 (72.2)	538 (68.8)	1288 (69.0)	1391 (71.9)	2364 (66.3)
Body mass index (kg/m^2)	24.7 ± 3.2	24.7 ± 3.3	24.8 ± 3.2	24.7 ± 3.0	24.6 ± 3.1	24.6 ± 3.1	24.7 ± 3.1
Diabetes mellitus	1019 (33.4)	1006 (33.8)	940 (32.5)	228 (29.2)	534 (28.6)	676 (35.0)	1299 (36.4)
Hypertension	1909 (62.5)	1823 (61.3)	1759 (60.9)	456 (58.3)	1102 (59.0)	1217 (62.9)	2232 (62.6)
Hyperlipidemia	1147 (37.6)	1086 (36.5)	1378 (47.7)	296 (37.9)	615 (32.9)	699 (36.1)	1433 (40.2)
Current smoker	882 (28.9)	869 (29.2)	830 (28.7)	220 (28.1)	565 (30.2)	608 (31.4)	967 (27.1)
Family history of CAD	110 (3.6)	199 (6.7)	232 (8.0)	52 (6.6)	88 (4.7)	127 (6.6)	173 (4.9)
Previous MI	158 (5.2)	148 (5.0)	150 (5.2)	39 (5.0)	76 (4.1)	89 (4.6)	274 (7.7)
Previous CHF	64 (2.1)	79 (2.7)	61 (2.1)	24 (3.1)	22 (1.2)	51 (2.6)	84 (2.4)
Previous PCI	454 (14.9)	322 (10.8)	340 (11.8)	55 (7.0)	158 (8.5)	182 (9.4)	680 (19.1)
Previous CABG	61 (2.0)	37 (1.2)	49 (1.7)	9 (1.2)	40 (2.1)	38 (2.0)	87 (2.4)
Renal failure	102 (3.3)	93 (3.1)	100 (3.5)	24 (3.1)	43 (2.3)	73 (3.8)	150 (4.2)
Cerebrovascular disease	251 (8.2)	219 (7.4)	207 (7.2)	55 (7.0)	120 (6.4)	127 (6.6)	271 (7.6)
Peripheral vascular disease	36 (1.2)	61 (2.0)	108 (3.7)	14 (1.8)	18 (1.0)	48 (2.5)	38 (1.1)
Chronic lung disease	89 (2.9)	61 (2.0)	77 (2.7)	19 (2.4)	44 (2.4)	34 (1.8)	91 (2.6)
Ejection fraction (%)	59.5 ± 10.9	59.1 ± 10.1	59.5 ± 9.8	59.5 ± 10.2	59.0 ± 9.6	58.3 ± 11.2	59.1 ± 10.7
Clinical presentation							
Stable angina	1270 (41.6)	1138 (38.2)	1188 (41.1)	291 (37.2)	791 (42.3)	776 (40.1)	1618 (45.4)
Unstable angina	1048 (34.3)	1005 (33.8)	929 (32.2)	272 (34.8)	521 (27.9)	604 (31.2)	1142 (32.0)
NSTEMI	334 (10.9)	478 (16.1)	421 (14.6)	120 (15.3)	276 (14.8)	291 (15.0)	434 (12.2)
STEMI	401 (13.1)	355 (11.9)	350 (12.1)	99 (12.7)	280 (15.0)	263 (13.6)	373 (10.5)
Treated lesions per patient							
1	2053 (67.2)	2080 (69.9)	2098 (72.6)	619 (79.2)	1461 (78.2)	1338 (69.2)	2316 (64.9)
2	766 (25.1)	697 (23.4)	618 (21.4)	133 (17.0)	346 (18.5)	467 (24.1)	940 (26.4)
3	193 (6.3)	162 (5.4)	136 (4.7)	27 (3.5)	47 (2.5)	112 (5.8)	257 (7.2)
≥4	41 (1.3)	37 (1.2)	36 (1.2)	3 (0.4)	14 (0.7)	17 (0.9)	54 (1.5)

Data are shown as mean ± standard deviation for continuous variables and as absolute numbers (percentage) for dichotomous variables.
Abbreviations: Bi-BES, biomatrix biolimus-eluting stent(s); CABG, coronary-artery bypass grafting; CAD, coronary artery disease; CHF, congestive heart failure; CoCr-EES, cobalt-chromium everolimus-eluting stent(s); No-BES, Nobori biolimus-eluting stent(s); NSTEMI, non-ST-elevation myocardial infarction; MI, myocardial infarction; PCI, percutaneous coronary intervention; Pr-CoCr-EES, XIENCE PRIME cobalt-chromium everolimus-eluting stent(s); PtCr-EES, platinum-chromium everolimus-eluting stent(s); Re-ZES, Resolute zotarolimus-eluting stent(s); SES, sirolimus-eluting stent(s); and STEMI, ST-elevation MI.

3.2. Cutoff point of stent parameters and clinical impact

The median duration of clinical follow-up in the overall population was 3.4 years (interquartile range 2.6–4.2). During the entire follow-up period, 1272 patients (7.5%) had at least one TVF event, including 590 patients (3.5%) with cardiac death, 345 patients (2.0%) with target-vessel MI, and 847 patients (5.0%) with TVR. The results of univariable and multivariable Cox proportional hazard analyses to identify risk factors for the occurrence of TVF and TVR are summarized in Appendix Table 2. In the overall group, total stent length and minimum stent diameter were significantly associated with increased risks of TVF and TVR. Specifically, stent length or stent diameter was an independent predictor of TVF or TVR in

Table 2
Baseline lesion and procedural characteristics.

Characteristics	CoCr-EES (n = 4305)	PtCr-EES (n = 5423)	Re-ZES (n = 5410)	Bi-BES (n = 1331)	No-BES (n = 3099)	Pr-CoCr-EES (n = 3737)	SES (n = 5132)
Lesion location							
LM	285 (6.6)	208 (3.8)	283 (5.2)	23 (1.7)	32 (1.0)	86 (2.3%)	170 (3.3%)
LAD	1995 (46.3)	2260 (41.7)	2161 (40.0)	610 (45.9)	1378 (44.6)	1513 (40.5%)	2509 (48.9%)
LCX	855 (19.9)	1382 (25.5)	1295 (24.0)	317 (23.8)	778 (25.2)	959 (25.7%)	1075 (21.0%)
RCA	1157 (26.9)	1570 (29.0)	1650 (30.5)	380 (28.6)	904 (29.2)	1172 (31.4%)	1366 (26.6%)
Graft	13 (0.3)	3 (0.1)	17 (0.3)	0	1 (0.03)	5 (0.1)	11 (0.2)
ACC-AHA lesion type							
A	126 (2.9)	616 (11.4)	364 (6.7)	108 (8.1)	288 (9.3)	260 (7.0)	177 (3.4)
B1	955 (22.2)	1433 (26.4)	1225 (22.6)	339 (25.5)	741 (23.9)	765 (20.5)	915 (17.8)
B2	815 (18.9)	643 (11.9)	832 (15.4)	318 (23.9)	733 (23.7)	653 (17.5)	850 (16.6)
C	2409 (56.0)	2731 (50.4)	2989 (55.2)	566 (42.5)	1337 (43.1)	2059 (55.1)	3190 (62.2)
Restenotic lesions	198 (4.6)	137 (2.5)	135 (2.5)	18 (1.4)	29 (0.9)	78 (2.1)	274 (5.3)
Bifurcation lesions	893 (20.7)	1040 (19.2)	1449 (26.8)	214 (16.1)	764 (24.7)	1185 (31.7)	1190 (23.2)
Total occlusion	389 (9.0)	731 (13.5)	820 (15.2)	161 (12.1)	458 (14.8)	567 (15.2)	485 (9.5)
Moderate to severe calcification	483 (11.2)	582 (10.7)	407 (7.5)	73 (5.5)	165 (5.3)	300 (8.0)	562 (11.0)
Thrombus-containing lesion	355 (8.2)	300 (5.5)	266 (4.9)	81 (6.1)	163 (5.3)	186 (5.0)	392 (7.6)
No. of stents[a]	1.3 ± 0.6	1.2 ± 0.5	1.2 ± 0.5	1.1 ± 0.3	1.1 ± 0.4	1.2 ± 0.4	1.2 ± 0.5
Stent length (mm)[a]	29.4 ± 16.1	27.1 ± 12.9	29.6 ± 14.2	23.5 ± 9.0	24.3 ± 10.2	30.9 ± 14.5	31.4 ± 15.2
Stent diameter (mm)[a]	3.2 ± 0.4	3.1 ± 0.4	3.2 ± 0.4	3.2 ± 0.4	3.1 ± 0.3	3.1 ± 0.4	3.1 ± 0.4
Use of IVUS	2248 (52.2)	1542 (28.4)	2005 (37.1)	435 (32.7)	657 (21.2)	1163 (31.1)	2496 (48.6)

Data are shown as mean ± standard deviation for continuous variables and as absolute numbers (percentage) for dichotomous variables.
Abbreviations: ACC-AHA, American College of Cardiology-American Heart Association; IVUS, intravascular ultrasound; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; RCA, and right coronary artery; other abbreviations are as in Table 1.
[a] The number, length, and diameter of stents were calculated per lesion.

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the DES cohort of CoCr-EES, PtCr-EES, Re-ZES, or SES. However, these stent parameters were not independent predictors of TVF or TVR in the Bi-BES and No-BES cohorts. In addition, the distributional histogram of clinical outcomes according to stent parameters in each DES cohort is shown in the Appendix Fig. 1.

Receiver operator characteristic analysis with the Youden index was used to determine the optimal cutoff points of the total stent length and minimum stent diameter for predicting clinical events in each DES cohort (Fig. 1 and Appendix Fig. 2). For the occurrence of TVF, the optimal Youden index-based cutoff point of stent length was highest with Bi-BES (45.0 mm) and lowest with No-BES (29.0 mm), and the cutoff value of stent diameter was smallest with Pr-CoCr-EES (2.78 mm) and largest with No-BES (3.20 mm). For the occurrence of alternatively defined TVF adopting SCAI-defined MI, the overall findings were similar: the cutoff value of stent length was highest with Bi-BES (45.0 mm) and lowest with No-BES (29.0 mm), and the cutoff value of stent diameter was smallest with Pr-CoCr-EES (2.78 mm) and largest with No-BES (3.20 mm) (Appendix Fig. 3). For the occurrence of TVR, the cutoff value of stent length was highest with PtCr-EES (48.0 mm) and lowest with No-BES (29.0 mm), and the cutoff value of stent diameter was smallest with CoCr-EES (2.72 mm) and largest with first-generation SES (3.30 mm).

The Kaplan-Meier curves of the 3-year TVF and TVR rates according to the optimal Youden index-based cutoff points of stent length and diameter are illustrated in Appendix Fig. 4. These cutoff criteria of stent parameters (but not always for both stent length and diameter) discriminated well between the occurrence of TVF and TVR in the overall and each cohort of DES, except No-BES group. In the No-BES cohort, the stent parameters poorly discriminated between the risk of TVF and TVR.

On the basis of the presence or absence of long lesions and small vessels stratified according to the cutoff points of stent length and diameter, the 3-year event rates of TVF and TVR are shown in Table 3. In all patients, the risks of TVF or TVR varied substantially, with the four subgroups stratified according to one or two risk factors (i.e., long lesions and small vessels). Overall, there were incremental risks of TVF or TVR in higher-risk patients with long lesions and/or small vessels. However, the magnitude of the stepwise increase of clinical events varied according to the different types of DES. The rates of stent thrombosis and target-vessel MI according to stent parameters are shown in the Appendix Table 3.

4. Discussion

The present study, based on a pooled analysis of 17,068 patients enrolled in seven prospective stent-specific registries, is the largest report to date examining differential cutoff points of stent parameters (length and diameter) of different contemporary DES and its clinical impact. The major findings were as follows: (i) we have identified differential cutoff points of stent length and diameter for predicting the risk of TVF or TVR among different DES; (ii) the clinical impact of these stent parameters on clinical outcomes was not uniform and its magnitude varied according to the different types of DES; and (iii) in general, patients with long lesions and/or small vessels stratified according to the cutoff points of the stent parameters had a higher risk of developing TVF and TVR. However, the degree of incremental, stepwise, and length- and size-dependent association with increasing event rates varied according to the different types of DES.

Several previous studies have demonstrated that the relative efficacy and safety substantially differed according to stent length and diameter in comparison of DES and BMS, and among different DES [2,3,6,8]. Overall, the maximum benefit of better DES over a comparator device was pronounced in higher-risk patients with a longer stent length and a smaller stent diameter. Although stent length and diameter have been

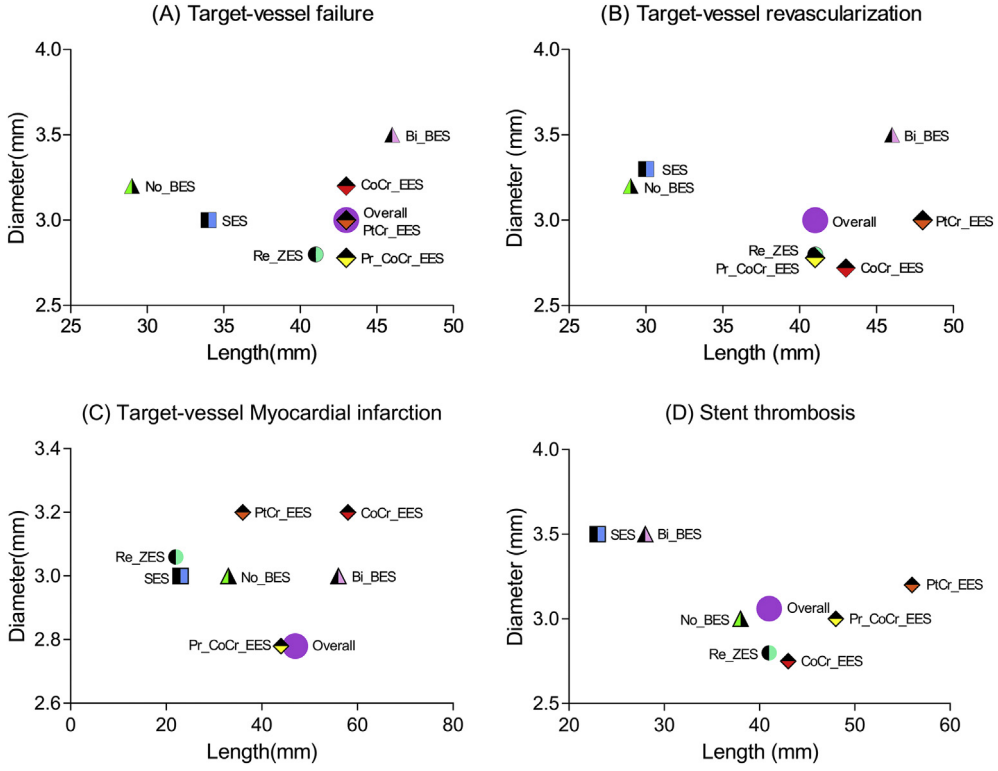

Fig. 1. Youden index-based cutoff point of stent length and stent diameter for predicting clinical events based on drug-eluting stent type. Differential cutoff points of stent length and stent diameters are shown for target-vessel failure (A); target-vessel revascularization (B); target-vessel myocardial infarction (C) and stent thrombosis (D). Target-vessel failure was defined as a composite of death of cardiac causes, target-vessel myocardial infraction, or target-vessel revascularization. Abbreviations: Bi-BES, biomatrix biodegradable-polymer biolimus-eluting stents; CoCr-EES, cobalt-chromium everolimus-eluting stents; No-BES, Nobori biodegradable-polymer biolimus-eluting stents; Pr-CoCr-EES, Xience Prime cobalt-chromium everolimus-eluting stents; PtCr-EES, platinum chromium everolimus-eluting stents; Re-ZES, Resolute zotarolimus-eluting stents; SES, sirolimus-eluting stents.

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Table 3
Rates of target-vessel failure and target-vessel revascularization in each stent cohort, according to determined cutoff values.[a]

DES type	Target-vessel failure[b]					Target-vessel revascularization				
	Stent length	Stent diameter	Event rate at 3 y (%)	Hazard ratio (95% CI)	*P* value	Stent length	Stent diameter	Event rate at 3 y (%)	Hazard ratio (95% CI)	*P* value
Overall	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(N = 17,068)	**43.0 mm**	**3.00 mm**				**41.0 mm**	**3.00 mm**			
	<(Short)	≥(Large)	5.3	Reference		<(Short)	≥(Large)	3.5	Reference	
	<(Short)	<(Small)	7.7	1.52 (1.32–1.76)	<0.001	<(Short)	<(Small)	4.8	1.48 (1.23–1.77)	<0.001
	≥(Long)	≥(Large)	7.2	1.35 (1.15–1.59)	<0.001	≥(Long)	≥(Large)	4.9	1.33 (1.09–1.62)	0.004
	≥(Long)	<(Small)	9.6	1.87 (1.64–2.14)	<0.001	≥(Long)	<(Small)	7.4	2.09 (1.79–2.45)	<0.001
CoCr-EES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 3053)	**43.0 mm**	**3.20 mm**				**43.0 mm**	**2.72 mm**			
	<(Short)	≥(Large)	4.5	Reference		<(Short)	≥(Large)	4.4	Reference	
	<(Short)	<(Small)	6.2	1.50 (1.05–2.15)	0.03	<(Short)	<(Small)	6.0	1.25 (0.65–2.41)	0.49
	≥(Long)	≥(Large)	6.2	1.41 (0.71–2.79)	0.32	≥(Long)	≥(Large)	5.6	1.45 (1.05–2.02)	0.02
	≥(Long)	<(Small)	9.0	2.34 (1.67–3.28)	<0.001	≥(Long)	<(Small)	11.0	2.44 (1.57–3.79)	<0.001
PtCr-EES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 2976)	**43.0 mm**	**3.00 mm**				**48.0 mm**	**3.00 mm**			
	<(Short)	≥(Large)	5.1	Reference		<(Short)	≥(Large)	3.0	Reference	
	<(Short)	<(Small)	8.5	1.71 (1.27–2.30)	<0.001	<(Short)	<(Small)	5.1	1.70 (1.17–2.45)	0.005
	≥(Long)	≥(Large)	7.4	1.35 (0.91–2.01)	0.12	≥(Long)	≥(Large)	5.6	1.64 (0.98–2.74)	0.06
	≥(Long)	<(Small)	11.7	2.25 (1.68–3.01)	<0.001	≥(Long)	<(Small)	9.8	2.96 (2.06–4.25)	<0.001
Re-ZES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 2888)	**41.0 mm**	**2.80 mm**				**41.0 mm**	**2.80 mm**			
	<(Short)	≥(Large)	4.4	Reference		<(Short)	≥(Large)	2.7	Reference	
	<(Short)	<(Small)	6.1	1.28 (0.83–1.97)	0.24	<(Short)	<(Small)	4.4	1.44 (0.86–2.40)	0.16
	≥(Long)	≥(Large)	5.1	1.16 (0.73–1.82)	0.52	≥(Long)	≥(Large)	3.0	0.99 (0.55–1.81)	0.99
	≥(Long)	<(Small)	7.7	1.61 (1.09–2.37)	0.02	≥(Long)	<(Small)	7.7	2.62 (1.73–3.98)	<0.001
Bi-BES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 782)	**45.0 mm**	**3.00 mm**				**45.0 mm**	**3.00 mm**			
	<(Short)	≥(Large)	4.3	Reference		<(Short)	≥(Large)	4.3	Reference	
	<(Short)	<(Small)	8.1	1.55 (0.90–2.67)	0.11	<(Short)	<(Small)	4.8	1.31 (0.68–2.52)	0.40
	≥(Long)	≥(Large)	16.7	3.45 (1.15–13.1)	0.03	≥(Long)	≥(Large)	7.2	3.52 (0.80–15.5)	0.09
	≥(Long)	<(Small)	15.5	2.98 (1.55–5.74)	0.001	≥(Long)	<(Small)	11.3	2.89 (1.33–6.26)	0.007
No-BES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 1868)	**29.0 mm**	**3.20 mm**				**29.0 mm**	**3.20 mm**			
	<(Short)	≥(Large)	3.6	Reference		<(Short)	≥(Large)	2.3	Reference	
	<(Short)	<(Small)	6.2	2.13 (1.29–3.53)	0.003	<(Short)	<(Small)	3.8	1.98 (1.07–3.63)	0.03
	≥(Long)	≥(Large)	4.9	2.11 (0.79–5.64)	0.13	≥(Long)	≥(Large)	3.3	1.83 (0.52–6.39)	0.33
	≥(Long)	≥(Small)	8.2	2.47 (1.45–4.20)	<0.001	≥(Long)	≥(Small)	4.5	1.97 (1.02–3.82)	0.04
Pr-CoCr-EES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 1934)	**43.0 mm**	**2.78 mm**				**41.0 mm**	**2.78 mm**			
	<(Short)	≥(Large)	5.3	Reference		<(Short)	≥(Large)	2.8	Reference	
	<(Short)	<(Small)	9.8	1.99 (1.32–3.02)	0.001	<(Short)	<(Small)	5.2	2.07 (1.19–3.59)	0.009
	≥(Long)	≥(Large)	6.6	1.34 (0.78–2.30)	0.28	≥(Long)	≥(Large)	3.6	1.39 (0.69–2.81)	0.35
	≥(Long)	<(Small)	9.8	2.07 (1.39–3.09)	<0.001	≥(Long)	<(Small)	6.4	2.38 (1.43–3.96)	<0.001
SES	**Cutoff value**	**Cutoff value**				**Cutoff value**	**Cutoff value**			
(n = 3567)	**34.0 mm**	**3.00 mm**				**30.0 mm**	**3.30 mm**			
	<(Short)	≥(Large)	5.4	Reference		<(Short)	≥(Large)	1.9	Reference	
	<(Short)	<(Small)	9.4	1.80 (1.29–2.53)	<0.001	<(Short)	<(Small)	4.6	2.54 (1.30–4.97)	0.006
	≥(Long)	≥(Large)	9.0	1.68 (1.24–2.28)	<0.001	≥(Long)	≥(Large)	5.1	2.57 (1.24–5.30)	0.01
	≥(Long)	<(Small)	8.8	1.76 (1.32–2.33)	<0.001	≥(Long)	<(Small)	6.8	3.80 (2.06–7.03)	<0.001

Abbreviations are as in Table 1.
[a] Cumulative 3-year rates of events based on Kaplan-Meier estimates.
[b] Target-vessel failure was defined as a composite of death from cardiac causes, target-vessel MI, or TVR.

proposed as robust predictors for ischemic events and restenosis after first-generation DES, until recently, the extent to which stent parameters serve as a proxy, integrating clinical, angiographic, and procedural factors, is not yet clearly delineated with diverse types of contemporary DES. Thus, our large-sized pooled analysis may substantially contribute to the understanding of the relative performance of different DES, and may provide insight on the optimal choice of DES according to lesion length and vessel size.

In the era of first-generation DES, several studies have suggested cutoff points of stent length or diameter for predicting adverse clinical events [21,22]. Moreover, some studies suggested an optimal threshold of stent length and diameter for higher risks of clinical events with second-generation DES [23]. In the current study, the DES with the most modern design, Re-ZES and Pr-CoCr-EES, had the smallest cutoff point of 2.78–2.80 mm for predicting adverse outcomes. This finding might suggest that the choice of either Re-ZES or Pr-CoCr-EES would be optimal for treating small-vessel disease. A recent study also reported that novel-sized Re-ZES (Resolute Onyx 2.0 mm) seems to be a feasible option for the treatment of coronary lesions in extremely small vessels [24]. In addition, with regard to stent length, our data suggest that a cutoff >38–40 mm may be feasible for most contemporary DES, except No-BES and first-generation SES, in terms of future risks of TVF and TLR.

In our study, the most traditional measure of stent parameter (length and diameter) estimating the future risk of adverse events and clinical restenosis was less discriminating with bioabsorbable polymer-based No-BES. A recent meta-analysis showed that bioabsorbable polymer-BES, including No-BES and Bi-BES, were associated with similar rates of cardiac death, MI, or TVR to those of second-generation durable polymer-DES [12]. However, few studies have evaluated the impact of stent parameters on outcomes with bioabsorbable polymer-BES; thus, the reason for the seemingly less prominent impact of stent length and diameter on adverse outcomes with bioabsorbable polymer-No-BES compared with durable polymer-DES, remains unclear. It might be, in part, attributable to the substantial differences in the stent platform itself, as well as the clinical and

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lesion characteristics that were considered to be more suitable for a specific DES type at the operator's discretion. In addition, there was a remarkable disparity of stent cutoff points and clinical impact between No-BES and Bi-BES. While two stents share drug and polymer, stent metallic platform (i.e., S-Stent platform for No-BES vs. Juno stent platform for Bi-BES, an ultra-thin parylene coating between the stent and the polymer) and their mechanical performance is likely to differ, especially in a segment where stents are stretched to their maximum diameter and often subject to dilatation through the cells.

Our study showed the differential rates of TVF and TVR across a wide spectrum of stent lengths and diameters in each cohort of different DES. Although the discriminating capacity of the cutoff points measured using receiver operator characteristic analyses was significantly diverse (ranging from poor to modest) according to DES type, overall trends toward poor clinical outcomes were observed for a greater stent length and a smaller stent diameter, suggesting the prognostic utility of stent parameters even in the current PCI practice with contemporary, second-generation DES.

4.1. Study limitations

Several limitations of our study should be considered. First, as this study is observational in nature, the overall findings should be considered hypothetical and hypotheses-generating only. Second, in our study, stent length and diameter were based on the manufacturers' specifications, not on physical measurements made at the completion of the case. Thus, there is a possibility of under- and overestimation of stent parameters. Third, in some DES cohorts, stent length or diameter was not significantly associated with the risks of TVF or TVR. Thus, the values of the area under the receiver operator characteristic curve of the cutoff threshold were relatively low, and therefore the clinical interpretation might be limited in this group. However, although the discriminating power is limited, there were at least 2-fold differences in clinical events in the subgroups stratified according to stent length and diameter, and these findings might be meaningful for the physician's consideration of specific types of DES. Fourth, in using TVR as one of our key outcomes, we did not determine whether revascularization of the target-vessel was due to restenosis of the index lesion or to de novo coronary lesions. However, in the clinical viewpoint, we believe that TVR is an appropriate patient-oriented outcome compared with angiographically defined restenosis, which may not be functionally significant. Finally, owing to the limited number of hard clinical end points (i.e., stent thrombosis and mortality), our study was underpowered to detect meaningful cutoff thresholds of stent parameters for predicting such serious safety outcomes.

5. Conclusions

In the contemporary PCI setting, the clinical impacts of stent length and diameter on the risk of TVF and TVR were different according to different types of DES. We have identified differential cutoff points of stent length and stent diameter for different DES for predicting the risks of TVF and TVR. Overall, in higher-risk patients with long lesions and/or small vessels, the rates of clinical outcomes were proportionally increased; however, this association was observed to a varying degree based on the different types of DES.

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Role of the sponsors

The sponsors played no role in this study. There was no industry involvement in the design or conduct of the study; the collection, management, analysis, and interpretation of the data; the preparation, review, and approval of the manuscript; or the decision to submit the manuscript for publication.

Disclosures

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2019.01.108.

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